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An updated review on potential therapeutic drug candidates, vaccines and an insight on patents filed for COVID-19

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ABSTRACT

The outbreak of COVID-19 was recognized in December 2019 in China and as of October5th, the pandemic was swept through 216 countries and infected around 34,824,108 individuals, thus posing an unprecedented threat to world's health and economy. Several researchers reported that, a significant mutation in membrane proteins and receptor binding sites of preceding severe acute respiratory syndrome coronavirus (SARS-CoV) to turned as novel SARS-CoV-2 virus and disease was named as COVID-19 (Coronavirus disease 2019). Unfortunately, there is no specific treatment available for COVID-19 patients. The lessons learned from the past management of SARS-CoV and other pandemics, have provided some insights to treat COVID-19. Currently, therapies like anti-viral treatment, immunomodulatory agents, plasma transfusion and supportive intervention etc., are using to treat the COVID-19. Few of these were proven to provide significant therapeutic benefits in treating the COVID-19, however no drug is approved by the regulatory agencies. As the fatality rate is high in patients with comorbid conditions, we have also enlightened the current in-line treatment therapies and specific treatment strategies in comorbid conditions to combat the emergence of COVID-19. In addition, pharmaceutical, biological companies and research institutions across the globe have begun to develop thesafe and effective vaccine for COVID-19. Globally around 170 teams of researchers are racing to develop the COVID-19 vaccine and here we have discussed about their current status of development. Furthermore, recent patents filed in association with COVID-19 was elaborated. This can help many individuals, researchers or health workers, in applying these principles for diagnosis/prevention/management/treatment of the current pandemic.

1. Introduction

The coronavirus, believed to be originated 800 years before from the bats, as confirmed by many researchers (Y. Chen et al., 2020; Paules et al., 2020). On basis of genetic features, family coronaviridae is categorized as α, β, λ, and δ, where alpha (α) and beta (β) coronavirus are proven as pathogenic to humans and mammalians. Coronaviruses are a form of positive strand non segmented RNA viruses that can cause serious respiratory and neurological illness (Weiss and Leibowitz, 2011). Six different types of coronaviruses can cause disease among the humans, two of them can cause middle east respiratory syndrome coronavirus (MERS-CoV) and severe acute respiratory syndrome (SARS-CoV), while the rest four (HKU1, 229E,NL63 and OC43) are less pathogenic will cause only common cold (Cui et al., 2019; S. Su et al., 2016). MERS-CoV and SARS-CoV outbreak was happened in Middle east (2012) and China (2002) respectively (Zaki et al., 2012; Zhong et al., 2003). Again, in December 2019, few patients who are linked with seafood market in Wuhan of China, were shown pneumonia like symptoms. Consequently, about 20,000 sequences from each sample were obtained to match the genome. Genome matches confirmed 85% similarity with SARS-like β-coronavirus (N. F. C. Zhu et al., 2020). Further investigations on isolated virus conforms the new strain of Coronavirus and named this new

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virus as SARS-CoV 2 (Fig. 1).

Based on its severity and rapid spread across the World, World Health Organization (WHO) declared COVID-19 (coronavirus disease-2019) as a global pandemic disease. Previously, MERS became endemic in majority of the Middle Eastern countries. Diversity, rapid animal to human spread and broad genetic variation makes coronaviruses to emerge periodically in future also. Since COVID-19 emerged, the face of research and development, health care systems and social containment measures were completely reorganized to manage the mounting number of patients. At the time of this review writing (October 4, 2021), more than 235.7 Million cases and 4.8 Million deaths were recorded throughout the world (*COVID-19 related analytics, graphs, and charts | Corona Tracker*, 2020). Unfortunately, there are no medications that are approved for treating the coronavirus infections. However, as per the existing evidence and based on clinical trial data anti-viral drugs like Remdesivir, Favipiravir; anti-inflammatory drug dexamethasone; anti coagulants along with multi vitamin and mineral therapy showing promising results to attenuate the COVID 19 disease. Currently, drug repositioning therapies are successfully employed in treating the SARS infections. drug repositioning, refers to the application of existing drugs to treat the diseases other than its intended use (Amy Maxmen, 2020). This strategy is found its application owing to, lower costs and comparatively less time to reach the market In contrast to this, drug repositioning strategy has few limitations like, patent barriers, lack of funding opportunities, heterogeneity of population and complexity in regulatory approval process (Mercorelli et al., 2018; Pushpakom et al., 2018).

Among the deaths reported, majority of patients are having high prevalence of concomitant diseases like hypertension, cardio-vascular complications, diabetes, renal failure, and COPD (chronic obstructive pulmonary disease). The fatality rate is high in elder patients, with foresaid comorbidities (W. Guan, Liang, et al., 2020; Sanyaolu et al., 2020).

Consequently, the researchers emphasised more on the development of vaccine. Globally, more than 170 teams of researchers are working to develop a potent vaccine for mitigating the coronavirus infections.

Patent is a form of intellectual joy, that gives its inventor the legal right to prohibit others from using, selling, or making the same invention for a limited period of time. In many jurisdictions, patent rights fall under the private law and in some industries, it is considered as a competitive advantage. Quite a few patents were filed related to coronavirus management or treatment or prevention. The present context emphasis on current inline treatment, treatment strategies in comorbid conditions, progress of vaccine development and additionally, patents filed related to COVID-19. Patent related information further helps the researchers to control or manage or treat the present pandemic situation.

2. Inline treatment

As on date there is no specific approved treatment for either complete prevention or treatment of the most prevailing pandemic COVID-19. The daily rise of positive cases led to the urgent need of medication. Hence, scientists and researchers initiated and conducting intense search for the application of existing drugs in combating the present worse condition through repurposing in addition to discovery trials for new chemical entities. National and international collaborations are witnessed in this pandemic time to fight against the COVID-19. Such combined efforts have led to the process of exploring potential areas like treatment strategies through small molecule drugs, immunotherapies, convalescent plasma, cell based therapies, antibodyand interferon therapies (G. Li and De Clercq, 2020).

Another key point of specific attention is the swift genomic sequencing of COVID-19 which became a challenge for researchers. However, highly conserved regions involving enzymes or proteins among the related viruses like SARS-CoV, MERS-CoV and SARS-CoV-2 has given scope to propose some treatment options (G. Li and De Clercq, 2020; Lythgoe and Middleton, 2020).

As per the present guidelines or preclinical and clinical outcomes, there are several proposed inline treatment strategies to combat the existing disease condition to possible extent. In this review a brief outline of such potential treatment strategies will be given in addition to the clinical trials status across the globe (As on October 30, 2021) (Fig. 2). A special focus is further given on treatment strategies for comorbidities like diabetes, hypertension, obesity, cardiovascular disease, etc.

2.1. Antivirals

As the present pandemic is of viral origin, the primary focussed repurposing of drugs is in the area of antivirals and the rapid trials are going on with antiviral drugs.

2.1.1. Lopinavir/ritonavir

As on date, 20 clinical trials are ongoing with combination of lopinavir/ritonavir as per the statistics at clinicaltrials.gov. Among them 13trials reached phase-2 and 11 trials were reached to phase-3. The priority for these drugs is due to their efficacy against earlier viruses SARS-CoV, MERS-CoV and HIV (Lythgoe and Middleton, 2020). Both of these drugs are protease inhibitors. Lopinavir has insufficient oral bioavailability due to the rapid catabolism by the specific enzyme, 3A4

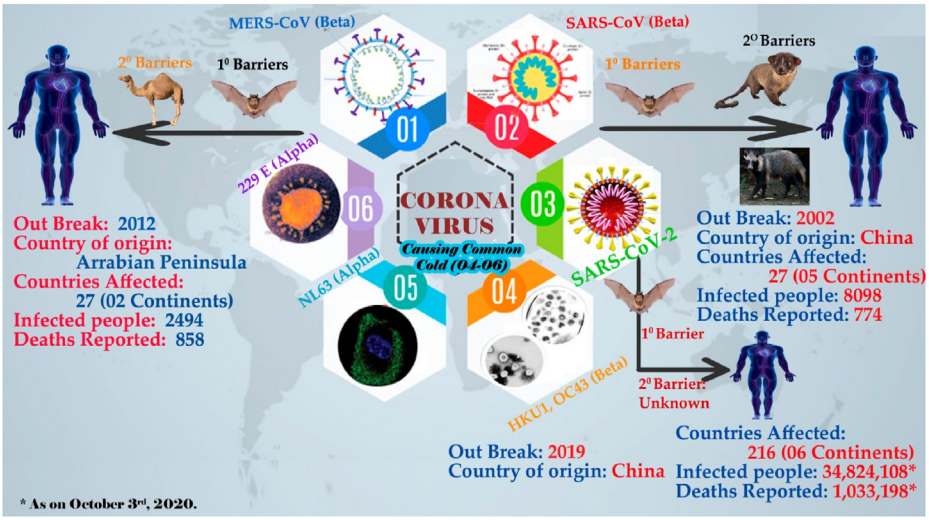

Fig. 1. Types of coronaviruses and their outbreaks.

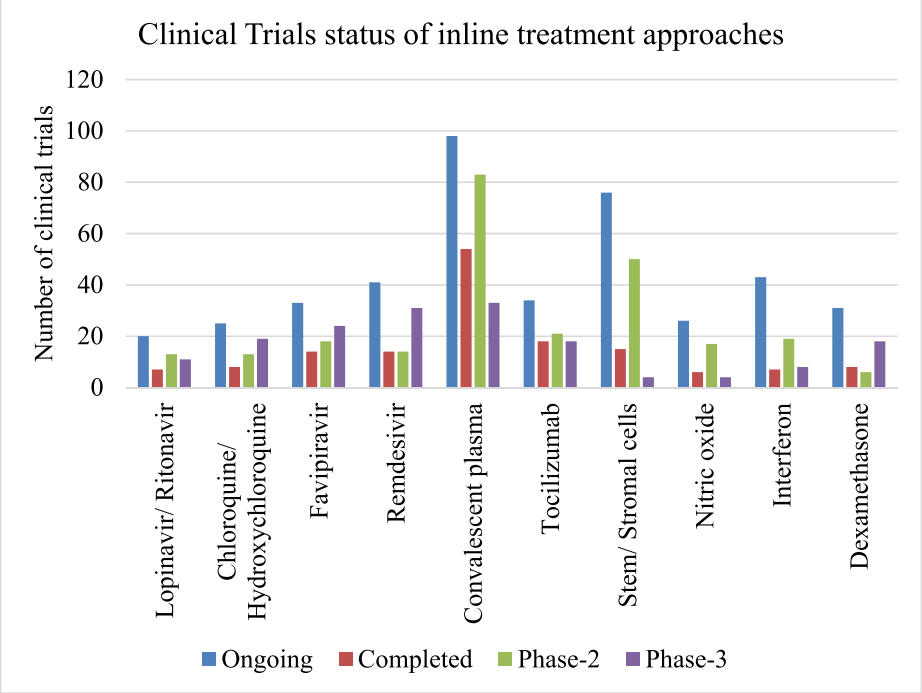

Fig. 2. Status of clinical trials of inline treatment approaches(Source: clinicaltrials.gov accessed on 30-09-2021).

isoenzyme which is a part of Cytochrome P450 enzyme system (Sham et al., 1998).In order to overcome this loss and significantly enhance the half-life of lopinavir, the concomitant administration of ritonavir is followed to inhibit the enzymatic catabolism of lopinavir. The combined efficacy of lopinavir/ritonavir has been proved against SARS-CoV during 2004 (Chu et al., 2004). However, yet no significant data is available to propose this combination against SARS-CoV-2 as trials are ongoing (Cao et al., 2020a).

Few earlier studies revealed that the use of lopinavir/ritonavir combination therapy has shown reduction in viral loads, fever, and pulmonary damage (Meini et al., 2020).

Cao et al. reported the results of a randomized controlled open-label clinical study where 99 severe COVID-19 patients received lopinavir/ritonavir and 100 patients received standard care for a duration of 2 weeks. The results of this study are statistically non-significant between the two groups, but shown more clinical improvement with the lopinavir/ritonavir patients compared with standard care (Cao et al., 2020b; Meini et al., 2020).

2.1.2. Remdesivir

A novel nucleotide analogue, Remdesivir, having antiviral effect against Ebola, Marburg, SARS-CoV and MERS-CoV has been in clinical trials to evaluate its effect against COVID-19 (Sheahan et al., 2017; M. Wang et al., 2020; Warren et al., 2016). Remdesivir is found to have a therapeutic benefit against COVID-19 based on the recovery rate in USA in remdesivir treated patients (Holshue et al., 2020; Lythgoe and Middleton, 2020). As on date there are 41 ongoing clinical trials to check the efficacy of remdesivir against COVID-19. CYP3A inhibitors are potential boosters of other antivirals as well, in particular remdesivir (Shytaj et al., 2021; Xie and Wang, 2021).

With a significant benefit of reducing the mortality of COVID-19 patients, USFDA has issued emergency use authorization for emergency use of remdesivir in COVID-19 positive patients (*Gilead Announces Results From Phase 3 Trial of Remdesivir in Patients With Moderate COVID-19*, 2020; Samudrala et al., 2020). It has been reported that treatment with remdesivir and chloroquine has shown effective response against recently emerged coronavirus (Khan et al., 2020; Samudrala et al., 2020; M. Wang et al., 2020). However, still additional scientific data is necessary to be developed to establish the treatment strategy and dosage regimen.

However, in another study the use of remdesivir has not shown statistically significant improvement in clinical benefits, however shown reduction in recovery time of COVID patients in clinical trials and non-significant reduction in mortality rate (Davies et al., 2020; Yeming Wang et al., 2020). As there is no other available treatment option at this emergency situation, USFDA has re-issued the emergency use authorization for use of this drug (*COVID-19 Update: FDA Broadens Emergency Use Authorization for Veklury (remdesivir) to Include All Hospitalized Patients for Treatment of COVID-19 | FDA*, 2020; USFDA, 2020).

2.1.3. Favipiravir

Favipiravir is found effective against wide range of viruses like resistant influenza, and able to inhibit RNA viruses like arena-, bunya- and filo-viruses (Delang et al., 2018; Jiancheng Zhang et al., 2020). Favipiravir has also shown potential benefit against SARS-CoV-2 (Cai et al., 2020).As a further attempt, a combination of favipiravir with interferon-α and also with baloxavirmarboxil are under clinical trials (Khan et al., 2020).

Based on the reports of Ministry of Science and Technology, China, favipiravir came into treatment strategy for COVID-19 based on the positive results in a clinical trial in Shenzhen and Wuhan cities. The symptoms like fever and severity of infections are managed with the application of favipiravir. However, a still confident and scientific data need to be assessed in this regard for its use in the treatment of COVID-19 patients with advanced stages (Samudrala et al., 2020).

2.1.4. Other antivirals

Antiviral drugs that are effective against influenza subtypes and other RNA viruses are also in investigation for their efficacy against COVID-19. Studies are also conducting on other antivirals like oseltamivir, ribavirin, umifenovir, triazavirin, danoprevir, azvudine, sofosbuvir, ledipasvir, sofosbuvir, daclatasvir, darunavir, cobicistat, emtricitabine, and tenofovir to test the efficacy of these drugs. (Lythgoe and Middleton, 2020).

EIDD-2801 is an antiviral drug that is providing potential results against SARS-CoV-2. EIDD-2801 is comparatively more preferred than remdesivir as the former is meant for oral administration whereas the

latter must rely on intravenous administration. EIDD-1931 is another analogue, that is found to be effective against several types of viruses like SARS-CoV, MERS-CoV, and even the newly emerging SARS-CoV-2 based on cell based assays (Jiancheng Zhang et al., 2020).

2.2. Corticosteroids

Corticosteroids are known to treat acute respiratory distress disease and sepsis due to their anti-inflammatory, antifibrotic effects and suppression of collagen deposition. Use of dexamethasone for COVID-19 therapy has been proposed with the reported advantages of minimum fatality rate and hospital stays of SARS infect patients (R. C. Chen et al., 2006).

However, adverse effects associated with high doses of corticosteroids like delayed viral clearance, secondary infections and viral resistance need to be considered while testing their application in treatment of COVID-19 patients. A low to moderate doses are found to be beneficial in seriously ill patients suffering with COVID-19 pneumonia as per the guidelines of WHO(*Interim Clinical Guidance for Management of Patients with Confirmed Coronavirus Disease (COVID-19)*, 2020).

The use of corticosteroids for SARS-CoV and MERS-CoV has reported detrimental effects with increased mortality and nosocomial infections for influenza and delayed virus clearance (J. W. Yang et al., 2020). Corticosteroids therapy has offered controversial implications in COVID-19. Even though there is an improvement in the symptoms and oxygenation with severe COVID-19 patients, there are also cases with increased fatality rate in observational studies. Hence, a more randomized controlled trials are to be conducted for better scientific understanding of the use of corticosteroids (J. W. Yang et al., 2020).

Early COVID-19 pneumonia was reported to be managed well with low-dose and short-term use of methylprednisolone (Yin et al., 2020). ARDS patients has shown decreased rate of mortality in a study with the use of methylprednisolone (C. Wu et al., 2020).

2.3. Anticoagulants

COVID-19 patients with high platelet count of elevated D-dimer may get beneficial effects with anticoagulant therapy [39]. Heparin is found to be showing better prognosis in patients affected with severe COVID-19 [40].The role of heparin is found to be promising as Microft-West et al. reported the interaction between heparin and SARS-CoV-2 spike S1 protein receptor binding domain (Mycroft-West et al., 2020). Another study results are suggesting that heparin is found to be effective in COVID-19 management beyond anticoagulant effect through its pleiotropic activity (Gozzo et al., 2020). However, studies with large number of subjects are necessary to confirm the benefits of heparin in management of COVID-19.

2.4. Antimalarials

2.4.1. Chloroquine and hydroxychloroquine

Chloroquine is a well-known drug for treating malaria and autoimmune diseases which is also known for its broad-spectrum antiviral action. In addition to the earlier reports on effect of chloroquine against SARS-CoV(Keyaerts et al., 2004; Savarino et al., 2006; Yiwu Yan et al., 2013), it has also been found effective against SARS-CoV-2 in improving the disease conditions like pneumonia, and pulmonary lesions (Gao et al., 2020; M. Wang et al., 2020). Chloroquine is known to decrease the severity and duration of disease (Jiancheng Zhang et al., 2020).In addition to chloroquine, its analogue and a relatively low toxic agent, hydroxychloroquine has been found to be another potential outcome for dealing with SARS-CoV-2 patients (J. Liu et al., 2020).

Chloroquine show antiviral effect by inhibiting the glycosylation of S-protein of angiotensin converting enzyme-2 and also by increasing the pH of acidic cellular organelles thereby avoiding the fusion of virus into the host cells (Savarino et al., 2003, 2006).These antimalarial agents are also shown to cause decreased expression of cytokines thereby minimizing the intensity of COVID-19 (Huang et al., 2020).Their low cost and high availability in addition to potency against COVID-19 has made them prominent for the treatment of COVID-19. Gautret et al. reported that a combination of hydroxychloroquine and azithromycin has shown significant reduction in viral load in COVID-19 patients (Gautret et al., 2020).

Later reports revealed that a short term use of hydroxychloroquine is safe and also the combination of chloroquine with azithromycin could develop other side effects like cardiovascular complications, angina, chest pain and heart failure (Lane et al., 2020). However, there are earlier reports as well as recovery trial stating that chloroquine and hydroxychloroquine were not effective against viral treatments like SARS-CoV-2 and no significant benefit over mortality rate (Group, 2020; Savarino, 2011).

2.5. Monoclonal antibodies

2.5.1. Tocilizumab and sarilumab

COVID-19 patients are known to invoke a hyperinflammatory state with multiple calls and mediators like interleukins (IL-1, IL-6, IL-12, IL-18), tumor necrosis factor alpha (TNFα) etc. Seriously ill patients infected with COVID-19 are found to have cytokine dysregulation majorly involved with IL-6. Hence, IL-6 inhibitors are proposed in the treatment strategies for COVID-19 (Cao et al., 2020b).

COVID-19 patients with cytokine storm, particularly IL-6 are found to be responding with IL-6 receptor antagonists namely tocilizumab and sarilumab. Numerous clinicals are going on with tocilizumab and sarilumab (Mehta et al., 2020).

Tocilizumab and sarilumab, the targeted monoclonal antibodies are found to reduce the evident features of cytokine driven hyperinflammation like dyspnoea, persistent fever and elevated markers showing improved clinical outcomes through decreased cell proliferation, differentiation, oxidative stress and exudation (Cao et al., 2020b). These antibodies are included in the international guidelines for management of severe of critically ill patients. Numerous clinical trials are going on for increased interest in testing the clinical implications of these drugs. Tocilizumab is reported to be reducing the likelihood of advancement to death in COVID-19 patients (Salama et al., 2020).

2.5.2. Bevacizumab

Bevacizumab is a recombinant humanized monoclonal antibody that was approved by USFDA for several types of cancers like metastatic colorectal cancer, lung cancer, renal cancer, cervical cancer, ovarian cancer, etc. As it acts against vascular endothelial growth factor (VEGF), bevacizumab is proposed to be used in treatment of COVID-19 because VEGF is responsible for acute respiratory distress, pulmonary edema, dyspnea, and acute lung injury. Clinical trials are initiated on this drug for confirming its application in clinical improvement of COVID-19 cases (Samudrala et al., 2020).Bevacizumab is well known to treat acute respiratory distress syndrome which is highly associated complication in COVID-19 ill patients (Jiancheng Zhang et al., 2020).

2.6. Ivermectin

In vitro studies revealed that the anti-parasitic agent, ivermectin could effectively act against SARS-CoV-2 growth in cell cultures (Caly et al., 2020).Further studies are necessary to prove its efficacy and safety for managing SARS-CoV-2 in animals or humans. Melo et al. reported that their study supports the use of immunomodulatory drugs like ivermectin to improve the clinical condition of COVID-19 infected patients (Melo et al., 2021).

2.7. Convalescent plasma therapy

Plasma therapy has shown improved signs of relief and treatment.

Here, in this treatment convalescent plasma collected from the recovered COVID-19 patients and it has been approved by several regulatory bodies for treatment (Roback and Guarner, 2020). USFDA has granted clinical permission for the application of convalescent plasma to the treatment of critically ill patients affected by COVID-19 (*Investigational COVID-19 Convalescent Plasma-Emergency INDs Frequently Asked Questions*, 2020).Several studies reported that, recovery from the infection was observed approximately after a week of transfusion of convalescent plasma.

2.8. Vitamins and mineral

Vitamin C and D are found to be beneficial in controlling the disease condition of COVID-19. Grant et al. reported the importance of vitamin D in reducing the viral replication and risk of respiratory tract infections in COID-19 patients (Grant et al., 2020).Zinc supplementation is thought to combat the loss of taste and smell symptoms in COVID-19 patients. In addition, the role of zinc as potential inhibitor of various RNA viruses such as SARS-CoV has initiated the clinical trials to test its effect against COVID-19 (Keyhan et al., 2020; Jiancheng Zhang et al., 2020).

2.9. Janus kinase inhibitors

A highly selective janus kinase (JAK) inhibitor, Baricitinib is found to be useful in the management of COVID-19 disease by impeding the hyperimmune responses and also by inhibiting the invasion of host cells with SARS-CoV-2 virus (Richardson et al., 2020).On the other hand, this agent may also cause inhibition of production of interferons which is detrimental in patients suffering from SARS-CoV-2. Hence, the use of baricitinib should be done very cautiously preferably in ill patients with abnormal biomarkers to yield some clinical benefits (Jiancheng Zhang et al., 2020).

2.10. Mesenchymal stem cells

A recent study revealed that transplantation of mesenchymal stem cells has shown improved functional outcomes at significant level with noticeable adverse effects in COID-19 patients during a study held at Beijing YouAn Hospital (Leng et al., 2020).

2.11. Other treatment strategies

The use of inhaled nitric oxide in SARS infected patients has shown improved arterial oxygenation and reduced the need of ventilation. Hence, clinical trials are going on for testing the application of inhaled nitric oxide in COVID-19 patients suffering with acute respiratory distress syndrome (L. Chen et al., 2004).

Interferon alpha-1a, alpha-1b, beta-1a, beta-1b are known to show beneficial effects in COVID-19 patients and hence numerous ongoing clinical trials are there in this area (Jiancheng Zhang et al., 2020).Intravenous immunoglobulins especially purified IgG products are meant for benefit in respiratory syndromes and hence clinical trials are initiated to test their application in COVID-19, however their numerous adverse effects like myalgia, thromboembolism, and renal failure need to be addressed.

Natural killer cell therapy, CYNK-001 comprising from placental hematopoietic stem cells has obtained investigational new drug application approved by USFDA (*Celularity Announces FDA Clearance of IND Application for CYNK-001 in Coronavirus, First in Cellular Therapy*, 2020).This therapy has found to show potential inhibition against SARS-CoV-2 via direct killing of infected host cells as well as indirect induction of immune response. However, the efficacy and safety of this therapy need to be confirmed by ongoing clinical trials (Jiancheng Zhang et al., 2020).Alpha-lipoic acid is an antioxidant that is reported to handle the oxidative stress which is playing a major role in coronavirus infections (Khan et al., 2020).

3. Treatment strategies for COVID-19 with comorbidities

It is reported that COVID-19 infected patients with comorbidities are at higher risk than others (Fang et al., 2020). Table 1 depicts the literature that represents the impact of comorbid diseases towards COVID-19 severity.

It is observed that major proportion of COVID-19 patients are having comorbidities and it might be giving a claim that patients suffering from diseases like diabetes, hypertension are more prone to infection by SARS-CoV-2. One of the reasons might be the over expression of angiotensin-converting enzyme 2 (ACE2)in these diseases (Gracia-Ramos, 2020).

The pathogenic viruses SARS-CoV and SARS-CoV-2 bind to the host cells through ACE-2 receptors which is expressed on different organs like lungs, kidneys, blood vessels and intestine (Wan et al., 2020). Patients (Type-1, type-2 diabetes, and hypertension patients) taking ACE inhibitors and angiotensin II type-I receptor blockers (ARBs) are known to show upregulation of ACE2 (X. C. Li et al., 2017). Thiazolidinediones and ibuprofen usage are also meant for over expression of ACE2.

These factors, in turn favour the infection of coronavirus in humans due to the overexpression of ACE2. However, this hypothesis may need strong scientific assessment with more clinical investigation. In addition, there is a conflict with ACE2 pharmacological effects and its polymorphic effects. COVID-19 patients treated with medicaments that increase ACE2 levels are at still higher risk due to comorbidities like diabetes, hypertension, and cardiac diseases (Fang et al., 2020).However, the prevalence of comorbid diseases varies from country to country based on the age factors and living styles. For example, China has highest prevalence of diabetes, hypertension, and cardiovascular diseases in their population (Du et al., 2019; *IDF Diabetes Atlas* 9th *edition 2019*, 2019; Z. Wang et al., 2018; Y. Xu et al., 2013).

Since non-steroidal anti-inflammatory drugs are commonly used in elderly patients, this may result in worsening of the condition of COVID-19 patients with adverse effects like renal failure, heart problems, and gastrointestinal toxicity. Hence, a proper management of the treatment should be done (Wongrakpanich et al., 2018).Overall, the severity of the diseaseis high in older population and the population who had more significant number of comorbid conditions than others. These results may suggest that age and comorbidities are risk factors for COVID-19 (J. Yang et al., 2020).

3.1. Diabetes

Diabetes is one of the most prevalent comorbidities that worsen COVID-19 to severe levels and even lead to mortality. Treatment for COVID-19 patients associated with diabetes is a challenging task as multiple implications need to be managed. Adequate glycaemic control is another challenge in addition to the goal of reducing the severity of coronavirus load. It needs an extensive team effort to manage the complications in COVID-19 patients with diabetes (Apicella et al., 2017).

The coronavirus on binding to the ACE2 receptors, especially on pancreatic beta-cells leads to acute loss of insulin secretory capacity in addition to cytokine storm which may lead to rapid metabolic deterioration. This lead to development of diabetic ketoacidosis or hyperglycaemic hyperosmolar syndrome (Hamming et al., 2004).

On August 26, 2020, Ministry of Health and Family Welfare, Govt. of India has released a document for clinical guidance on diabetes management at COVID-19 (Government of India & Ministry of Health & Family Welfare, n.d.).This guidance document has clearly given the instructions to screen every COVID-19 patient for hyperglycaemia for 1 pre-meal and 1 post-meal capillary blood glucose values. If found diabetic, every patient should be kept on diabetic diet as per the proposed diet chart following the timing and quantity of diet advised.The pre-meal and post-meal glucose values are specified as <140 and < 180 mg/dL respectively for continuing the existing oral anti-diabetic drugs if the patient is conscious, COVID symptoms are mild, kidney and liver function tests are normal.

A follow up capillary blood glucose testing over next 24 h is advised for those showing pre-meal and post-meal glucose values ≥ 140 or ≥180 mg/dL respectively. In case the values of pre-meal and post-meal are in the range of 140–150 and 180–200 mg/dL respectively, then diabetic meal is advised. If there is a significant elevation of values of pre-meal ≥150 and post-meal ≥200 mg/dL or the initial testing shows any value ≥ 200 mg/dL, then oral anti-diabetics or insulin are to be initiated along with diabetic diet (Government of India & Ministry of Health & Family Welfare, n.d.).

If the COVID-19 patient is proposed to be on steroids treatment of any drugs with potential effect on glycaemic or else the severity of COVID-19 is increasing which may lead to stress glycaemia, then there should be a repeated monitoring of blood glucose levels. At any point of testing if the blood glucose level is ≥ 250 mg/dL, urine/blood ketone levels are to be tested and if found positive, then an endocrinologist need to be consulted immediately. At any point, if the blood glucose level of pre-meal is ≥ 300 mg/dL and/or post-meal is ≥ 400 mg/dL, then an endocrinologist needs to be consulted immediately irrespective of ketone levels in order to initiate the insulin infusion. In the follow up testing on later days, fasting plasma glucose ≥126 mg/dL and/or HbA1c ≥ 6.5% are considered to be as diabetic mellitus positive.

In case the patient has no earlier diabetes, history but found to be diabetic during these tests with pre-meal blood glucose value 150–180 mg/dL and/or post-meal blood glucose value 200–250 mg/dL, then an endocrinologist needs to be consulted for initiating the oral anti-diabetic drug treatment. In emergency cases to avoid delay in treatment, metformin and gliptin are advised. In case of excess values, insulin infusion can be initiated as advised by an endocrinologist.

Earlier reports reveal that administration of chloroquine or hydroxychloroquine may lead to hypoglycaemia especially in patients taking insulin or sulfonylureas, because of their effect on insulin secretion and degradation (Ünübol et al., 2011). Also, antiviral drugs proposed for COVID-19 like lopinavir and ritonavir are known to cause hyperglycaemia and cause imbalance in the glycaemic control (Paengsai et al., 2019). These antiviral agents can also cause hepatic and muscular toxicity when used along with statins in patients with fatty liver disease (Bruno et al., 2006). Pharmacokinetic interactions are noticeable with antivirals against anti-diabetic drugs (*Liverpool COVID-19 Interactions*, 2020). Use of glucocorticoids in COVID-19 patients with severe ARDS can worsen insulin resistance, glycaemic control, causing sever hyperglycaemia and sustained gluconeogenesis. This might be due to reduced insulin sensitivity and insulin secretion exerted by glucocorticoids and also by interfering with GLP-1 effects along with enhanced production of glucagon.

3.2. Hypertension

Hypertension is another most frequent comorbidity observed in COVID-19 patients (J. Yang et al., 2020). Use of ACE inhibitors or ARBs in COVID-19 patients with hypertension has shown a lower rate of severe disease and a lower inflammatory response (Meng et al., 2020). ACE inhibitors are found to be unlikely to account for the connection of hypertension with COVID-19 (Reynolds et al., 2020).De Abajo et al. reported a case-population study with 1139 adult COVID-19 positive patients taking antihypertensive drugs. In these patients, they used predominantly ACE inhibitors and ARBs; in few patients they have given aldosterone antagonists or renin inhibitors. Comparing with other antihypertensive agents, the use of RAAS inhibitors were found to be not associated with increased risk of COVID-19 that need hospital admission (odds ratio 0.94, 95% CI 0.77–1.15) or increased risk of severity in complications with COVID-19 that needs intensive care or leading to a fatal outcome (1.08, 0.80–1.47). These observations are not influenced by age, sex or background cardiovascular risk (de Abajo et al., 2020; Williams and Zhang, 2020). Use of ACE inhibitors in hypertensive patients and also associated with type 2 diabetes patients especially those with poor control over blood glucose may increase severity of COVID-19 (Cure and Cumhur Cure, 2020).

3.3. Obesity

Obesity associated COVID-19 lead to severe illness and death (Cariou et al., 2020; Shi et al., 2020).Possible proposed mechanisms include detrimental restrictive ventilatory effect of abdominal fat, impaired lung perfusion due to intravascular disseminated coagulation, deep venous thrombosis, immune dysregulation, and chronic inflammation causing organ failure in severe COVID-19 cases (Connors and Levy, 2020; Sattar et al., 2020; Simonnet et al., 2020; Wichmann et al., 2020).Low--molecular weight heparin was reported to reduce mortality rate in such COVID-19 associated obesity cases (Tang et al., 2020).

There is an increased risk of severity in COVID-19 patients with a BMI of >25 kg/m^2 and fatty liver disease than in patients without obesity (Zheng et al., 2020).Obese patients due to physical inactivity, insulin resistance and gut dysbiosis, may result in inflammatory response to infection with COVID-19.Obese individuals suffer with chronic inflammation particularly elevated levels of IL-6 might be get beneficial results with the use of tocilizumab. It can reduce the fever and oxygen requirement, however it may not be beneficial with acute therapy (X. Xu et al., 2020). Horby et al. reported that dexamethasone use in obese patients with severe COVID-19 can reduce mortality rate by 8–26% (Horby et al., 2020). Limited information is available for the use of other treatment options like statins, nonsteroidal anti-inflammatory drugs and ARBs for obese patients with COVID-19 (Popkin et al., 2020).

3.4. Cardiovascular diseases

COVID-19 patients association with cardiovascular disease are also more prevailing and are at a higher risk of mortality (Babapoor-Farrokhran et al., 2020; B. Li et al., 2020). Kim et al. reported a COVID-19 patient associated with acute myocarditis (Kim et al., 2020). Buja et al. reported the cardiopulmonary pathology of coronavirus disease where an autopsy reported that 13 out of 23 patients shown cardiac manifestations associated with pulmonary issues (Buja et al., 2020). Li et al. has reported the influence of novel coronavirus on heart injury (J. J. W. Li et al., 2020). Atrial fibrillation and heart failure are also reported as major implications for death in covid affected patients (Gawałko et al., 2020; Sanyaolu et al., 2020).

Acute myocarditis has been found as a reverse stress-induced syndrome in COVID-19 patients (Sala et al., 2020). Possible mechanisms for cardiovascular complications might include reduced systemic oxygenation due to pneumonia with increased cardiac demand, immune dysregulation, electrolyte imbalance, or associated with adverse effects of drugs like azithromycin and hydroxychloroquine (Babapoor-Farrokhran et al., 2020).

For venous thromboembolic complications, anticoagulation therapy with low molecular weight heparin is found to reduce the mortality risk.COVID-19 patients with cardiovascular disease under treatment with antiplatelet agents and anticoagulants may show significant drug-drug interactions with antiviral therapies like remdesivir, lopinavir/ritonavir and antibody therapies like tocilizumab or sarilumab (Bikdeli et al., 2020).

Statins are known to be commonly prescribed for cardiovascular patients with COVID-19 for their anti-inflammatory effects which involves Myd88 and downstream nuclear factor kappa B signal pathways. They show beneficial effect on influenza infection and hyper-inflammatory ARDS (Calfee et al., 2018; Y. B. Su et al., 2020).

Chloroquine and hydroxychloroquine in combination with azithromycin can lead to QT prolongation in cardiovascular patients with COVID-19. They may also cause rare complications like cardiomyopathy, atrioventricular and bundle branch block (Chatre et al., 2018).

ACE inhibitors and ARBs are not known to affect the morbidity and mortality of COVID-19 patients with cardiovascular disease.

3.5. Others

High levels of c-reactive protein, ferritin, procalcitonin, neutrophil-to-lymphocyte ratio, inflammatory cytokines and chemokines are associated with both COVID-19 severity and mortality (Henry et al., 2020; Petrilli et al., 2020; Zhou et al., 2020). Severe inflammatory infiltration of lungs, hear, spleen, kidneys and lymph nodes is found with COVID-19 patients of severity (chen et al., 2020; Diao et al., 2020; Z. Xu et al., 2020; Jin jin Zhang et al., 2020). COVID-19 is also associated with increased coagulation activity (Tang et al., 2020). Pulmonary intravascular coagulation has been reported in COVID-19 patients (McGonagle et al., 2020).

4. Current status of COVID-19 vaccines development

Vaccines are said to the most successful approach in preventing several infectious diseases in view of the fact that they are more effective than the treatment and can trim down the morbidity and mortality rate devoid of long-lasting effects (André, 2001; C. Zhang et al., 2019). Since two decades, three corona viruses namely SARS-CoV, MERS-CoV, and SARS-CoV-2, were emerged throughout the world, creating significant threat to global health (Guarner, 2020). Scientific experts feel that the pandemic of SARS-CoV-2 might be curtailed only by vaccination. Historically, there have been several difficulties faced by researchers in developing the vaccine for coronavirus. Coronavirus vaccines are not proven as effective in preventing the acquisition of disease, besides they found to be immunogenic in animal models (Koirala et al., 2020). There is a concern that, vaccination may not induce lifelong immunity as with the natural infection and re-infection may be observed. Disappointedly, vaccines for SARS-CoV and MERS-CoV raised some safety concern related to Th2 mediated immunopathology in animal studies (Edridge et al., 2020; Roper and Rehm, 2009).

Coronaviruses consists of a helical nucleocapsid (N) covering single strand RNA genome and outer envelope having spike proteins (S), matrix proteins (M) and envelope protein (E) (Boopathi et al., 2020). The S protein contains receptor binding domain (RBD), which is responsible for binding of ACE2 receptor and entry into the cell. Among all structural proteins, S protein was the major target antigen in vaccine development, as it found to elicit neutralizing antibody (Buchholz et al., 2004; Walls et al., 2020).

In current pandemic emergency of COVID-19, to contest this threatful condition, the world is truly required the potential vaccine. Vaccines approved for human use are generally live attenuated vaccines or inactivated viruses or protein polysaccharide conjugates or virus like particles etc. Multiple strategies as shown in Fig. 3 have been applied for SARS-CoV-2 vaccines to overcome the roadblocks that are associated with traditional vaccine development.

DNA and RNA composed vaccine, recombinant proteins and viral vectors are amongst them (X. X. Liu et al., 2020). As of October 01, 2021, more than 150 vaccines racing at various development stages in global COVID-19 vaccine research and development landscape and the progress was showed in Fig. 4. As per the existing data, 452 vaccine trails are in the various stages of development, their strategy and characteristics were given in Table 2 (approved) and Table 3(ongoing).

Just weeks after the identification of SARS-CoV-2 genetic sequence, Moderna Company together with NIAID, BARDA, made an announcement that mRNA-1273 (company's experimental COVID-19 vaccine) is all set for human trails (Zhai et al., 2020). This vaccine is one of the most hopeful and a notable fast vaccine development cycle was observed thereafter.

4.1. mRNA-1273

Moderna applied lipid nanocarrier technology for mRNA-1273 to deliver the mRNA into the host cell unlike the conventional vaccination approach i.e., using of weakened strain of the virus to obtain SARS-CoV-2 specific antibodies and effective immune responses. mRNA vaccine was proven to be superior in contrast to other conventional vaccines, as it possess high potency, safety and short production cycle (Ahn et al., 2020; Moderna, 2020). Dose dependent, open label Phase –I trail was conducted in 45 healthy volunteers to assess its safety with respect to effective dose. Few of the volunteers were identified with several adverse effects such as fatigue, fever, headache, pain at the site on administration and muscle ache. Phase III studies were started in July 2020 at 89

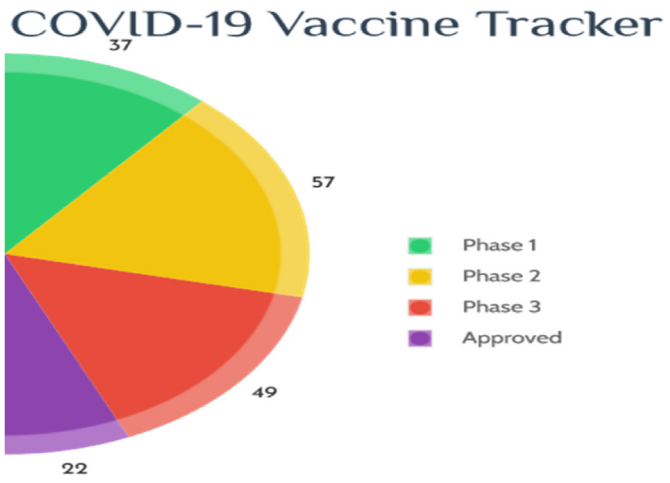

Fig. 4. COVID Vaccine tracker.

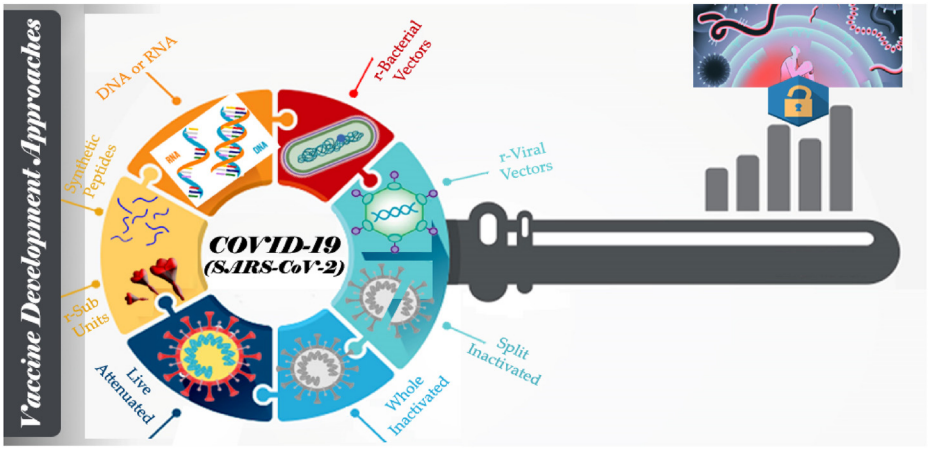

Fig. 3. Strategies applied to develop vaccines against COVID-19.

Table 1
Percent of comorbid cases in COVID-19 positive cases.

Comorbid disease	Percent reported	Patients population	Reference
Cerebrovascular diseases	22%	52 patients	(X. Yang et al., 2020)
Diabetes	22%		
Hypertension	23·7%	1099 patients	(W. Guan, Ni, et al., 2020)
Diabetes mellitus	16·2%		
Coronary heart diseases	5·8%		
Cerebrovascular disease	2·3%		
Hypertension	30%	140 patients	(Jin jin Zhang et al., 2020)
Diabetes	12%		
Case-fatality rate cardiovascular disease	10.5%	1023 deaths among 44,672 confirmed cases	(Z. Wu and McGoogan, 2020)
Diabetes	7.3%		
Chronic respiratory disease	6.3%		
Hypertension	6.0%		
Cancer	5.6%		
Diabetes	8.9%	146 patients	Fadini et al. (2020)
Diabetes	8.2%	1590 patients	(W. J. Guan et al., 2020)
Diabetes	34.7%; 9.7%	4103 patients (hospitalized vs non-hospitalized)	Petrilli et al. (2020)
Obesity	39.5%; 30.8%		
Diabetes	24%	258 patients	(Y. Zhang et al., 2020)
Diabetes	9.8%	16003 patients	Kumar et al. (2020)
Diabetes	2.79%	1382 patients	Roncon et al. (2020)
Diabetes	19%	191 patients	Zhou et al. (2020)
Diabetes	13%	7337 patients	(L. L. Zhu et al., 2020)
Diabetes	25%	193 patients	Yongli Yan et al. (2020)
Diabetes	44%	59 patients	Sardu et al. (2020)
Diabetes	4.8%	61414470 patients	Barron et al. (2020)

Table 2
List of approved COVID-19 vaccines.

S. No	Name	Vaccine type	Primary developers	Country of origin
	Moderna COVID-19 Vaccine (mRNA-1273); also called Spikevax	mRNA-based vaccine	Moderna, BARDA, NIAID	US
	Comirnaty (BNT162b2)	mRNA-based vaccine	Pfizer, BioNTech; Fosun Pharma	Multinational
	COVID-19 Vaccine AstraZeneca (AZD1222); also known as Vaxzevria and Covishield	Adenovirus vaccine	BARDA, OWS	UK
	Sputnik V	Recombinant adenovirus vaccine (rAd26 and rAd5)	Gamaleya Research Institute, Acellena Contract Drug Research and Development	Russia
	Sputnik Light	Recombinant adenovirus vaccine (rAd26)	Gamaleya Research Institute, Acellena Contract Drug Research and Development	Russia
	COVID-19 Vaccine Janssen (JNJ-78436735; Ad26.COV2.S)	Non-replicating viral vector	Janssen Vaccines (Johnson & Johnson)	The Netherlands, US
	CoronaVac	Inactivated vaccine (formalin with alum adjuvant)	Sinovac	China
	BBIBP-CorV	Inactivated vaccine	Beijing Institute of Biological Products; China National Pharmaceutical Group (Sinopharm)	China
	EpiVacCorona	Peptide vaccine	Federal Budgetary Research Institution State Research Center of Virology and Biotechnology	Russia
	Convidicea (PakVac, Ad5-nCoV)	Recombinant vaccine (adenovirus type 5 vector)	CanSino Biologics	China

locations in the United States with almost 30,000 participants. An interventional, randomized and placebo-controlled study was designed to check for its immunogenicity and safety.

4.2. CoronaVac

CoronaVac, developed by SinoVac have the virions which are inactivated using radiation or chemicals or with/without adjuvant and antigenically similar to the live virus. Phase II studies among 600 volunteers, confirms the immunogenicity in showing 92% seroconversion even at lower doses. Pain at the site of injection and mild in severity were observed adverse effects. Phase III study was started in various location of China, Brazil, Bandung and Indonesia with a sample size of 8870 (Yan-Jun Zhang et al., 2020). Double blind, randomized design was employed for this study.

4.3. Sinopharm vaccine

Similar product of CoronaVac developed by Sinopharm in association with Wuhan Institute of Biological Products and China National Pharmaceutical Group (*Chinese Clinical Trial Register (ChiCTR) - The world health organization international clinical trials registered organization registered platform*, 2020). Neutralizing antibodies were produced after 14 days with 2 doses of administration. 21,000 healthy volunteers are participating in Phase III trials in United Arab Emirates and Bahrain.

4.4. Ad5-nCoV

Yet another approach on basis of Cansino's adenovirus type 5 as a vector was proposed by CanSino Biologics to load the SARS-CoV-2 gene fragments in order to express the S-protein. Preclinical data from the animal study demonstrated that Ad5-nCoV can show the strong immune response and encouraging safety profiles (F. C. N. Zhu et al., 2020). Dose escalation, open-label, non-randomized phase 1 trials were conducted in healthy adults aged between 18 and 60 years. Subjects were divided into three dose groups (5×10^{10}, 1×10^{11}, 1.5×10^{11} viral particles) to receive the test by intramuscular injection and safety was assessed over 28 days. The Ad5 vectored vaccine was concluded as tolerable and immunogenic and rapid specific T-cell responses were noted. Phase II studies conducted in 508 volunteers, showed the neutralizing antibody and T Cell responses.

Another phase 1/2 a studies were conducted on Ad26.COV2.S, a non-replicating adenovirus 26 based vector in 402 healthy volunteers. Ad26.COV2.S was administered at a dose level of 5×10^{10}, 1×10^{11} viral

Table 3
Vaccines in the various stages of development, their characteristics.

S. No	Candidate	Mechanism	Sponsor	Trial Phase	Institution
	Unnamed vaccine candidate	Recombinant vaccine (Sf9 cells)	WestVac Biopharma Co., Ltd.; West China Hospital; Sichuan University;	Phase 3	Jiangsu Province Centers for Disease Control and Prevention
	ARCoV	mRNA-based vaccine	Walvax Biotechnology Co., Ltd.; Abogen Biosciences Co. Ltd.; Yuxi Walvax Biotechnology Co., Ltd.	Phase 3	Xiangfen CDC
	NVX-CoV2373	Nanoparticle vaccine	Novavax	Phase 3	Novavax
	Unnamed vaccine candidate	Plant-based adjuvant vaccine	Medicago; GSK; Dynavax	Phase 3	Medicago
	VLA2001	Inactivated vaccine	Valneva; UK National Institute for Health Research	Phase 3	Multiple NIHR testing sites
	Corbevax	Adjuvanted protein subunit vaccine	Biological E, Baylor College of Medicine, Dynavax, CEPI	Phase 3	Various
	Vidprevtyn	Recombinant protein vaccine	Sanofi; GlaxoSmithKline	Phase 3	Various
	Nanocovax	Recombinant vaccine (Spike protein)	Nanogen Biopharmaceutical	Phase 3	Military Medical Academy (Vietnam)
	V-01	Recombinant protein vaccine	Guangdong Provincial Center for Disease Control and Prevention; Gaozhou Municipal Center for Disease Control and Prevention; Zhuhai Livzonumab Biotechnology Co., Ltd.	Phase 3	Livzon Mabpharm Inc.
	Razi Cov Pars	Recombinant vaccine (Spike protein)	Razi Vaccine and Serum Research Institute	Phase 3	Tehran Rasoul Akram Hospital; Karaj, Hesarak, Razi Vaccine and Serum Research Institute
	GBP510	Nanoparticle vaccine	SK bioscience Co., Ltd.; GSK; University of Washington; CEPI	Phase 3	Various
	CVnCoV	mRNA-based vaccine	CureVac; GSK	Phase 2b/3	CureVac
	Bacillus Calmette-Guerin (BCG) vaccine	Live-attenuated vaccine	University of Melbourne and Murdoch Children's Research Institute; Radboud University Medical Center; Faustman Lab at Massachusetts General Hospital	Phase 2/3	University of Melbourne and Murdoch Children's Research Institute; Radboud University Medical Center; Faustman Lab at Massachusetts General Hospital
	INO-4800	DNA vaccine (plasmid)	Inovio Pharmaceuticals; Advaccine	Phase 2/3	Center for Pharmaceutical Research, Kansas City. Mo.; University of Pennsylvania, Philadelphia
	No name announced	Adenovirus-based vaccine	ImmunityBio; NantKwest	Phase 2/3	
	UB-612	Multitope peptide-based vaccine	Vaxxinity	Phase 2/3	United Biomedical Inc. (UBI)
	GRAd-COV2	Adenovirus-based vaccine	ReiThera; Leukocare; Univercells	Phase 2/3	Lazzaro Spallanzani National Institute for Infectious Diseases
	SCB-2019	Protein subunit vaccine	GlaxoSmithKline, Sanofi, Clover Biopharmaceuticals, Dynavax and Xiamen Innovax; CEPI	Phase 2/3	Linear Clinical Research (Australia)
	BBV154	Intranasal vaccine	Bharat Biotech	Phase 2/3	Various

particle per one dose of vaccine. The safety and immunogenicity after a single dose, supports for further clinical development (Sadoff et al., 2020).

4.5. AZD1222

This vaccine comes under the category of recombinant vaccine/viral vectors vaccine. It was developed by Oxford vaccine trial group together with AstraZeneca. Earlier phase studies concluded the formation of spike-specific antibodies and neutralizing antibodies on 28th and 56th day respectively. Additionally, paracetamol was administered for some participants to enhance the tolerability. Pedro M et al. group used adenovirus as a vector in this vaccine and this vector carries the gene that expresses the spike protein of SARS-CoV-2. This study was registered with clinicaltrials.gov and the registration number is NCT04324606.In this study they assessed the safety, tolerability, reactogenicity and immunogenicity of the vaccine.

In this study ChAdOx1 nCoV-19Vaccine formulation compared with control vaccine that is quadrivalent conjugate meningococcal vaccine (MenACWY). This study is single blind, randomized controlled study conducted in UK at 5 clinical sites. For this study they recruited 1077 healthy adults aged 18–55 years and with no history of laboratory confirmed COVID 19 or of COVID-19-like symptoms. All the participants were randomly assigned to receive either ChAdOx1 nCoV-19 or MenACWY vaccine at the dose of 5×10^{10} viral particles as a single intramuscular injection. After the vaccine dose, Anti spike IgG response peaked on day 28 and in more than 90% of participantsneutralising antibodies, humoral and cellular immunogenicity was generated.

Local and systemic adverse events such as fatigue, headache, and local tenderness occurred commonly in a group of volunteers who have received ChAdOx1 nCoV-19. However, all these symptoms were very mild and tolerable. This study results supported that this vaccine has good safety profile and able to induce both humoral and cell mediated immunity. This encouraging result supports the large-scale evaluation of this vaccine in phase 3 trial. Phase III interventional studies were conducting among 30,000 volunteers in 20 various locations of United Kingdom.Surprisingly, on 8thof September, AstraZeneca announced that, they voluntarily paused the randomized clinical trial of AZD1222 as the volunteers developed an unexpected illness and should allow sufficient time to review the safety data (Samudrala et al., 2020).

4.6. BNT162

Another mRNA approach was observed with BNT162 vaccine, a lipid

nano formulation containing nucleoside-mRNA that encodes trimerized SARS-CoV-2 S-glycoprotein RBD developed by BioNTech. Strong RBD-binding of IgG and neutralizing antibodies were reached to maximum level after 7 days of booster dose administration. Mark J. Mulligan et al. reported the safety, immunogenicity and tolerability data from the placebo controlled, observer-blinded dose escalation studies in 45 healthy adults (18–55 years of age) (Mulligan et al., 2020). Subjects are received two doses of 10 μg, 30 μg or 100 μg separated by 21 days. Increased reactogenicity and increased immunogenicity was observed after a single dose compared to 30 μg of dose, accordingly 100 μg dose was not administered. These results support further evaluation of this mRNA vaccine candidate.

4.7. Sputnik V

On Aug 11, 2020, The Russian vaccine named Sputnik is the first approved vaccine against severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) by the Russian government. The vaccine, which is based on two adenovirus vectors, namely recombinant adenovirus type 26 (rAd26) vector and a recombinant adenovirus type 5 (rAd5) vector was developed by the Gamaleya National Center of Epidemiology and Microbiology, Russia. The phase 1/2 results have been published in The Lancet. This vaccine consisting of two components, rAd26 vector and a rAd5 vector, both these vectors are carrying the gene for SARS-CoV-2 spike glycoprotein (rAd26-S and rAd5-S). Sputnik V was prepared in two formulations namely, frozen, and lyophilised forms. They have conducted phase 1 and phase 2 studies in 38 participants each and the design of the trial was open and non-randomized. In Phase 1 each formulation was received by 9 volunteers and in phase 2, 20 volunteers received the rAd26-S and rAd5-S (Logunov et al., 2020). The primary objective of the study was to determine the safety and antigen specific humoral immunity and secondary outcome was to measure the antigen-specific cellular immunity and change in neutralizing antibodies. As per their findings both the vaccine formulations were safe, well tolerated and shown only very common side effects. In phase 2, 85% of participants had detectable antibodies at 14 days after the priming dose, rising to 100% by day 21, with substantial titre rises after the boosting dose. All the participants who were treated with the formulations were produced both humoral and cell mediated immunity. Based on these findings Russian government and regulatory agencies has given approval for this vaccine to release into the Russian market for the common public.

However, scientific fraternity and regulatory agencies concerns that without the results of phase 3 study the approval is premature. Also, few scientists are stating that data on immune response alone would not generally be an adequate basis for approving a vaccine and "Immune response might not be directly proportional to the degree of protection.

Vaccine development is an organized, tedious, and long-run process, which usually takes around 10 years for the successful development. Nevertheless, researches and the developers are facing numerous challenges in diverse fronts, like regulatory constraints, time and worsening of disease, scale up as per the demand etc., that seems to be difficult to meet (Lv et al., 2020). A different line of trouble can be recognized, in producing large number of doses and their distribution among the worldwide population as it may require well-coordinated activities that should run in parallel (WHO Ebola Response Team, 2016). Impediment in vaccine distribution can results in several consequences as illustrated in 2013/14 Ebola epidemic in West Africa, which killed around 11,000 people along with economic burden over 53 billion dollars (Huber et al., 2018). The first vaccine was approved by FDA in 2019, after 43 years of Ebola viral outbreak. Tragically, the SARS 2003 epidemic was ended prior to complete vaccine development. All these challenges can result in accretion of invested resources, that finally elevates the financial risk. Consequently, several funding agencies diverted the allocated funds, leaving the manufacturers with huge financial loss. On September 4th' 2020, The WHO (World Health Organization) insist that it would never approve a vaccine that has not established its safety and effectiveness, amid concern in the hurry to develop the COVID-19 vaccine. Safety, efficacy, and potential adverse effects of currently used COVID-19 vaccines were summarized in Table 4.

5. Recent patents filed connected to COVID-19

5.1. Technological prospection

The present section confers on latest patents filed, connected with various applications in the management/preventing COVID-19. Excavation of patent portfolios was retrieved from The Lens (Free, open patent and scholarly search) portal. Database was searched with keywords a) [Title: COVID or Abstract: COVID or Claims: COVID]orb) [Title: Corona or Abstract: Corona or Claims: Corona] and Filters [Patent filed date (December 1, 2019–September 31, 2021)].A total of 202 patents were found in the database, but many of them are on basis of corona treatment, which is high frequency discharge that can augment the adhesion of plastic surfaces. Subsequently, we filtered these patents as they were out of the present scope of study and thus, selected 35 patents, which were having the application with respect to the COVID-19. Furthermore, we removed the patents which were not filed in English languages and duplicate patents. The short-listed patents are described in Table 5, (Patent analysis (COVID-19), 2020) which contains basic details like, Jurisdiction (country of protection), Classification, Publication number, Title, Applicants and Inventors.Of all these, majority of the patents (14) were filed from United Kingdom (UK) Jurisdiction. Country wise sharing of these patents were depicted in Fig. 5.

5.2. Expert opinion

5.2.1. Classification of patent and concordance

Patent classification in the process of a grouping of patents as per their technical features. Earlier this was used only for the sorting of documents. The most accurate and finest way to search for patents is through their technical classification. There are numerous classifications used in many countries and this can be because of their own/independent patent laws. So, to consolidate patents, all the countries came together and formed a common code. These were mainly classified as CPC (Cooperative patent classification) and IPC (International patent classification). CPC came into action from Q4 of 2010 as an extension of IPC and managed by USPTO and EPO. CPC and IPC classifications were compared in Table 6.

Majority of the patents filed (15) were belongs to class A, contains patents related diagnosis, surgery, identification, analyzing, and biological material, etc. Subsection, A61P deals for the inventions for RNA viruses. Few subsections like A61K and A61L covers the preparations for medical, dental, or toilet purposes or pharmaceutical compounds or materials for deodorisation/disinfection/sterilisation of surgical materials or compositions thereof. Smoke or soap bubble toys used for producing smoke images were represented in the sub-class A63H. It was observed that, G01 N class occupies the subsequent place, which comprises measuring or testing process involving enzymes or microorganisms other than immunoassay and this was followed by G06 subclass, dealing with organisational models like scheduling, planning or allocating time or utilizing human of machine resources. Few patents were filed under C12Q class [synthesis of nucleic acids for analysis with precedence to polymerase chain reaction and colony counters etc] and G16H [covering healthcare informatics to handle or process the healthcare or medical data]. Fig. 6 shows the filed patents distribution among IPC classifications.

Since December 2019 to till date, numerous inventions were filed to receive intellectual protection on different strategies as shown in Fig. 7. No comprehensive literature has been published, in listing out all these recent patents filed in relation with COVID-19, that the present section intends to.

Table 4
Efficacy and potential adverse effects of COVID-19 vaccines.

Name	Company/ developer	Platform	Efficacy against symptomatic COVID-19 in clinical trials	Storage requirements	Common side effects	Rare adverse effects
BNT162b2	Pfizer/BioNTech	mRNA	95% (95% CI 90–98) after median of 2 months follow-up 91% (95% CI 89–93) after median of 6 months follow-up	Ultracold freezer (−90 to −60 °C) then freezer (−25 to −15 °C) for up to 2 weeks cumulative time then refrigerated (2–8 °C) for up to 1 month	Local injection site reactions Systemic symptoms (fevers, chills, fatigue, myalgias, headache)	Anaphylaxis (approximately 5 per million) Myocarditis/pericarditis (approximately 16 per million among 16–39 year olds)
mRNA-1273	Moderna	mRNA	94% (95% CI 89–97) after median of 2 months follow-up	Freezer (−25 to −15 °C) then refrigerated (2–8 °C) for up to 30 days	Local injection site reactions Systemic symptoms (fevers, chills, fatigue, myalgias, headache)	Anaphylaxis (approximately 2.8 per million) Myocarditis/pericarditis (approximately 16 per million among 16–39 year olds)
Ad26.COV2.S	Janssen/Johnson & Johnson	Replication-incompetent adenovirus 26 vector	67% (95% CI 59–73) against moderate to severe COVID-19 after median of 2 months follow-up	Refrigerated (2–8 °C)	Local injection site reactions Systemic symptoms (fevers, chills, fatigue, myalgias, headache)	Thrombotic complications associated with thrombocytopenia: For females 30–39 years old: 12.4 cases/million For females 40–49 years old: 9.4 cases/million For females in other age ranges and males: 1.3 to 4.7 cases/million Guillain-Barre syndrome (approximately 8 cases/ million)
ChAdOx1 nCoV-19/ AZD1222	AstraZeneca/ University of Oxford/Serum Institute of India	Replication-incompetent chimpanzee adenovirus vector	70% (95% CI 55–81) after median of 2 months follow-up	Refrigerated (2–8 °C)	Local injection site reactions Systemic symptoms (fevers, chills, fatigue, myalgias, headache)	Very rare thrombotic complications associated with thrombocytopenia: Cerebral venous sinus thrombosis (169 of ≈34 million) Splanchnic vein thrombosis (54 of ≈34 million) Guillain-Barre syndrome (227 cases/51 million)

5.2.2. Patents filed on diagnostic assays

Xu Teng, projected a patent on application of COVID-19 infection host marker. The gene expression difference between a COVID-19 positive patient and a COVID-19 negative patient is analyzed, an obtained gene with differential expression is used as the host marker. The most marker comprises any one of the following genes of RNR1, MFSD11, SYNE3 and SLC10A3 and this can be successfully used to prepare COVID-19 infection detection reagent or detection equipment. In another invention, device and method for screening of COVID-19 drugs were disclosed. Sequence and structure similarity information between viruses and pharmaceutical chemical structure was constructed using walkalgorithm to develop a screening model. This can be effectively used in reducing the development cost, enhancing the screening speed and accuracy. Cogley Thomas Paul, invented a device for the detection of Covid-19. The device consists of scintillator, which maximizes the light emissions positioned to a patient and produces light image of that patient on the screen with the help of a camera in operative proximity to the scintillator screen. Additionally, this was connected to a computer with specific software to capture and analyze the light images, followed by diagnosis for treatment of patient.

Patent CN 111060691 A, discloses a fluorescence immuno chromatography device for detecting a novel coronavirus COVID-19 and stated device is strong in specificity, high in sensitivity, strong specificity and short detection time (10–15 min). The invented device can be used in diverse places such as disease control centers, hospitals and airports etc. In another invention, COVID-19 nucleic acid testing method was applied, and the virus detection can be judged as per the obtained fluorescence signal data. This method can be helpful in monitoring all the stages of infection and capable of escalating the accurate rate. Drozd Sergej Feliksovich patented the method for detecting SARS-COV-2 coronavirus by polymerase chain reaction using synthetic oligonucleotide primers.

5.2.3. Patents filed on treatment strategies

Suzhou Aoteming Pharmaceutical Tech Co Ltd, invented mVSV virus vector vaccine, which comprises of a) Heterologous antigen which can fuses or embeds with the target virus between L and G genes of mVSV vector and b) antigen that can envelop or embeds the antigen that encoding the target virus.Another patent was filed on basis of proposed therapy in reducing the effects of viral infections. The inventors disclosed that combination of vitamin supplements and lifestyle changes etc., can lessen the impact of several virus infections. US 2020/0179367 A1 described that administering a pharmaceutical formualtion containing isomyosmine can reduce the oxidative stress, inhibit mitochondrial reactive oxygen species (mtROS) and thus can help in treating of coronavirus. Covid-19 Suitable Triple Knockout Dnai oligomer remedy was developed by Kim seung chan, which contains the single strand DNA coupled with three parts and transported by liposome to remove the virus genome. Lachlak Nassira developed a probiotic from immunised cows by transferring the natural passive immunity to treat COVID-19. Immunised cows produced colostrum, rich in anti-SARS-COV-2 IgG antibodies. Produced colostrum can be stored using simple cold lyophilisation technique to keep 99% of antibodies viable. Patients recovered by these probiotics are developed these antibodies, that can be evident from serological tests.Application of macleaya cordata benzylisoquinoline alkaloid and resveratrol composition was invented and filed the patent by Jin xiaofei. The foresaid composition has exceptional binding activity in coronavirus related protein target and expected to become a key

Table 5
Patents filed on COVID-19/corona virus from December 2019 to till date.

S. No	Juris-diction	Kind	Publication Number	Title	Applicants	Inventors
1	CN	A	CN 111041089 A	Application Of Covid-19 Infection Host Marker	Guangzhou Vision Gene Tech Co Ltd	Xu Teng
2	CN	A	CN 111081316 A	Method And Device For Screening Candidate Drugs For Covid-19	Geneis Tech Beijing Co Ltd	Peng Lihong
3	US	A1	US 2020/ 0214649 A1	Detection of Covid-19	Cogley Thomas Paul	Cogley Thomas Paul
4	CN	A	CN 111060691 A	Fluorescence Immunochromatography Device For Detecting Covid-19 And Using Method Thereof	Shenzhen Bioeasy Biotechnology Co Ltd	Zhou Hongwei
5	CN	A	CN 111024954 A	Colloidal Gold Immunochromatography Device For Combined Detection Of Covid-19 Antigen And Antibody And Use Method Thereof	Shenzhen Bioeasy Biotechnology Co Ltd	Chen Yiyao
6	CN	A	CN 111074008 A	Covid-19 (coronavirus Disease, 2019) Nucleic Acid Testing Method Capable Of Increasing Accurate Rate	Nanjing Synthgene Medical Tech Co Ltd	Tong Kun
7	CN	A	CN 111088283 A	Mvsv Virus Vector And Virus Vector Vaccine, And Covid-19 Vaccine Based On Mvsv Mediation	Suzhou Aoteming Pharmaceutical Tech Co Ltd	Qin Xiaofeng
8	AU	A4	AU 2020/ 101189 A4	Green Human Resource Management Practices Framework For Healthcare Organizations Under Stressful Covid-19	A Velsamy Mr	
9	AU	A4	AU 2020/ 100400 A4	Proposed Therapy To Reduce Effects Of Viral Infections (may Help With Covid 19) 16 Mar. 2020	Thompson Edgar	Thompson Edgar Geoffrey
10	GB	D0	GB 202004993 D0	Covid-19 Control	Enterobiotix Ltd	
11	GB	D0	GB 202005556 D0	Covid Face Mask	Aga Nanotech Ltd	
12	GB	D0	GB 202007366 D0	Covid-19 Washable Mask	Prabdial Yakeen	
13	GB	D0	GB 202007652 D0	Compounds For Treating Covid-19	Katholieke Univ Leven	
14	US	A1	US 2020/ 0179367 A1	Method Of Treating Coronavirus	Mymd Pharmaceuticals Inc	Williams Jonnie R
15	GB	D0	GB 202005097 D0	Treatment And/or Prevention Of Covid-19 Infection	Mead Johnson Nutrition Co	
16	GB	D0	GB 202003632 D0	Sars-cov-2 (sars2, Covid-19) Antibodies	Harbour Antibodies Bv	
17	KR	A	KR 20200032050 A	Covid-19 Knockout Dna Covid-19 Suitable Triple Knockout Dnai Remedy	Kim Seung Chan	Kim Seung Chan
18	GB	D0	GB 202003869 D0	Method To Cure The Patients Of Covid-19 By Using Co2 In Special Rooms	Zaki George Abdel Messih	
19	GB	D0	GB 202003870 D0	Method To Cure The Patient Of Covid-19 By Using Ozone In Special Rooms	Zaki George Abdelmessih	
20	GB	D0	GB 202008314 D0	Chemical Compounds For Use In The Therapy Or Prohylaxis For The Medical Condition Covid-19	Sheridan Richard John	
21	GB	D0	GB 202005536 D0	Space-time, 4-d Forces, 4-mechanics For Developing An Antibiotic For Covid-19 Corona Virus & Free Body Diagram	Moaqat Tarek Nadim Mahmood	
22	NO	A1	NO 20200436 A1	System And Method For The Removal Of Alveolar (thorax) Fluids In Patients With Infectious And/or Virus Diseases (Covid-19)	Modi Vivendi As	Myhr Gunnar
23	GB	D0	GB 202007897 D0	Essential Oil Formulation And Method For Delivery Through A Nebulizer For Use In Covid-19 And Other Upper Respiratory Tract Infections	Havercroft Nicholas Anthony	
24	WO	A2	WO 2020/ 143892 A2	Probiotic Which Cures Covid 19 Patients By Transfer Of Natural Passive Immunity From Immunised Cows	Lachlak Nassira	
25	AU	A4	AU 2020/ 100564 A4	Coronavirus Impact On The World Economy Problems Solving: I Invent The Equation For Solving The Forecast Of Number Of Covid-19 Cases In The Future So To Help A Country Can Re Open The Business As Early As Possible In The Minimizes Of Covid-19	Phan Hung Thanh Mr	Phan Hung Thanh
26	GB	D0	GB 202003829 D0	Permanently Removing Nitrogen Dioxide, Carbon Particlulates And Covid 19 From The Air That We Breath Along With Other Viruses That Cause Respiratory Problems	Fordham Joseph Henry	
27	CN	A	CN 110960532 A	Anti-coronavirus Macleaya Cordata Benzylisoquinoline Alkaloid And Resveratrol Composition And Application Thereof	Jin Xiaofei	Jin Xiaofei
28	AU	A4	AU 2020/ 100641 A4	Quadruple Regime Using Azithromycin 500 mg Daily Plus Vitamin C Gram Twice Daily Plus Zinc 500 mg Daily Plus Low-dose Aspirin 100 mg Daily For 12 Weeks To Be Used As Prophylaxis To Prevent Covid-19 Virus/Corona Virus/ Sars Covid 2 Virus Infection In Nursing Home/Aged Care Population In Illawarra Region Nsw Australia.	Balasubramaniam Vaidyanathan Dr	
29	AU	A4	AU 2020/ 100453 A4	Disinfectant Bomb - Disinfectant Dispersal System For Small, Medium And Large Areas. Disinfectant Slow Release Spray For All Modes Of Transport, Homes And Offices.	Giumelli Colin Boyd Mr	Giumelli Colin Boyd
30	GB	A	GB 2580006 A	Bubbles For Air Decontamination	Michael Anthony Holmes	Michael Anthony Holmes
31	GB	D0	GB 202006266 D0	Bubbles For Air Decontamination	Holmes Michael Anthony	
32	RU	C1	RU 2727054 C1	Method For Detecting Cdna Of Sars-cov-2 Coronavirus Using Synthetic Oligonucleotide Primers In Polymerase Chain Reaction	Drozd Sergej Feliksovich	Drozd Sergej Feliksovich
33	US	A1	US 2020/ 0231128 A1	Apparatus And Systems With Timer For Air-borne Cleaning Of Surfaces	Nuvinair Llc	Bailey Kyle

(*continued on next page*)

Table 5 (*continued*)

S. No	Juris-diction	Kind	Publication Number	Title	Applicants	Inventors
34	US	A1	US 2020/ 0237689 A1	Prevention And Treatment Of Coronavirus And Other Respiratory Infections Using Nanoemulsion Compositions	Bluewillow Biologics Inc	Peralta David
35	KR	A	KR 20200063275 A	Corona Virus Prevention And Treatment Drugs	Choi Gi Eun	

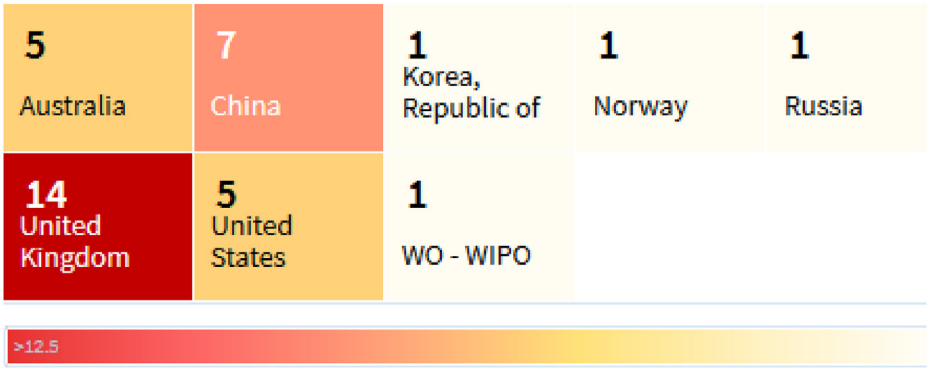

Fig. 5. Heat map of country-wise patents filed on COVID.

Table 6
Patent classifications along with entity.

CPC Classification Section	Entity	IPC Classification Section
A	Human necessities	A
B	Performing operations transporting (notes & warnings)	B
C	Chemistry metallurgy (notes & warnings)	C
D	Textiles paper	D
E	Fixed constructions	E
F	Mechanical engineering lighting heating weapons blasting (notes & warnings)	F
G	Physics (notes & warnings)	G
H	Electricity (notes & warnings)	H
Y	Tagging of new technological developments	–

Fig. 6. Word count representation of patents distribution among IPC classifications.

ingredient in preparing anti-corona drugs. Balasubramaniam

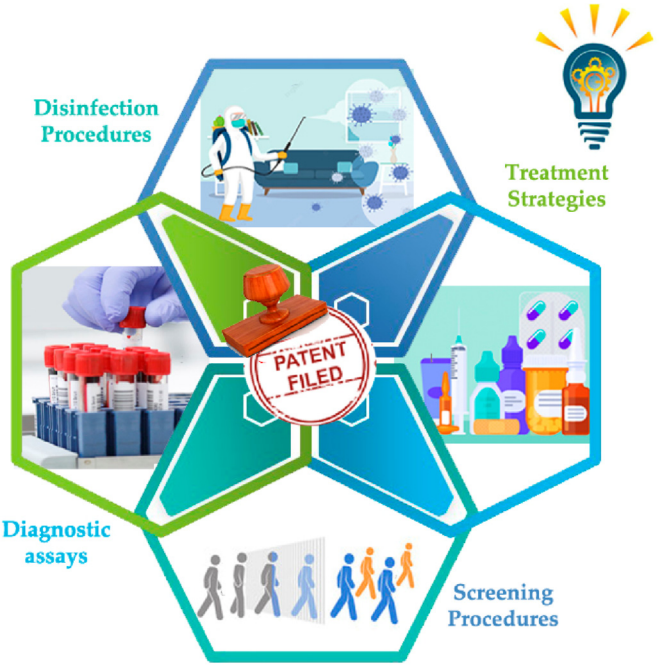

Fig. 7. Different strategies in patents filed related to COVID-19.

vaidyanathan invented that quadruple regimen consists azithromycin (500 mg Daily), vitamin c (1 Gram Twice Daily), zinc (500 mg Daily) and aspirin (100 mg Daily), for 12 weeks can acts as a prophylaxis in preventing COVID-19 infections.

5.2.4. Patents filed onscreening and disinfection procedures

Disinfectant Bomb, was invented to disinfectant commercial areas and also helps in slow release spray for homes, offices and all modes of transports. Similar invention was developed to decontaminate the air using soap bubbles, comprising a solvent, surfactant (sodium laury/laureth sulphate) and evaporation suppressant (glycerol/polyethylene glycol). Moreover, the process can be handled by connecting to wired or wireless devices to deliver or cease the production of soap bubbles.In

another invention, apparatus and systems for cleaning of surfaces especially in an enclosable environment was described. The device or container spells out an air borne spray, spreads throughout the closed area and contact with the surfaces to be sterilized. The enclosableenvironment is maintained closed for an effective disinfection.

Majority of the researchers were focused not only on the treatment strategies and but also on diagnostic and disinfection devices, as evident from the above patent data. As the efficient diagnostic system helps for quick detection and isolation of COVID-19 effected patents, accordingly, mitigate the spread of the disease. Additionally, these tests can help to improve the understanding the virus spread and effectiveness of control measures. Health authorities throughout the world, are struggling to limit transmission of coronavirus. Disinfection is one of the suitable approaches. Disinfection will not reduce the spread of COVID-19, but also plays a significant role in flattening of the curve. Several inventors were filed the patents on all these strategies. Application of all these principles or methods can be effectively prevents/manage the current pandemic.

6. Potential influence of novel virus variants on the therapeutic approach

SARS-CoV-2, right from its onset, has shown multiple new variants of concern that made the therapeutic approach more complicated. Even the vaccine efficiency is encountered as a challenge with the changing variant of concerns. Due to the shared mutations in spike proteins mostly on S1 unit, there is a higher transmissibility rate and alter the viral virulence and clinical outcome. Even the mutations in non-structural proteins also became a challenge for researchers towards their vaccine development or therapeutic strategies. Several variants like alpha, beta, gamma, and delta are becoming complicated towards the management of patients. Hence, a combination of therapeutic strategies against viral cycle as well as immune host responses are in current trends (Khateeb et al., 2021).

7. Conclusion

COVID-19 cases are rising day by day due to release of lockdown and community spread. Cumulative death factor is increasing across the globe. Several scientists are working for development of diagnostics, vaccines, drugs and struggling to understand the disease conditions. Comorbid diseases are noted as more favourable conditions for easy spread and severity of coronavirus infection. Throughout the world, so many countries are involved in the drug discovery and development either as industries, academia, research institutes, or collaborations. Till date, no vaccine or drug has been discovered or developed. Drug repurposing is the only symptomatic remedy as of now with emergency use authorizations of some existing drugs. The present review helps researchers or individuals or health workers to understand and know about the severity of disease, vaccine development status, patents filing and clinical trials progress, and available inline treatment strategies.

Conflict of interest

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CRediT authorship contribution statement

G.S.N. Koteswara Rao: Resources, Writing – original draft, Formal analysis. **Buduru Gowthami:** Resources, Writing – original draft. **N. Raghavendra Naveen:** Conceptualization, Resources, Writing – original draft, Formal analysis, Project administration. **Pavan Kumar Samudrala:** Conceptualization, Validation, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interestsor personal relationships that could have appeared to influence the work reported in this paper.

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