Resurgence of hypertension and cardiovascular diseases in patients recovered from COVID-19: An Indian perspective

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ABSTRACT

Objective: The aim of this study was to understand the prevalence, extent, clinical approach of hypertension and cardiovascular disease (CVD) in patients recovered from COVID-19. Methods: The round table meetings (RTMs) and survey convened a diverse panel of specialists including cardiologists, endocrinologists, diabetologists, consultant physicians, and family physicians from various geographical zones of India. A standard questionnaire including 10 questions was developed pertaining to the resurgence of hypertension and CVD in patients recovered from COVID-19. The RTMs and survey were held virtually. The collected opinions and recommendations were compiled to derive a consensus document. Results: A total of 3066 health-care practitioners (HCPs) participated. Hypertension was the most prevalent comorbidity in patients recovered from COVID-19 followed by diabetes, dyslipidemia, and coronary artery disease. Almost two-thirds of HCPs reported that 10%–30% newly diagnosed hypertension in patients recovered from COVID-19. Uncontrolled hypertension in 10–20% of COVID-19 recovered patients opined by 45% of the HCPs. About, 35% HCPs reported CV complications in 10–20% of Covid-19 recovered patients and 63% HCPs reported exacerbations of CAD in 10–30% of patients. Majority of HCPs preferred to switch to dual combination therapy from monotherapy for hypertension management (52.0%) and ARBs and its combination is most preferred combination for hypertension control (60%). Majority of the HCPs suggested follow-up after 1-2 weeks (39.0%). Close monitoring on symptoms including chest pain and breathlessness (45.0%), adherence to medication and regular monitoring of lab parameters (25%) is recommended for these patients. Conclusion: Overall observations indicate an increased incidence of hypertension and CVDs post recovery from COVID-19. A dual therapy of ARBs was the preferred choice for management of hypertension. Regular follow-up and close monitoring of symptoms to prevent further CV complications in COVID-19 recovered patients is recommended.

Keywords: Cardiovascular, coronavirus, diabetes, dyslipidemia, hypertension

Introduction

COVID-19 caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is relatively a novel disease, with an
extensive clinical spectrum ranging from asymptomatic infection to lethal disease. Scientists engaged in rigorous clinical research on COVID-19 come up with new data on a continual basis about different aspects of this disease and its management, particularly in terms of post-recovery events.

Several million patients have recovered from COVID-19 infection but some of the after-effects may have a considerable impact in their future. Since the recovered patients could still carry the SARS-CoV-2 within their system, regular follow-up and laboratory test is recommended to constrain the infection as well as monitor future complications.[3] Radiological and physiological abnormalities are reported in a considerable proportion of COVID-19 survivors 3 months post-discharge.[2] Post COVID-19 infection, recovered patients may continue to experience various mild to moderate symptoms such as lethargy, body ache, cough, sore throat, breathlessness, and even substantial end-organ dysfunction.[3] A cross-sectional, questionnaire-based study assessed the prevalence and features of post-COVID-19 manifestations in recovered patients. A statistically significant association was observed between the severity of COVID-19 infection and post-COVID-19 manifestations. A noteworthy majority (94.9%) experienced at least one post-COVID-19 symptom, of which fatigue (82.9%) was the predominant manifestation while few patients manifested with stroke, renal failure, myocarditis, and pulmonary fibrosis.[4,5]

Hypertension (HTN) is the major risk factor to cardiovascular (CV) morbidity and mortality in India and is responsible for 28% of total deaths.[6] Studies report that HTN and cardiovascular diseases (CVD) are the most frequent co-morbidities in patients with COVID-19 infection.[4,7]

COVID-19 significantly impacts CV system by causing complications such as acute coronary syndrome and myocardial infarction, blood pressure fluctuations or worsening pre-existing CVDs.[10,11] Cardiovascular diseases associated with COVID-19 probably involve dysregulation of the renin-angiotensin-aldosterone system (RAAS)/ACE2 system.[12] Importantly, ACE2 is expressed in the heart, intestinal epithelium, vascular endothelium, and the kidneys, making all of these organs as potential targets.[11] This may be a primary phenomenon in COVID-19, but may also act as secondary to acute lung injury, which leads to increased cardiac workload, potentially challenging in patients with pre-existing heart failure, acute cardiac injury, myocardial injury, arrhythmias. Prominent increase in cardiac troponin levels is reported that is associated with other inflammatory markers, such as C-reactive protein, ferritin, and interleukin-6, suggesting inflammatory damage leading to myocarditis.[13]

Apart from complications during the active phase of infection, long-term sequelae of the disease remain a possibility despite complete viral clearance.[11] Recovered patients may have persistently increased cardiometabolic demand and may be associated with reduced cardiac reserve, corticosteroid use and dysregulation of the renin–angiotensin–aldosterone system (RAAS).

Considering the substantial influence of COVID-19 on patients with non-communicable diseases and limited data available with regards to increased HTN and CVD in COVID-19 recovered patients from India, it is imperative to obtain more data on this aspect. This study attempts to understand the prevalence, extent and clinical approach of hypertension and CVD in patients recovered from COVID-19.

Methodology

The round table meetings (RTMs) and survey convened a diverse panel of specialists including, cardiologists, endocrinologists, diabetologists, consultant physicians and family physicians from the various geographical zones of India to discuss the resurgence of HTN and CVD in patients recovered from COVID-19.

The standard questionnaire pertaining to the resurgence of HTN and CVD in patients recovered from COVID-19 and clinical approach after recovery was prepared, discussed, and evaluated by the experts from the field. The questionnaire included 10 questions regarding post-COVID-19 resurgence of HTN, CVD and clinical approach in COVID-19 recovered patients.

The identified HCPs were sent an introductory email containing a link of the survey and requested voluntary participation. The survey was held virtually, over 6 weeks from September 2020 to October 2020. The survey results were discussed during the 75 pan India RTMs between November 2020 to January 2021 and opinions from the HCPs were noted. Further, these collected opinions and recommendations were compiled and scrutinized to derive a general recommendation.

Results

A total of 3066 HCPs participated in the survey and RTMs. Majority of HCPs were consulting physicians (n = 2117), followed by, cardiologists (n = 414), diabetologists (n = 285), family physicians (n = 184) and endocrinologists (n = 66).

HTN was the most prevalent comorbid condition in patients with COVID-19 followed by diabetes, dyslipidemia, and coronary artery disease (CAD). Newly diagnosed hypertension, resurgence of hypertension, CVD and associated comorbidities, clinical approach and recommendations for COVID-19 recovered patients were discussed in the following points.

Uncontrolled hypertension in COVID-19 recovered patients

In total, 45.0% of HCPs opined that 10%–20% of COVID-19 recovered patients presented with uncontrolled hypertension when they revisited hospital for follow-up [Table 1].

Newly diagnosed HTN in COVID-19 recovered patients

In COVID-19 recovered patients about 10–30% of them were newly diagnosed with hypertension; opined by 62% of HCPs.
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Whereas 10% of HCPs reported 30% recovered patients diagnosed with hypertension [Table 1].

Predominantly, the consulting physicians responded the presence of new-onset HTN in 10-20% of patients and 20-30% of patients were revisiting hospitals with uncontrolled blood pressure after recovery from COVID-19 [Figure 1].

**Emerging CV complications with or without pre-existing CV conditions**

As per analysis, 25.0% of HCPs reported 20%-30% patients developed CV complications independent of pre-existing conditions after COVID-19 recovery [Table 1]. About, 35.0% of HCPs reported CV complications in 10-20% of COVID-19 recovered patients. Myocarditis and pulmonary embolism were the serious complications observed in COVID-19 recovered patients. Situation is more awful in COVID-19 recovered patients those having prior history of pre-existing CAD. Total 63.0% of HCPs reported exacerbations of CAD in 10%-30% of patients. However, 29.0%, of HCPs reported exacerbations of pre-existing CAD in <10% COVID-19 recovered patients [Table 1].

Predominantly, the consulting physicians responded the presence of development of CV complications in 20%-30% of patients recovered from COVID-19, independent of pre-existing conditions. Exacerbation of CAD was reported majorly by family physicians in >50% of patients with pre-existing CAD, who were recovered from COVID-19 [Figure 2].

**Increased in blood glucose and alteration in lipid parameter in COVID-19 recovered patients with pre-existing conditions**

There was an increase in blood glucose level in 10%-30% of diabetes population after recovered from COVID-19, opined by 68% of HCPs. About 18.0%, of HCPs reported <10% diabetes patients had increased blood glucose level in post-recovery to COVID-19 infection. Total 58.0% of HCPs reported alteration in lipid parameters in 10%-30% of patients with dyslipidemia, whereas 37% HCPs reported lipid alternation in <10% patients those recovered from COVID-19 infection [Table 1].

**Management of HTN in patients recovered from COVID-19**

Control of hypertension in COVID-19 recovered patients become more challenging as per the reported data from HCPs across India. Nearly 52% HCPs switch to dual combination from monotherapy, 20.0% increased the dose of dual therapy, 15.0% increased the dose of monotherapy and 13% switch to triple therapy in COVID-19 recovered patients to control blood pressure [Figure 3].

Most preferred combination for hypertension control is angiotensin II receptor blockers (ARB) and its combination (60.0%) followed by beta-blockers and its combinations (13.0%), ACE inhibitor (ACEI) and its combinations (11.0%) and CCBs and its combinations (10.0%) [Figure 3].

**Follow-up and advices to prevent CV complications in post-COVID-19 recovery**

Nearly 39.0% HCPs advised a follow-up after 1-2 weeks post-COVID-19 recovery. And about 11%, 38% and 12% of HCPs opined follow-up within a week, 2-4 weeks and after 4 weeks respectively. Three important advices which is recommended by HCPs to prevent further complications are:

1. Close monitoring on symptoms including chest pain and breathlessness (45.0%)
2. Suggested adherence to medication (30.0%)
3. Regular monitoring with the laboratory parameters including lipid profile and blood glucose levels (25.0%).

**Discussion**

A large number of patients with COVID-19 have pre-existing HTN and/or CVD or may develop new-onset HTN and cardiac diseases during the course of infection. However, the understanding about their impact on the clinical outcomes in COVID-19 is still ambiguous. This article is

| Questionnaire survey                                                                 | HCPs Response (%) |
|--------------------------------------------------------------------------------------|-------------------|
| What percentage of COVID-19 recovered patients are revisiting hospitals with uncontrolled blood pressure? | <10% 21 10-20% 45 20-30% 27 30-50% 6 >50% 1 |
| What percentage of COVID-19 recovered patients developing a newly diagnosed hypertension? | <10% 28 10-20% 38 20-30% 24 30-50% 8 >50% 2 |
| What percentage of patients with pre-existing diabetes developed an increase in glucose level post COVID-19 infection? | <10% 18 10-20% 35 20-30% 33 30-50% 13 >50% 1 |
| What percentage of patients with pre-existing dyslipidemia developed an exacerbation post COVID-19 infection? | <10% 37 10-20% 37 20-30% 21 30-50% 4 >50% 1 |
| Percentage of COVID-19 recovered patients developed a CV condition, independent of pre-existing conditions | <10% 27 10-20% 35 20-30% 25 30-50% 9 >50% 4 |
| What percentage of patients with pre-existing CAD developed an exacerbation post COVID-19 infection? | <10% 29 10-20% 38 20-30% 25 30-50% 7 >50% 1 |

Data shown as %, CAD: coronary heart disease, CV: cardiovascular.
who revisited to the hospital. Majority of the HCPs observed that the hypertensive patients recovered from COVID‑19 who revisited the hospital were obese. This might be attributable to the physical inactivity, unhealthy diet, or discontinuation of medication. In particular, unavailability of medicine in the initial days of lockdown or some viral messages circulating on social media regarding the risk of contracting COVID‑19 infection due to anti‑hypertensive medications, particularly ACE inhibitors/ARBs, might be responsible for discontinuation of medications.

According to the participating HCPs, the patients recovered from COVID‑19 have exhibited a high prevalence of new‑onset HTN. Major factors contributing to the development of HTN are anxiety and medications used to treat COVID‑19. Patients with COVID‑19 infection are usually treated with steroids and other medications such as tocilizumab that cause fluid retention leading to rise in blood pressure. Central arterial pressure has to be monitored compared to the peripheral arterial pressure of the revisited and newly diagnosed HTN patients with the Echocardiograph as well as other measurements.

Most studies published, highlighted the correlation of pre‑existing HTN with the risk of COVID‑19 infection. However, there exists a paucity of the data to support persistent HTN after recovery from COVID‑19 in patients with no prior history of HTN. A retrospective cohort study conducted in New York showed that HTN was reported in 36% of patients who revisited the hospital. Majority of the HCPs observed that the hypertensive patients recovered from COVID‑19 who revisited the hospital were obese. This might be attributable to the physical inactivity, unhealthy diet, or discontinuation of medication. In particular, unavailability of medicine in the initial days of lockdown or some viral messages circulating on social media regarding the risk of contracting COVID‑19 infection due to anti‑hypertensive medications, particularly ACE inhibitors/ARBs, might be responsible for discontinuation of medications.

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In the present study majority of the HCPs agreed that COVID-19 recovered patients may developed CV complication in this pandemic situation. A cohort study of 100 German patients recently recovered from COVID-19 infection and independent of pre-existing condition demonstrated abnormal CV magnetic resonance findings in 78 patients and myocardial inflammation in 60 patients indicating the need for investigation of the long-term CV consequences of COVID-19.[24] Elevated cardiac troponin level is one of the most commonly reported cardiac abnormality in COVID-19 patients and found to be associated with severe illness and mortality.[19]

The majority of participating HCPs agreed that ≈20% of patients with pre-existing coronary artery disease (CAD) revisited the hospital with exacerbation of CAD symptoms after recovery from COVID-19. On the basis of reported evidence, Shi et al.[20] assumed that an intense inflammatory action overlaid with pre-existing CVD may provoke cardiac injury in patients with COVID-19 infections. Likewise, Guo et al.[21] reported myocardial injury and significantly higher mortality as manifested by elevated troponin T levels compared to those with normal troponin T levels (p < 0.001). Moreover, increased mortality was observed in those with elevated troponin T levels in pre-existing CVD (64.4%) than without pre-existing CVD (37.5%), indicative of association of myocardial injury and the risk of mortality. A 30-Day echocardiographic follow-up study showed left ventricular impairment during the acute phase of COVID-19 infection that was worse in critically ill patients. However, this impairment was reversible after recovery irrespective of the severity of infection.[22] Tachycardia is one of the common symptoms in COVID-19 recovered patients and beta blockers are preferred drug in hypertensive patients to control heart rate.

Primary physicians play an important role in the management of COVID-19. As most of the times patients visit family physicians for the treatment of disease. Family physicians can help in early diagnosis of the infection in their patients and facilitate timely treatment for them. The HCPs discussed whether pre-existing diabetes increased glucose level leading to the exacerbation post COVID-19 infection. The HCPs agreed that pre-existing diabetes patients revisited the hospital with increased glucose level post COVID-19 recovery. COVID-19 causes considerable risks to patients with diabetes. Patients with uncontrolled hyperglycemia exhibit a longer hospital stay and higher mortality compared to those without diabetes, while those with well-controlled blood glucose are associated with improved outcomes in infected patients.[23] Severe infections cause more difficulty in controlling blood glucose and indirect risk posed by the pandemic such as lifestyle changes, anxiety, depression is likely to reduce the medication compliance affecting the blood glucose levels.[24]

The HCPs in the present study showed that 10-20% patients with pre-existing dyslipidemia developed an alteration in lipid parameter in post COVID-19. The protease inhibitor-based antiretroviral and immunosuppressive therapies used to treat COVID-19 probably exacerbate hyperlipidemia, hence statins may be particularly effective in these patients.[25] A large cohort of 4252 patients with COVID-19 showed reduced mortality in statin users than non-statin users. Hence, patients with high CVD risk factors along with diabetes should continue to use the statins during COVID-19 era.[26]

Symptoms such as breathlessness and chest pain were majorly reported by the patients revisiting to hospital after recovery from COVID-19 infection. Majority of HCPs suggested the change from monotherapy to dual while others opined for intensification of dual therapy dose, intensification of monotherapy, and shifting to triple therapy to maintain the HTN levels to near normal ranges and to prevent the further worsening of CV complications. Most of the patients with HTN require a dual combination of antihypertensive agents to decrease blood pressure as they offer greater strength and lesser side effects than the high dose monotherapy. Patient not responding to dual therapy need a combination of three drugs including a RAAS inhibitor, a CCB and a natriuretic to lower blood pressure.[27]

Majority of HCPs recommended ARBs and its combination as shared in study. Other HCPs opined the use of ACEI and its combinations, beta blockers and its combination, CCB and its combination, and few recommended diuretics and its combination. Studies have shown that ARBs and ACEI are frequently used to treat HTN in patients with COVID-19.[28] They are observed to lower the disease severity and improve clinical outcomes in these patients.[29] However, a recent state-of-art review, suggested that ARBs could be a better treatment approach in COVID-19 patients due to fewer side effects than ACEIs.

The European society of cardiology (ESC) guidelines are supportive in the management of HTN during the COVID-19
Antihypertensive therapy with ACEIs or ARBs is the basis for treating as per the ESC/European Society of Hypertension (ESH) guidelines for the management of arterial hypertension (2018) with pleotropic effects making them the drug of choice. The recommended treatment of HTN for most patients is a combination of ACEI or ARB with a CCB or thiazide/thiazide like diuretic.

International society of hypertension (ISH) completely endorses the content of two recent statements made by the Council on Hypertension of the ESC and ESH stating that there is no good evidence to alter the use of ACEI or ARBs for the management of hypertension in patients with COVID-19 infection to avoid contraindications. Due to lack of compelling data the ISH strongly advocated that use of ACEI or ARBs should not be discontinued in patients with hypertension because of COVID-19 infection.

Recommendations by the Government of India, Ministry of health & family welfare declared a post-COVID-19 management protocol to all the physicians and patients for further follow-up as mentioned below: a) follow-up visit (physical/telephone) should be done within 7 days after discharge; b) subsequent treatmentfollow-up visits in any nearest hospital and avoid post therapy for any adverse events or serious adverse events; c) home isolated patients should visit if any persistent symptoms occur; and d) in case of any severity more stringent follow-up is required.

To prevent CV complications in recovered patients, the HCPs advised to give aspirin to all the patients without any previous history as well as those with CV complication and particularly to the those receiving anti-coagulant or anti-thrombotic medications.

Post-COVID-19, patients may have sudden cardiac arrest or sub-acute state, or some may even have late-onset myocarditis which can present as an arrhythmia or acute combination both. Close monitoring of respiratory symptoms such as chest pain and breathlessness is recommended to prevent CV complications after COVID-19 recovery. Patients should be monitored for a possible precipitation of acute cardiac syndrome. Many HCPs recommended the adherence to medication and regular monitoring with the laboratory parameters like lipid profile and blood glucose levels to prevent further complications. If any symptoms arise, it should be reported immediately to HCPs.

The study has few limitations. There is a paucity of evidence of post-COVID-19 sequelae and further research is warranted to determine the long-term outcomes in recovered patients to understand the disease and to prepare better for potential outbursts in the future. Epidemiological, clinical, immunological studies and longer-ranging observational studies are warranted to derive the robust and comprehensive data of health consequences attributable to COVID-19 and measures to prevent and treat them. Furthermore, there was difference in opinions of HCPs due to their varied clinical experience across India which has limited to gather a robust and general recommendations for patients from Indian settings.

Conclusion

This study highlighted an increased incidence of HTN and CVDs post recovery from COVID-19. Patients can develop CV conditions, new-onset HTN and exacerbations of pre-existing comorbidities such as HTN, CVD, diabetes and dyslipidemia after recovering from COVID-19. Therefore, early recognition, prevention and strategic methods are vital factors that will help to prevent further complications post COVID-19 recovery. A routine 1-2-week follow-up and a close attention for warning signs of respiratory symptoms post-COVID-19 recovery to prevent CV complications was strongly recommended. India is already under the strain of CVD burden and further COVID-19 pandemic has amplified this burden on health infrastructure of India. The timely management of HTN, diabetes, and CV complications, and follow-up of HCP's advice on treatment recommendations will definitely ensure the best possible outcomes in COVID-19 recovered patients.

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Conflicts of interest

Dr. Mahesh Abhyankar and Dr. Santosh Revankar are employees of USV Pvt Ltd. All other authors have no conflicts of interest to declare.

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COVID-19 recovered patients are prone to develop CVD and HTN, independent of pre-existing co-morbid conditions. Patients with pre-existing comorbidities such as HTN, coronary heart diseases, diabetes and dyslipidemia may develop exacerbation after recovery from COVID-19 infection. COVID-19 recovered patients may require dual or triple drug therapy for aggressive BP control to prevent post complications. Anti-hypertensive therapy with ARBs and combinations are widely accepted for HTN management and prevention of CV complications. Follow-up after 1-2 weeks of recovery and close monitoring of respiratory symptoms are critical. Adherence to medications and regular monitoring with the laboratory parameters (lipid profile and blood glucose levels) will help to prevent further complications.

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