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Original Research Paper

Radiodiagnosis

HRCT FINDINGS IN COVID-19 IN CARDIAC PATIENTS – A PERSPECTIVE FROM TERTIARY CARDIAC CARE CENTRE

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ABSTRACT

Objective. The increasing number of cases of confirmed coronavirus disease (COVID-19) in India is striking. The purpose of this study was to study the chest CT findings in COVID-19 pneumonia in patients who also had underlying cardiac disease.

Materials and Methods. Data on 42 cases of patients with underlying cardiac morbidity and confirmed COVID-19 pneumonia were retrospectively collected from U.N. Mehta Institute of Cardiology and Research Centre, India. Basic clinical characteristics, demographics and detailed imaging features were evaluated.

Results. Patients 20–78 years old who had underlying cardiac condition and were studied also infected with Covid. Most patients with COVID-19 pneumonia had typical imaging features, such as predominant peripheral ground-glass opacities (GGO) (39 [92.8%]) with multifocal multilobar involvement. A significant finding that was found in patients with underlying cardiac condition was pleural effusion (10 [23.8%]).

Conclusion. Patients with confirmed COVID-19 pneumonia have typical imaging features that can be helpful in early screening of highly suspected cases and in evaluation of the severity and extent of disease. Most patients with COVID-19 pneumonia have GGO or mixed GGO and consolidation and vascular enlargement in the lesion. Patients with underlying cardiac cause have additional imaging finding in form of pleural effusion, which is not a common finding in those with COVID-19 pneumonia alone.

KEYWORDS : COVID-19, Cardiovascular co-morbidity, high resolution computed tomographic scan.

INTRODUCTION

In December 2019, a series of cases of pneumonia of unknown causation emerged in Wuhan, Hubei, China, and quickly raised intense attention around the world [1]. After the first reported case in Wuhan, several exported cases were confirmed in rest of the world [2-5]. On January 31, 2020, the World Health Organization [6] declared the outbreak of coronavirus disease (COVID-19) a Public Health Emergency of International Concern. SARS-CoV-2 proved to have the ability for efficient human-to-human transmission [7-9]. Early detection and efficient control of the route of transmission (i.e., isolation of suspected cases, disinfection) are still the most effective way to fight the COVID-19 outbreak. For the large number of cases of suspected COVID-19, laboratory detection is time-consuming. These challenges increase the risk of spread by free movement of people with highly suspected disease. In addition, the laboratory test can have false-negative results. Imaging plays an important role in the diagnosis and management of COVID-19 pneumonia. CT is considered the first-line imaging modality in highly suspected cases and is helpful for monitoring imaging changes during treatment. Therefore, CT has been identified as an efficient clinical diagnostic tool for people with suspected COVID-19 [10]. It has potential for identifying people with negative results of a reverse transcription–polymerase chain reaction (RT-PCR) assay but in whom COVID-19 is highly suspected [11, 12].

The purpose of this study was to list the chest CT features in laboratory-confirmed cases of COVID-19 with underlying cardiac cause to further help clinicians for managing such cases.

MATERIALS AND METHODS

This study received medical ethical committee approval, whose number was UNMICRC/ALLIED/2020/03.

Patients

We retrospectively collected the records of cardiac patients with confirmed COVID-19 during the month of May 2020. A total of 42 patients (8 women, 34 men; range, 20–78 years) who had underlying cardiac morbidity, underwent CT in the first week of admission. These patients also underwent RTPCR.

INCLUSION CRITERIA – All patients with confirmed RTPCR and cardiac comorbidity positive covid.

EXCLUSION CRITERIA – Critically ill patients, patients on ventilator support.

Imaging Technique

All patients underwent a non-contrast chest CT with a multidetector 128 slice SOMATOM Definition AS+ (Siemens Healthcare, Germany) CT scanner. The parameters were set at 120 kVp; 100– 200 mAs; pitch, 1-1.2; and collimation, 128 × 0.6. The slice thickness of 1 mm was used after sharp reconstruction algorithm. All images were viewed with both

lung (width, 1200 HU; level, −600 HU) and mediastinal (width, 350 HU; level, 50 HU) settings.

Imaging Interpretation

Two radiologists (more than 10 years of experience) reviewed chest CT scans blindly and independently in consensus. All images were viewed with both lung and mediastinal settings.

In all the patients, CT findings like ground glass opacities, pleural effusion, pulmonary fibrosis, mosaic attenuation, interstitial septal thickening, emphysematous changes, subpleural bands, fibroatelectatic changes were recorded.

STATISTICAL ANALYSIS

All statistical tests were carried out using IBM SPSS program version 20. Mean±SD values were used to express Quantitative variable. $P < 0.05$ was considered statistically significant.

RESULTS

The age distribution as well as the finding on HRCT thorax are as shown in Table 1and table 2. Most patients had typical imaging features of COVID, such as multifocal, multilobar, peripheral, patchy, GGO with crazy paving appearance and vascular enlargement. (39 [92.8%]), (Fig. 1). In additional to these findings, bilateral pleural effusion (10 [23.8%]) with interstitial septal thickening, (figs 2 and 3) were also observed in significant number of these patients. This could to attributed to underlying cardiovascular disease. Pleural effusion (P value < 0.001) in addition to GGO was found to be a significant finding in patients with underlying cardiac co-morbidity.

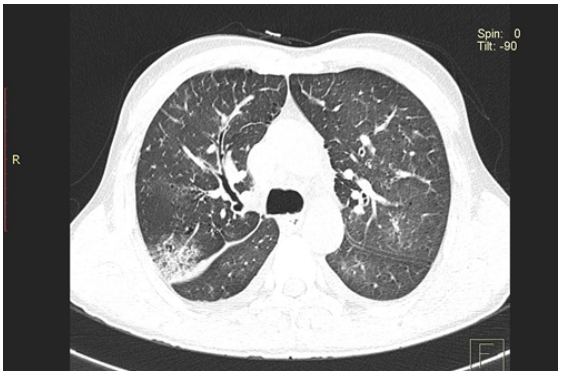

Figure 1: Mild COVID pneumonia. Axial lung window CT image showing focal rounded ground glass opacities in posterior segment of right upper lobe with interstitial septal thickening.

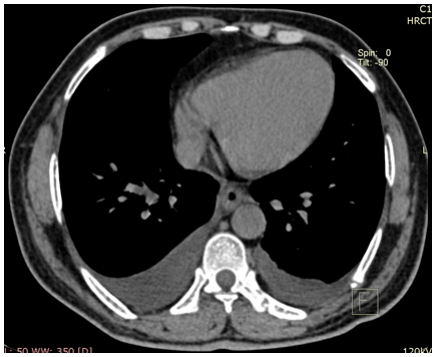

Figure 2: Axial mediastinal window CT image showing bilateral pleural effusion with interstitial septal thickening in same patient.

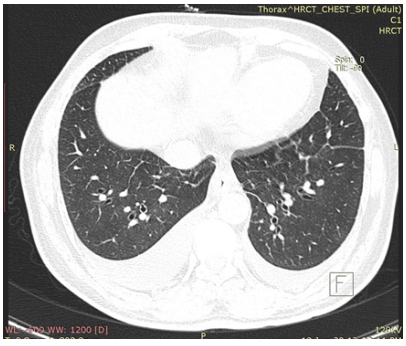

Figure 3: Axial lung window CT image showing bilateral pleural effusion in same patient.

Table 1: The age distribution as well as the finding on HRCT thorax.

	RTPCR +ve CT +ve (n=42)
Age (Years)	54.69 ± 14.28
Sex (M/F)	(34/8)(80.9%/19.1%)
Ground Glass Opacities	39 (92.8%)
Pleural Effusion	10 (23.8%)
Pleural Fibrosis	7 (16.6%)
Interstitial Septal Thickening	11 (26.2%)
Paraseptal Emphysema	7 (16.6%)
Subpleural Bands	5 (11.9%)
Fibro-Calcified	2 (4.7%)
Cyst	7 (16.6%)
Fibro-Atelectatic	3 (7.1%)

Table 2 : HRCT findings in RTPCR positive patients with cardiovascular co-morbidity

Correlations														
		COVIDCT POSITIVE	GGO	PE	PF	ML	MA	IST	PES	SB	FC	Cyst	FA	FL
COVID CT POSITIVE	Pearson Correlation	1	.469**	-.332**	-.053	.324*	-.274*	.115	.080	.103	-.011	.156	-.263*	.178
	Sig. (2-tailed)		.000	.009	.686	.011	.033	.379	.539	.428	.935	.229	.041	.169
	N	61	61	61	61	61	61	61	61	61	61	61	61	61
GGO	Pearson Correlation	.469**	1	-.075	-.304*	.230	-.372**	.172	.206	-.114	-.078	.070	-.419*	.131
	Sig. (2-tailed)	.000		.564	.017	.075	.003	.185	.111	.384	.549	.591	.001	.314
	N	61	61	61	61	61	61	61	61	61	61	61	61	61
Pleural effusion (PE)	Pearson Correlation	-.332**	-.075	1	.019	.052	.060	.097	-.204	-.123	-.005	-.179	.127	-.053
	Sig. (2-tailed)	.009	.564		.884	.690	.644	.458	.115	.343	.968	.167	.328	.687
	N	61	61	61	61	61	61	61	61	61	61	61	61	61
Pulmonary fibrosis (PF)	Pearson Correlation	-.053	-.304*	.019	1	-.116	-.086	-.053	.166	-.155	.091	-.056	.197	.048
	Sig. (2-tailed)	.686	.017	.884		.374	.508	.684	.202	.233	.488	.669	.129	.713
	N	61	61	61	61	61	61	61	61	61	61	61	61	61
Mosaic attenuation (MA)	Pearson Correlation	-.274*	-.372**	.060	-.086	.040	1	-.100	-.077	-.061	-.042	.201	.201	-.049

	Sig. (2-tailed)	.033	.003	.644	.508	.759		.441	.557	.642	.749	.120	.120	.709
	N	61	61	61	61	61	61	61	61	61	61	61	61	61
Interstitial septal thickening (IST)	Pearson Correlation	.115	.172	.097	-.053	.039	-.100	1	-.117	.082	-.124	-.097	-.097	.328**
	Sig. (2-tailed)	.379	.185	.458	.684	.764	.441		.369	.532	.341	.459	.459	.010
	N	61	61	61	61	61	61	61	61	61	61	61	61	61
Paraseptal emphysema (PES)	Pearson Correlation	.080	.206	-.204	.166	-.051	-.077	-.117	1	-.137	.119	-.025	.249	.077
	Sig. (2-tailed)	.539	.111	.115	.202	.695	.557	.369		.291	.360	.850	.053	.558
	N	61	61	61	61	61	61	61	61	61	61	61	61	61
Subpleural bands (SB)	Pearson Correlation	.103	-.114	-.123	-.155	-.041	-.061	.082	-.137	1	-.075	.198	.198	.135
	Sig. (2-tailed)	.428	.384	.343	.233	.756	.642	.532	.291		.565	.126	.126	.300
	N	61	61	61	61	61	61	61	61	61	61	61	61	61
Fibroatelectatic (FA)	Pearson Correlation	-.263*	-.419**	.127	.197	-.213	.201	-.097	.249	.198	.136	-.007	1	-.103
	Sig. (2-tailed)	.041	.001	.328	.129	.099	.120	.459	.053	.126	.295	.957		.430
	N	61	61	61	61	61	61	61	61	61	61	61	61	61
**. Correlation is significant at the 0.01 level (2-tailed).														
*. Correlation is significant at the 0.05 level (2-tailed).														

Pleural effusion, pericardial effusion, lymphadenopathy, cavitation, CT halo sign, and pneumothorax are some of the uncommon but possible findings seen with disease progression.

DISCUSSION

We comprehensively evaluated and analyzed the radiographic characteristics of 42 patients with COVID-19 pneumonia and cardiac comorbidity from our institute. The basic epidemiologic and clinical features were reported.

To better appreciate the links between cardiovascular disease (CVD) and COVID-19, it is important to understand the underlying molecular biology of coronavirus infection. SARS-CoV-2 binds to the transmembrane ACE2 protein to enter type II alveolar epithelial cells, macrophages, and other cell types [13]. ACE2 is particularly highly expressed in pericytes, in addition to type II alveolar epithelial cells, according to the single-cell human heart atlas [14]. High expression of ACE2 in pericytes could lead to development of microvascular dysfunction, [15] explaining greater propensity for acute coronary syndromes (ACS) [16]. Moreover, ACE2 expression is up-regulated in failing human hearts, suggesting a plausible explanation for a higher infectivity of virus and a higher mortality in patients with heart failure [17].

A number of key comorbidities are associated with worse clinical outcomes in patients with COVID-19. Pre-existing CV conditions seem to be particularly important predictors of COVID-19 severity.

The imaging features to be kept in mind while suspecting superimposed COVID-19 changes on background of underlying cardiac condition are summarized in Table 3.

Table 3: Imaging features of superimposed COVID-19 changes on background of underlying cardiac condition
Classical peripheral ground glass opacities (observed in COVID-19)
Pleural effusion (usually bilateral)
Interstitial septal thickening and Kerley's lines
Mosaic attenuation
Central ill-defined ground glass opacities (suggestive of congestive changes)

Since there is a significant overlap between congestive and COVID-19 ground glass opacities, sometimes it is difficult to discern between the two; and usually features of both are seen. Hence laboratory test like RTPCR are needed for confirmation.

The Novel Coronavirus Pneumonia Emergency Response Epidemiology Team recently analysed all COVID-19 cases reported to China's Infectious Disease Information System up to 11 February 2020 [18]. The investigators found that the fatality rate for patients with no comorbidities was 0.9%, whereas the CFR was much higher for patients with comorbidities. This included mortality of 10.5% for patients with CVD. [19-21].

These observations are confirmed by a recent meta-analysis, based largely on these studies and an additional 44 672 patient data set reported by the China CDC [19]. In this large cohort, CVD was reported in 4.2% of the total population and in 22.7% of those who died [19]. By extension, it is expected that comorbidities are associated with higher rates of hospitalization in patients with COVID-19, but any effects that comorbidities may have on susceptibility to infection remain conjectural.

Diagnostic tests to be done in patients with COVID-19 and cardiovascular involvement are summarized in Table 4.

Table 4 Diagnostic tests in patients with COVID-19 and cardiovascular involvement

Test	Diagnostic considerations in COVID-19 patients
NT-pro BNP/BNP	Conflicting data on NT-proBNP. In a MERS-CoV cohort, NT-proBNP was increased but it may be normal in COVID-19-affected patients. Higher NT-proBNP levels in the Chinese cohort are associated with a greater need for ICU care.
Troponin	High-sensitivity troponin assay may be helpful for risk assessment in patients requiring ICU care and to identify individuals with silent myocardial injury.
D-dimer	Reports show a key relationship with a requirement for ICU care and mortality.
Procalcitonin	A marker of bacterial infection; it is more likely to be raised in patients who will require ICU care.
Full blood count	Often shows leucopenia/lymphocytopenia Low platelets associated with adverse outcome
IL-6	Where available; high concentrations are associated with adverse outcome.
Ferritin	A marker of poor outcome; very significant changes reported in COVID-19 patients.
Cardiac CT	To be considered in uncertain cases of patients with elevated troponins with and without signs of obstructive coronary artery disease (EACVI position166)
ECG	In MERS-CoV, the 12-lead ECG generally shows diffuse T wave inversion where there is myocardial involvement; this can be dynamic. Changes in COVID-19 were also described.

Echocardiography	May show global or regional myocardial systolic dysfunction with or without a pericardial effusion and vice versa.

Heart failure patients are at increased risk of acute events or exacerbation; viral illness can potentially destabilize atherosclerotic plaques through systemic inflammatory responses [22]. Cytokine storm, as well as specific changes of immune cell polarization towards more unstable phenotypes. All of these have been observed in COVID-19. In the case of SARS and MERS, acute MI [23, 24] has been reported in two out of the five deaths in early reports. [25]

In addition, the cytokine storm can contribute to development of endothelial dysfunction through well-characterized mechanisms. [26–29]

Impact of COVID-19 on routine and emergency cardiovascular care

In preparation for the COVID-19 pandemic, many healthcare providers have had to scale down outpatient services and also defer elective cardiac procedures and surgeries. The long-term clinical impact of scaling down outpatient activity, reduced access to diagnostics, and deferral of routine procedures is likely to be significant and extend beyond the pandemic. Similarly, the perceived risk of being exposed to COVID-19 has led to a decline or a delay in presentation of acute cardiac emergencies which is likely to contribute to cardiac mortality and morbidity.

Key unanswered questions

In this comprehensive review, we aimed to highlight the current state of the art information regarding COVID-19 and CVD (Table 3). Our understanding of CV risk and consequences of COVID-19 is developing continuously. However, there are many knowledge gaps and there are many unanswered questions. Below we point out a few burning unknowns at the moment.

Table 5. Summary of current key considerations in COVID-19 diagnosis and treatment

Key take-home messages:

- Cardiovascular patients are at increased risk of severe COVID-19 and its complications. Intensive preventive measures should be followed in this group in accordance with WHO and CDC guidelines. This should include wider use of telemedicine tools in day to day monitoring of the patients during the out- break to limit their exposure.
- The heterogeneity of responses between individual patients indicates that it is unlikely that it can be considered as a single disease phenotype. Host characteristics promotes more or less severe progression of the disease.

Cardiovascular comorbidities

- Hypertension is one of the most common risk-associated comorbidities, but this association is cofounded by age. It is not clear if hypertension is an age- independent risk factor of COVID-19-associated outcomes. As a precaution, it is essential that hypertension remains well controlled.
- There is no evidence that ACEIs or ARBs are associated with worse prognosis, and patients should not discontinue use of these medications.
- COVID-19 may lead to plaque instability and MI, which has a common cause of death in SARS/COVID-19 patients. However, the evidence of effectiveness of primary PCI for type 2 MI during acute viral disease is limited.
- ACE2 can be considered as a Cinderella of cardiovascular medicine. A molecule which has been underappreciated in cardiovascular pathology is taking centre stage in understanding and potentially combating COVID-19.

What are the factors, genetic or otherwise, that influence interindividual variability in susceptibility to COVID-19, its severity, or clinical out- comes? The mechanisms through which CVDs worsen the prognosis in COVID-19 are unknown. It remains to be addressed to what extent individual CVDs are exacerbated by COVID-19. Do pre-existing hypertension and CVDs increase infection risk and/or worsen the course of disease progression? Is the severity of CVDs related to high expression levels of ACE2, the SARS-CoV-2 receptor, in the heart and blood vessels? The answers will be found in integrated approaches by expertise coming together.

These questions need to be answered with the highest quality science and clinical research since the current pandemic of coronavirus might not be the last.

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REFERENCES

1. World Health Organization website. Novel coronavirus: China. www.who.int/csr/don/ 12-january-2020-novel-coronavirus-china/en/. Published January 12, 2020. Accessed January 19, 2020 [Google Scholar]
2. World Health Organization website. Novel corona-virus: Thailand (ex-China). www.who.int/ csr/don/14-january-2020-novel-coronavirus-thailand/en/. Published January 14, 2020. Accessed February 18, 2020 [Google Scholar]
3. World Health Organization website. Novel corona-virus: Japan (ex-China). www.who.int/csr/don/16-january-2020-novel-coronavirus-japan-ex-china/en/. Published January 16, 2020. Accessed February 18, 2020 [Google Scholar]
4. World Health Organization website. Novel coronavirus: Republic of Korea (ex-China). www.who.int/csr/don/21-january-2020-novel-coronavirus-republic-of-korea-ex-china/en/. Published January 21, 2020. Accessed February 18, 2020 [Google Scholar]
5. U.S. Centers for Disease Control and Prevention website. First travel-related case of 2019 novel coronavirus detected in United States. www. cdc. gov/media/releases/2020/p0121-novel-coronavirus-travel-case.html. Published January 21, 2020. Accessed February 18, 2020 [Google Scholar]
6. World Health Organization website. Statement on the second meeting of the International Health Regulations (2005) Emergency Committee regarding the outbreak of novel coronavirus (2019-nCoV). www.who.int/news-room. Published January 30, 2020. Accessed February 25, 2020 [Google Scholar] 7. Chan JF, Yuan S, Kok KH, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. Lancet 2020; 395:514–523 [Crossref] [Medline] [Google Scholar]
8. Phan LT, Nguyen TV, Luong QC, et al. Importation and human-to-human transmission of a novel coronavirus in Vietnam. N Engl J Med 2020 Jan 28 [Epub ahead of print] [Google Scholar]
9. Li Q, Guan X, Wu P, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. N Engl J Med 2020 Jan 29 [Epub ahead of print] [Google Scholar]
10. China National Health Commission website. Notice on issuing a new coronavirus infected pneumonia diagnosis and treatment plan (trial version 5). bgs.satcm.gov.cn/zhengcewenjian/2020-02-06/12847.html. Published February 4, 2020. Accessed February 18, 2020 [Google Scholar]
11. Huang P, Liu T, Huang L, et al. Use of chest CT in combination with negative RT-PCR assay for the 2019 novel coronavirus but high clinical suspicion. Radiology 2020 Feb 12 [Epub ahead of print] [Google Scholar]
12. Xie X, Zhong Z, Zhao W, Zheng C, Wang F, Liu J. Chest CT for typical 2019-nCoV pneumonia: relationship to negative RT-PCR testing. Radiology 2020 Feb 12 [Epub ahead of print] [Google Scholar]
13. Hoffmann M, Kleine-Weber H, Schroeder S, Kruger N, Herrler T, Erichsen S, Schiergens TS, Herrler G, Wu NH, Nitsche A, Muller MA, Drosten C, Pohlmann S. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell 2020;doi: 10.1016/ j.cell. 2020. 02.052.
14. Shi Y, Wang Y, Shao C, Huang J, Gan J, Huang X, Bucci E, Piacentini M, Ippolito G, Melino G. COVID-19 infection: the perspectives on immune responses. Cell Death Differ 2020;doi: 10.1038/s41418-020-0530-3.
15. Bairey Merz CN, Pepine CJ, Shimokawa H, Berry C. Treatment of coronary microvascular dysfunction. Cardiovasc Res 2020;116:856–870.
16. 5. Shi S, Qin M, Shen B, Cai Y, Liu T, Yang F, Gong W, Liu X, Liang J, Zhao Q, Huang H, Yang B, Huang C. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. JAMA Cardiol 2020;doi: 10.1001/jamacardio.2020.0950.
17. Liu K, Fang YY, Deng Y, Liu W, Wang MF, Ma JP, Xiao W, Wang YN, Zhong MH, Li CH, Li GC, Liu HG. Clinical characteristics of novel coronavirus cases in tertiary hospitals in Hubei Province. Chin Med J (Engl) 2020; doi:0.1097/ Cm9. 0000000000000744.
18. Novel Coronavirus Pneumonia Emergency Response Epidemiology Team. [The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) in China]. Zhonghua Liu Xing Bing Xue Za Zhi 2020;41:145–151.
19. Epidemiology Working Group for NCIP Epidemic Response. The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) in . China. Chin J Epidemiol 2020;41:145–151.
20. The Novel Coronavirus Pneumonia Emergency Response Epidemiology Team. The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19)—China, 2020. China CDC Weekly 2020;2:x.

21. Ruan S. Likelihood of survival of coronavirus disease 2019. Lancet Infect Dis 2020; doi: 10.1016/S1473-3099(20)30257-7.
22. Maffia P, Monaco C. Immune cell census in murine atherosclerosis: cytometry by time of flight illuminates vascular myeloid cell diversity. Cardiovasc Res 2018;114:1360–1371.
23. Steven S, Dib M, Hausding M, Kashani F, Oelze M, Kroller-Schon S, Hanf A, Daub S, Roohani S, Gramlich Y, Lutgens E, Schulz E, Becker C, Lackner KJ, Kleinert H, Knosalla C, Niesler B, Wild PS, Munzel T, Daiber A. CD40L controls obesity- associated vascular inflammation, oxidative stress, and endothelial dysfunction in . high fat diet-treated and db/db mice. Cardiovasc Res 2018;114:312–323..
24. Kusters PJH, Lutgens E, Seijkens TTP. Exploring immune checkpoints as potential therapeutic targets in atherosclerosis. Cardiovasc Res 2018;114:368–377.
25. Peiris JS, Chu CM, Cheng VC, Chan KS, Hung IF, Poon LL, Law KI, Tang BS, Hon TY, Chan CS, Chan KH, Ng JS, Zheng BJ, Ng WL, Lai RW, Guan Y, Yuen KY, HKU/ UCH SARS Study Group. Clinical progression and viral load in a community out- break of coronavirus-associated SARS pneumonia: a prospective study. Lancet 2003; 361:1767–1.
26. Levy BI, Heusch G, Camici PG. The many faces of myocardial ischaemia and angina.Cardiovasc Res 2019;115:1460–1470.
27. Carnevale D, Wenzel P. Mechanical stretch on endothelial cells interconnects innate and adaptive immune response in hypertension. Cardiovasc Res 2018;114:1432–1434.
28. Petrie JR, Guzik TJ, Touyz RM. Diabetes, hypertension, and cardiovascular disease:clinical insights and vascular mechanisms. Can J Cardiol 2018;34:575–584..
29. Wilk G, Osmenda G, Matusik P, Nowakowski D, Jasiewicz-Honkisz B, Ignacak A, Czesnikiewicz-Guzik M, Guzik TJ. Endothelial function assessment in atherosclerosis: comparison of brachial artery flowmediated vasodilation and peripheral arterial tonometry. Pol Arch Med Wewn 2013;123:443–452.