Research Article

# Covid -19 and Cardiovascular Assessment in Critically Ill Patients: A Multidisciplinary Experience Report

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**Received:** 27 July 2020; **Accepted:** 04 August 2020; **Published:** 14 August 2020

**Citation:** Cipani S, Bartolini V, Berardinelli M, Pazzi M, Stera C, Ciapetti C, Renieri L, Pavoni V. Covid -19 and Cardiovascular Assessment in Critically Ill Patients: A Multidisciplinary Experience Report. Cardiology and Cardiovascular Medicine 4 (2020): 418-427.

## Abstract

Since its recognition in december 2019, Covid -19 has rapidly spread all over the world with a global pandemic . This virus invades cells through the angiotensin converting enzyme 2 (ACE 2) receptor, particularly developed in hypertensive, atherosclerotic and congestive heart failure patients. This observation suggest that patients with pre-existing cardiovascular diseases are prone to more severe complications of Covid -19 with increased mortality. To date early reports indicate two possible patterns of myocardial injury with Covid -19. We summarize our clinical experience with 30 patients hospitalized in our ICU during march and april 2020.

**Keywords:** Covid-19; Cardiovascular involvement; ACE 2 receptor; Citokine storm

## 1. Introduction

SARS-Cov-2 infection is caused by the binding of spike protein to the human angiotensin-converting enzyme2 (ACE 2) receptor. A transmenbrane protease serine 2 (TMPRSS2) activates the spike protein before human cells invasion [1]. ACE 2 is expressed in lung (predominant portal of entry), heart, intestinal

epithelium, vascular epithelium and the kidneys providing a mechanism for the multi-organ dysfunction. Physiologically ACE 2 inibitors act by homolog of ACE converting angiotensin II to angiotensin 1-7 thereby diminishing vasoconstriction mediated by the renin angiotensin system [1]. Many patients with cardiovascular diseases use daily ACEi and ARB for hypertension management, congestive heart failure and avoid cardiac remodelling. There are concerns regarding the use of renin-angiotensin-aldosterone system (RAAS) inhibitors that may increase ACE 2 expression [2] leading to suggestions that these drugs may be detrimental in patients exposed to SARS-Cov-2 [3]. However ACE 2 appears to be protective against acute lung injury [4] by a reduction of angiotensin II and alveolar edema. In a murin model binding of the SARS-Cov spike protein to ACE 2 caused ACE 2 downregulation, leading to an increase in angiotensin II with increased pulmonary vascular permeability and reduced lung function. The treatment with recombinant ACE 2 [4] and losartan [5] mitigated the degree of lung injury.

Since patients with Covid -19 with cardiovascular comorbidities (diabete mellitus, hypertension, cardiovascular diseases (CVD)) have higher mortality [6], and the severity of infection correlates with cardiovascular manifestation. The same authors found that patients with underlying CVD were more likely to have cardiac injury (troponin elevation) compared with patients without CVD (54,5% vs 13,2%) [7]. The mechanism of cardiovascular injury from Covid -19 have been not fully elucidated and are likely multifactorial. In some cases of cardiac tissue viral particles have been identified by RT-PCR [8]. Cardiac injury can result via direct or indirect mechanism. The direct mechanism is characterized by cardiomyocyte death, inflammation due viral invasion into myocardial tissue. Cardiac inflammation secondary to severe systemic hyperinflammation and hypoxemia due to respiratory failure are the causes of indirect mechanism [9]. Early reports indicate that there are two patterns of myocardial injury with Covid -19. The first one is characterized not only by the increase of hs-cTnI but also with other infiammatory biomarkers (ferritin, interleukin-6, lactate dehydrogenase, D-dimer) reflecting cytokine storm or secondary hemophagocytic lymphohistiocytosis more than isolated myocardial injury. In contrast, reports of patients presenting with predominantly cardiac symptoms suggest the second pattern, characterized by a potentially viral myocarditis or stress cardiomyopathy [1].

## Pattern 1: Cytokine storm, lynfocitopenia and secondary hemophagocytic lymphohistiocytosis

The cytokine storm provides one of the mechanism by which it develops the state of hyperinflammation in severe cases of Covid-19 and it is triggered by an imbalaced response by type 1 and type 2 T helper (Th) cells [10]. After virus entry via host ACE2 receptor and its replication, the innate immunity activation occurs namely monocytes and macrophages and the release of numerous cytokines among IL-6 and IL-1 play a fundamental role. For the activation and differentiation of innate and adaptive immune cells it is to underlines the Notch signaling. In human there are four receptors (Notch 1-4) activated by binding with ligands (Jagged 1, 2 and Delta-like ligands (DII) 1,3,4). In macrophages DII4/Notch signaling promotes the production of inflammatory cytokines including IL-6 which in turn increases the expression of Notch ligands (DII 1,4), thus establishing a positive feedback circuit. In Th cells the Noch signalling triggered by DII1/DII4 ligands promotes the production of inflammatory Th1/Th17 cytokines [11]. The systemic increase of

numerous cytokines including IL-6, IL-2, IL-7, granulocyte colony-stimulating factor, C-X-C motif chemokine 10 (CXCL10), chemokine (C-C motif) ligand 2 and tumour necrosis factor-α have all been observed in subjects with Covid-19 [12] which corresponds to the characteristics of a cytokine release syndrome (CRS). High serum values of IL-6 are frequent in CRS.

An other important aspect of systemic inflammation is lymphocytopenia which is associated with adverse outcomes. It seems that SARS-CoV 2 has the capacity for direct leukocyte infection and in particulary a relative predilection for lymphocytes. T-cell reduction is especially important considering the role they play in immune homeostasis and prevention of excessive inflammation after infection. It is demonstrated, by electron microscopy, that in a high percentage of lymphocytes (over 50%) viral particles are insides. Most of these lymphocytes are T cells and both $CD4^+$ and $CD8^+$ decrease. Systemic inflammation conveys leukocytes on the site of infection, increases vascular permeability and promotes macrophage activation [13]. Overproduction of IL-1β by tissue macrophages triggers secondary hemophagocytic lymphohistiocytosis (sHLH), also called macrophage activation syndrome, that is characterized by pancytopenia, hyper-coagulation, acute kidney injury and hepatobiliary dysfunction. All the patients scored positive for the hemophagocytosis score (HScore) were diagnosed with secondary hemophagocytic lymphohistocytosis (sHLH) [14]. The HScore is developed by experts and provides points for each of nine variables: degree of core temperature; hepatomegaly and/or splenomegaly; number of cytopenias; concentrations of triglycerides, fibrinogen, ferritin, aspartate aminotransferase; history of immunosuppression; and bone marrow hemophagocytosis [15]. All these mechanisms (cytokine storm, lynfocitopenia and sHLH), representing Pattern1, can contribute to cardiovascular disease (CVD) in Covid-19. CVD may be secondary to the lung disease, since acute lung injury itself leads to increased cardiac workload and can be problematic especially in patients with pre-existing heart failure (HF). Immune system activation along with immunometabolism alterations may result in plaque instability, contributing to development of acute coronary events. It has been shown that hypertension is associated with circulating lymphocytes in patients and CD8 T cell dysfunction with development of CVD [16].

## Pattern 2: Viral myocarditis and stress cardiomiopathy

Potential mechanisms of cardiovascular injury have been identified and include direct myocardial injury from hemodynamic derangement or hypoxemia, inflammatory myocarditis, stress cardiomyopathy, microvascular dysfuntion or thrombosis due to hypercoagulability or systemic inflammation (cytokine storm), which may also destabilize coronary artery plaques [17]. Autopsies show inflammatory infiltrates composed of macrophages and CD4+ T cells. These mononuclear infiltrates are associated with regions of cardyomyocyte necrosis which, by Dallas Criteria, defines myocarditis [18-19]. Reports of myocarditis in Covid-19 without evidence of direct viral infiltration implicate the heart as one such target of systemic inflammation. Lymphocytopenia is a prominent feature and is associated with adverse outcomes; patients with severe disease eventually develop higher white blood cell and neutrophil counts. This suggest a high vulnerability of lynfocytes to viral infection and destruction. Over 50% are T cells both CD4+ that CD8+. This decrease in regulatory T cells is

expecially notable, given their critical role in immune homeostasis and prevention of excessive inflammation after infection [9]. A greater myocardial reactivity to sympathetic stimulation (caused indirectly by pneumonia) combined with abnormal vascular reactivity (induced directly by the virus) could determine the onset of Takotsubo syndrome, but there is not consensus on the underlying mechanism. Tako-tsubo Cardiomyopathy, also known as Apical Ballooning Syndrome or Broken Heart Syndrome, presents similar to an acute myocardial infarction but there is no evidence of obstructive coronary artery disease on cardiac catheterization. It mostly affects postmenopausal women and a history of stress or acute illness can often be elicited preceding the presentation [20]. This virus can cause damage vascular integrity and cause myocardial abnormalities observe in Takotsubo syndrome.

### 2.1 COVID 19 and hypercoagulability

Covid-19 is known to be associated to hypercoagulability, despite the exact pathogenetic mechanisms are not clear yet. Increased levels of pro-coagulant factors and low levels of the naturally occurring anti-coagulant ones have been noted, nevertheless one additional explanation might be the presence of a high number of circulating microvesicles that stem from platelets leading to the procoagulant asset of the parent cell. Microvesicles are determinants of venous thromboembolism and it is known they are increased in number in septic patients [21-22]. Moreover, activated neutrophils can produce neutrophil external traps (NET) adding another procoagulant substances to plasma as demonstrated in animal models [23]. Pro-inflammatory cytokines might constitute another formidable trigger to explain the procoagulant imbalance in patients with Covid-19 and finally [24], endothelial derangement may play an additional role. In this way acute coronary syndromes may be increased due to heightened thrombotic proclivity, as evidenced by significatly elevated D- dimer levels. This condition is particularly dangerous in patients with previous CAD. There are several tests to investigate the pro-coagulant state of a patient, one of them is the Rotational Thromboelastometry (ROTEM) technology which provides a rapid and dynamic assessment of haemostasis in vitro. ROTEM is useful because not only does it measure the hypercoagulability, but it also detects any impairment of the fibrinolysis [25].

## 2. Materials and Methods

### 2.1 Patients and study design

This is a retrospective, single-center, observational study. We included all consecutive patients admitted on our hospital with diagnosis of pneumonia due to Covid-19 from March 17$^{th}$ to May 21$^{th}$ 2020. Clinical data were retrospectively collected and stored in a database. The following data were collected and reviewed: age, sex, obesity, BMI, COPD, pharmacological history, co-morbidities, time from onset of symptoms to ICU admission, temperature > 38° C, SOFA score and P/F at admission, D dimer, IL6, PCT and PCR. All patients underwent chest X-ray and lung US on admission.

### 2.2 Outcome assessment

The endpoint of this study is evaluating the risk factors for mortality in ICU. Patients discharged to ward or rehab were considered survivors and any death occurred afterwards was not considered in this study.

### 2.3 Statistical analysis

Demographics and clinical characteristics were compared between subjects dead in ICU and survivors (i.e. discharged to ward or rehab). For

continuous measures, means and SD, medians and interquartile ranges (IQR) are presented and p-values calculated with the Mann-Whitney U or Kruskal-Wallis test as they were non-Gaussian continuous variables. Normality distribution was tested with Shapiro Wilk's test. For categorical measures, frequencies and percentages are presented and p-values calculated with a two-tailed Fisher's exact test because of the low number of cases in the non-survivor group. Considering the low number of cases, a multivariate analysis was not performed. Statistical analysis has been performed with STATA 15.1 (Stata Corp LLC – 4905 Lakeway Dr).

## 3. Results

A total of 30 Covid-19 patients have been admitted to Santa Maria Annunziata Hospital ICU and their main characteristics are reported in Table 1. All of them were screened on admission by Transthoracic Echocardiography (TTE) and Compressive Ultrasound (CUS) to detect systolic or diastolic dysfunctions and Deep Vein Thrombosis (DVT) prevalence respectively. Among them, 22 (73,3%) were males and the median age was 61 years (range 39-79) while females were 8 (26,7%), presenting a median age of 59 years (range 25-76). Comorbidities were present in 56.7% of patients with hypertension being the most common one (17, 56,7%), followed by type II diabetes mellitus (9, 30%) and chronic obstructive pulmonary disease (COPD) (5, 16,7%). In addition to this, 17 (56,7%%) had a body mass index (BMI) higher than 30. Their Charlson Comorbidity Index was 2,3 (range 0-6). At ED presentation, 29 (96,7%) patients had a SOFA ≥2 points and 9 (30%) had a PaO2/FiO2 index <200. Transthoracic Echocardiography (TTE) on admission did not reveal any important systolic alteration on the overall population with an average Ejection Fraction (EF) of 57,7 (range 45-60) and a normal Mitralic Annular Plane Excursion (MAPSE) (15,8, range 13,6-16,2). TTE imaging was also used to titrate protective Mechanical Ventilation (MV) and restrictive fluid management. All patients underwent TTE and CUS every 3 data or more frequently according to clinical evidences till ICU discharge. Increased lactate dehydrogenase (LDH) occurred in 28 (93,3%) patients while 20 (66,7%) had a D-dimer >1000 ng/ml. Twelve (40%) patients required Intubation for Mechanical Ventilation (MV) while eighteen (60%) received Non-Invasive Ventilation (NIV) mainly Helmet Continuous positive Airway Pressure (CPAP) as first-line treatment. All patients received appropriate supportive and antiviral therapies on the day of the admission and throughout hospital stay following local guidelines based on the best available evidence at that moment. ("Vademecum"- SIMIT Lombardia, PERCORSO ASSISTENZIALE PER IL PAZIENTE AFFETTO DA COVID-19 PROCEDURA AREA CRITICA , SIAARTI). Tocilizumab was administered according to and in the context of the TOCIVID-19 clinical trial (NCT04317092). All patients received anticoagulant prophylaxis with low-molecular-weight heparin standardized-doses. As of May 21, 2020, 24 (80%) patients were discharged from ICU, 1 (3,3%) was still in-hospital, with improving condition, while 5 (16,7%) died, specifically 4 (13,3%) during ICU stay and 1 (3,3%) after ICU discharge. Troponin level and EKG were strictly monitored. No patients shown Acute Coronary Syndrome (ACS) while 5 out of 30 patients presented DVT (12,5%). Particularly CVC related thrombosis was detected in 4 out of 5 and only 1 patient reported asyntomatic pulmonary embolism As shown in Table 1, non-survivors had both higher BMI (p=0,028) and higher D-dimer level on admission (p=0,0151): the mean time from symptom onset and hospital admission was conversely shorter (p=0,014). No statistically

significant difference was observed in terms of previous comorbidities, other than obesity, between survivors and non-survivors.

| | **Total (n=30)** | **Survivors (n=26)** | **Not Survivors (n=4)** | ***p-value*** |
|---|---|---|---|---|
| ***Baseline characteristics*** | | | | |
| Age, years | 61 ± 12,3 | 59 ± 12,3 | 69,8 ± 6,8 | 0,101781 |
| Sex Male , (%) | 22 (73, 3) | 19 (73, 1) | 3 (75%) | 1 |
| Charlson Comorbidit Index (CCI) | 2,3 ± 1,6 | 2.2 ± 1,6 | 2,8 ± 1,6 | 0.427 |
| Obesity (BMI > 30), (%) | 13 (43, 3) | 10 (38, 5) | 3 (75) | 0.29 |
| **BMI, median (IQR)** | **29,3 ± 5,7** | **29,1 ± 5,5** | **33,9 ± 3,7** | **0.028** |
| Diabetes | 9 (30) | 8 (30,8) | 1 (25) | 1 |
| COPD (including asthma) | 5 (16, 6) | 4 (15, 4) | 1 (25) | 0.609 |
| Coronary artery disease | 2 (6, 6) | 1 (3, 8) | 1 (25) | 0.296 |
| Hypertension | 17 (56, 7) | 13 (50) | 4 (100) | 0.113 |
| Ace inhibitors/ Sartans | 7 (23, 3) | 5 (19,2) | 3 (75) | 0.069 |
| Cerebrovascular disease (including vascular dementia) | 0 (0) | 0 (0) | 0 (0) | n.s. |
| Chronical renal failure | 1 (3, 3) | 0 (0) | 1 (25) | 0.647 |
| **Onset of symptoms to hospital admission** | **6 ± 3** | **7 ± 3** | **3 ± 1** | **0.014** |
| Onset of symptoms to ICU admission | 9 ± 4 | 9 ± 4 | 5 ± 1 | **0.0092** |
| Clinical features, imaging and laboratory findings on admission | | | | |
| Temperature > 38 C° | 22 (73, 3) | 20 (76, 9) | 4 (100) | 0,1287 |
| SOFA score at admission, median (IQR) | 4 ± 2 | 4 ± 2 | 6 ± 2 | 0.087 |
| Patients with SOFA >=2 | 29 (96, 6) | 25 (96, 2) | 4 (100) | 0,5726 |
| $PaO_2/FiO_2$, median (IQR) | 236 ± 70,8 | 245 ± 69 | 177 ± 58 | 0.072 |
| $PaO_2/FiO_2$ < 200 | 9 (30) | 6 (23, 1) | 3 (75) | 0.274 |
| Leukocytes × $10^9$ per L, median (IQR) | 6,7 ± 4,7 | 6,5 ± 3,6 | 9,3 ± 8,1 | 0.669 |
| Leukocytes < 4 × $10^9$ per L | 8 (26, 6) | 7 (27) | 1 (25) | 1 |
| Leukocytes > 10 × $10^9$ per L | 5 (16, 6) | 4 (15, 4) | 2 (50) | 0.17 |
| Lymphocytes × $10^9$ per L, median (IQR) | 0.60 ± 0,40 | 0,63 ± 0,42 | 0,56 ± 0,24 | 0.54 |
| Lymphocytes < 0.8 × $10^9$ per L | 23 (76, 7) | 19 (73, 1) | 3 (75) | 0,9088 |
| Platelets× $10^9$ per L, median (IQR), | 256 ± 122 | 260 ± 128 | 199 ± 46 | 0.36 |

| | | | | |
|---|---|---|---|---|
| Platelets < 150 × $10^9$ per L | 6 (20) | 6 (23, 1) | 1 (25) | 0.9047 |
| ALT, median (IQR) | 51 ± 34 | 52 ± 36 | 42 ± 13 | 0,694679 |
| ALT > 40 U/L | 17 (65, 3) | 15 (57, 7) | 2 (50) | 0.6827 |
| LDH, median (IQR) | 392,1 ± 137 | 384 ± 126 | 470 ± 211 | 0,659884 |
| LDH > 250 U/L | 28 (93, 3) | 25 (96, 2) | 3/3 (100) | 1 |
| Creatinine median mg/dl (IQR), | 0.91 ± 0,41 | 0.91 ± 0,40 | 1,19 ± 0,72 | 0,991354 |
| **D-dimer median ng/ml (IQR),** | 3939 ± 6431 | 2514 ± 4122 | 11835 ± 11386 | 0.0151 |
| D-dimer > 1000 ng/ml | 20 (66, 7) | 16 (61, 5) | 4 (100) | 0.287 |
| D-dimer > 3000 ng/ml | 9 (30) | 6 (23, 1) | 3 (75) | 0.126 |
| C-reactive protein median mg/dl (IQR) | 15 ± 9,7 | 15 ± 9 | 18,9 ± 6,6 | 0.31 |
| Procalcitonine median ng/ml (IQR) (n=62) | 0.8 ± 1,4 | 0.64 ± 0,98 | 2,9 ± 3,1 | 0.107 |
| Troponine ng/L | 15,1 ± 12,3 | 14,9 ± 12,4 | 13,9 ± 11,7 | 1 |
| Interleukin 6 pg/ml | 64,5 ± 70,3 | 65,3 ± 72,2 | 63,8 ± 20,1 | 0.63 |
| **Cardiovascular imaging on admission** | | | | |
| **MAPSE** | 15,76 ± 0,74 | 15,88 ± 0,67 | 15 ± 0,82 | 0,044 |
| TDI S' (mitral anulus) | 0,12 ± 0,07 | 0,12 ± 0,016 | 0,11 ± 0,018 | 0,1016 |
| **MAP (mmHg)** | 84,6 ± 9,7 | 86 ± 9,1 | 72 ± 8 | 0.016 |
| FE (%) | 57,14 ± 2,03 | 57,24 ± 2,07 | 56,5 ± 1,91 | 0,34 |

**Table 1:** Characteristics of Covid-19 patients.

## 4. Discussion

With short-term follow ups and front-line clinical data analysis the study has revealed that there was not evidence of pattern 2 of miocardial involvement. In the setting of Covid -19, myocardial injury, defined by an increased troponin level, occurs especially due to non ischemic myocardial processes, including severe respiratory infection with hypoxia, sepsis, systemic inflammation, pulmonary thrombosis and embolism, cardiac adrenergic hyperstimulation during cytokine storm syndrome. Transthoracic Echocardiography (TTE) on admission did not reveal any important systolic alteration on the overall population with an average Ejection Fraction (EF) of 57,7% and a normal Mitralic Annular Plane Excursion (MAPSE). Although there are isolated Covid-19 report of depressed ventricular function, the majority of patients presents with normal heart function. Consistent with the possibility that heart failure with preserved ejection fraction may be more common, some case reports from Wuhan highlights the coexistence of elevated troponine and Brain -type natriuretic peptide (BNP) levels in a critically ill Covid 19 patients with normal echocardiographic ejection fraction [26]. A total of 30 Covid-19 patients admitted to our ICU 73,3% were males while females were 26,7%. Comorbidities were present in 56,7% of patients with hypertension being the most common one followed by type II diabetes mellitus and chronic obstructive pulmonary disease. Over 56% of admitted patients had a body mass index (BMI) higher than 30.

Obesity represents an important risk factor for Covid -19. This condition is probably due to the fact that obese patients have an overexpression of IL-6 and therefore a chronic inflammatory state. This base condition alterates the immunologic response (over expression) in case of sepsis, presenting as indiscriminate attack of overreacting immune system on many organs. Also an heightened thrombotic proclivity, as evidenced by significantly elevated D-dimer levels, represents a crucial risk factor for acute coronary syndrome, pulmonary embolism and venous thrombosis. As shown in Table 1, non-survivors had both higher BMI (p=0,028) and higher D-dimer level on admission (p=0,0151). These findings suggest us extreme attention to these patients with obesity and an heightened thrombotic proclivity on admission in ICU for Covid – 19. Elevated levels of IL-6 in obese patients should be treated in time with monoclonal antibodies targeting IL-6 or il-6 receptor with the target of attenuating the sequelae of inflammation. Also early depurative support tecniques with particular filtres should be considered. Another concern regarding thromboprophylaxis is the drug-drug interaction between some antiviral treatment and direct oral anticoagulants. Adeguate anticoagulation (low molecular weight heparin) and its monitoring is mandatory to improve the outcomes of these critical ill patients.

## 5. Conclusion

Covid-19 is a global pandemic evolving in real time. Cardiovascular comorbidities are common in patients with Covid-19 and such patients are at higher risk of morbidity and mortality. Differentiating between the various causes of myocardial injury is crucial to determining the treatment course. As previuos mentioned obesity and elevated D-dimer represent the major risk factors of mortality in our patients.

## Acknowledgements

To all my collegues for their precious collaboration to collect data in a very difficult condition.

## Conflict of Interest

The authors declare no conflict of interest

## References

1. Clerkin J Kevin, Fried Justin A, Jayant Raikhelkar, Gabriel Sayer, Jan M Griffin, Amirali Masoumi, et al. Corona virus Disease 2019 and cardiovascular disease. Circulation 141 (2020): 1648-1655.
2. Carlos M Ferrario, Jewell Jessup, Mark C Chappell, David B Averill, K Bridget Brosnihan, E Ann Tallant, et al. Effect of angiotensin-converting enzyme inhibition and angiotensin II receptor blockers on cardiac angiotensin-converting enzyme 2. Circulation 111 (2005): 2605-2610.
3. Danser AHJ, Epstein M, Batlle D. Renin-angiotensin system blockers and the COVID 19 oandemic: at present there is no evidence to abandon renin-angiotensin system blockers. Hypertension 75 (2020): 1382-1385.
4. Yumiko Imai, Keiji Kuba, Shuan Rao, Yi Huan, Feng Guo, Bin Guan, et al. Angiotensin-converting enzyme 2 protects from severe acute lung failure. Nature 436 (2005): 112-116.
5. Keiji Kuba, Yumiko Imai, Shuan Rao, Hong Gao, Feng Guo, Bin Guan, et al. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. Nat Med 11 (2005): 875-879.
6. China CDC. The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (Covid-19)- China, 2020. China CDC Weekly 2 (2020): 113-122.

7. Tao Guo, Yongzhen Fan, Ming Chen, Xiaoyan Wu, Lin Zhang, Tao He, et al. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (Covid 19). JAMA Cardiol (2020).
8. Yao X H, Li T Y, He Z C, Ping Y F, Liu H W, Yu S C, et al. A pathological report of three Covid-19 cases by minimally invasive autopsies. Zhonghua Bing Li Xue Za Zhi 49 (2020): E009.
9. Akhmerov A, Marban E. Covid 19 and the heart. Circulation research 126 (2020): 1443-1455.
10. Ying-Ying Zheng, Yi-Tong Ma, Jin-Ying Zhang, Xiang Xie. COVID-19 e il sistema cardiovascolare. Nat Rev Cardiol 17 (2020): 259-260.
11. Paola Rizzo, Francesco Vieceli Dalla Sega, Francesca Fortini, Luisa Marracino, Claudio Rapezzi, Roberto Ferrari. COVID-19 in the heart and the lungs: could we "Notch" the inflammatory storm? Basic Res Cardiol 115 (2020): 31.
12. Chaolin Huang, Yeming Wang, Xingwang Li, Lili Ren, Jianping Zhao, Yi Hu, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. The Lancet 395 (2020): 497-506.
13. Akbarshakh Akhmerov, Eduardo Marbán. Covid 19 and the heart. Circulation Research 126 (2020): 1443-1455.
14. Evangelos J Giamarellos-Bourboulis, Mihai G Netea, Nikoletta Rovina, Karolina Akinosoglou, Anastasia Antoniadou, Nikolaos Antonakos, et al. Complex Immune Dysregulation in Covid-19 Patients with Severe Respiratory Failure. Cell Host & Microbe 27 (2020): 992.e3-1000.e3.
15. Laurence Fardet, Lionel Galicier, Olivier Lambotte, Christophe Marzac, Cedric Aumont, Doumit Chahwan, et al. Development and validation of a score for the diagnosis of reactive hemophagocytic syndrome (Hscore). Arthritis & Rheumatology 66 (2014): 2613-2620.
16. Andreini Daniele, Arbelo Elena. ESC Guidance for the Diagnosis and Management of CV Disease during the COVID-19 Pandemic. The European Society of Cardiology (2020).
17. Up to date Application Questions and answer CORONA virus disease (2019).
18. Aretz HT. Myocarditis: the Dallas Criteria. Hum Phatol 18 (1987): 619-624.
19. Gabriel Fung, Honglin Luo, Ye Qiu, Decheng Yang, Bruce McManus. Myocarditis. Circ. Res 118 (2016): 496-514.
20. Chadha S. Covid-19 Pandemic Anxiety induced Tako –tsubo cardiomyopathy. QJM: An international Journal of Medicine 113 (2020): 488-490.
21. Paolo Bucciarelli, Ida Martinelli, Andrea Artoni, Serena M Passamonti, Emanuele Previtali, Giuliana Merati, et al. Circulating microparticles and risk of ven ous thromboembolism. Thromb Res 129 (2012): 591-597.
22. Raeven P, Zipperle J, Drechsler S. Extracellular Vesicles as Markers and Mediators in Sepsis. Theranostics 8 (2018): 3348-3365.
23. Kapoor S, Opneja A, Nayak L. The role of neutrophils in thrombosis. Thromb Res 170 (2018): 87-96.
24. Eduardo Vazquez-Garza, Carlos Jerjes-Sanchez, Aline Navarrete, Jorge Joya-Harrison, David Rodriguez. Venous thromboembolism: thrombosis, inflammation, and

immunothrombosis for clinicians. J Thromb Thrombolysis 44 (2017): 377-385.

25. Vittorio Pavoni, Lara Gianesello, Maddalena Pazzi, Caterina Stera, Tommaso Meconi, Francesca Covani Frigieri. Evaluation of coagulation function by rotation thromboelastometry in critically ill patients with severe COVID-19 pneumonia. Journal of Thrombosis and Thrombolysis 11 (2020): 1-6.
26. American College of Cardiology. ACC-CCA Webinar: Covid19 Severe Case management (2020).