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Patent intelligence of RNA viruses: Implications for combating emerging and re-emerging RNA virus based infectious diseases

Pratap Devarapalli^{a,1}, Pragati Kumari^{b,1}, Seema Soni^c, Vandana Mishra^d, Saurabh Yadav^{e,*}

^a University of Tasmania, Centre for Law and Genetics, Faculty of Law, Hobart, Australia

^b S-02, Scientist Hostel, Chauras campus, Srinagar Garhwal, Uttarakhand 246174, India

^c Queensland University of Technology, Faculty of Law, Brisbane, Australia

^d A-206, Twin Tower, AWHO, Greater Noida, UP, India

^e Department of Biotechnology, H.N.B. Garhwal University (A Central University), Srinagar (Garhwal) 246174, Uttarakhand, India

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ABSTRACT

The recent outbreak of one of the RNA viruses (2019-nCoV) has affected most of the population and the fatalities reported may label it as a modern-day scourge. Active research on RNA virus infections and vaccine development had more commercial impact which leads to an increase in patent filings. Patents are a goldmine of information whose mining yields crucial technological inputs for further research. In this research article, we have investigated both the patent applications and granted patents, to identify the technological trends and their impact on 2019-nCoV infection using biotechnology-related keywords such as genes, proteins, nucleic acid etc. related to the RNA virus infection. In our research, patent analysis was majorly focused on prospecting for patent data related to the RNA virus infections. Our patent analysis specifically identified spike protein (S protein) and nucleocapsid proteins (N proteins) as the most actively researched macromolecules for vaccine and/or drug development for diagnosis and treatment of RNA virus based infectious diseases. The outcomes of this patent intelligence study will be useful for the researchers who are actively working in the area of vaccine or drug development for RNA virus-based infections including 2019-nCoV and other emerging and re-emerging viral infections in the near future.

1. Introduction

Owing to the emerging and re-emerging diseases, viral infections pose an ever-increasing threat to the humankind [1]. RNA viruses cause respiratory infections that range from the common cold to severe illness, even death in humans. Specifically, infections caused by RNA viruses are more harmful as RNA viruses interact with the human proteins that function both in cellular specific processes and in intracellular transport within the cell [2]. Some of the major RNA virus infections include Severe Acute Respiratory Syndrome (SARS), Middle East Respiratory Syndrome (MERS) and Human immunodeficiency virus (HIV) [3]. Rise in infections caused by RNA viruses has led to the increase in active research in the field of genetic engineering, biotechnology, and other emerging omics technologies, for advanced diagnosis, treatment and vaccine development [4]. Due to commercial interests, the intensity of research on RNA viruses has been coupled with the strategic approaches

to protect the intellectual property (IP) emerged from the R&D conducted on RNA viruses [5]. Specifically, research organisations and commercial entities, are proactive to protect the advanced technologies using IP instruments such as patents and trade secrets etc., due to the commercial interests and impact of the novel technologies in the diagnosis and treatment of viral infections [6]. Patents are one of the important IP instruments that provides protection to patentable intellectual assets for a specified period (20 years) and grants exclusive monopoly rights.

Emerging RNA infectious diseases such as COVID-19 and prospects of its re-emergence at different time interval posed immense fatalities across globe [7]. The confirmed cases of COVID-19 were reported around 12 billion and deaths associated was around 6 million as per world data by August 2022 [8]. Considering this recent outbreak which is again a RNA virus based infection, a patent intelligence analysis helps in early policy-making processes like licensing, merging or trading

* Corresponding author.

E-mail address: saurabhyadav40@rediffmail.com (S. Yadav).

¹ Equal contribution.

towards a more informed path to take up arms against such pandemic [9]. Patents are important for the technological growth of any country and the world [10]. Patent directly aims at commercial value and has competing interests under non-pandemic period but after the onset of pandemic or global medical emergency, human benefits must outweigh patent monopoly rights. Innovation metrics may be assessed by patents in the life science sectors and always serve as a bedrock for futuristic technologies specially in healthcare industries [11]. A patent landscape helps in providing potential information about existing important inventions having techno-commercial value in a given technology bracket and provides deep insights about the past, present inventions and related modifications to crucial lacunae and potential thrust areas [12]. The patent landscape study involves three main stages viz. performing searches as per design, data mining [13] and data analysis and interpretation [14]. Similar patent intelligence analysis related to the implication of genetic engineering in ethanol production, induced pluripotent stems cells, and wound healing were previously reported and provided insights on the impact of patent research on advanced technologies [15–17].

Considering the recent advancement of RNA virus research and patent activity, the aim of this study was to capture pre-defined patent documents to critically investigate various facets employable for efficient vaccine or drug development. In this study, extensive analysis of patent applications and granted patents was executed, with main focus on genes, proteins, related genetic engineering and biotechnological technologies that are directed towards diagnosis and treatment of RNA virus infections. The nucleic acid-based vaccines are safer and stable in addition to eliciting a potential immune response. Considering this, our study was focused on patent analysis of RNA viruses and underlined the global patent situation utilizing the available patent information on RNA viruses in public domain. The outbreak of COVID-19 pandemic made IP area as a hotbed both for competing to file a patent and also to derive meaningful information from the previous patent documents [18]. The technological trends provided in this study would be useful to the researchers who are actively working in this area by exploiting the useful insights which would assist them to avoid the gaps to reach the destined research goals. The technological forecasting thus serves as a first-hand information for IP managers to avoid unproductive investments. Specifically, our patent analysis is exclusively related to biotechnological research with a specific focus on genes and proteins associated to RNA virus based infectious diseases. The results of our analysis will be useful in the years to come, till the global fight for RNA based viral infections goes on.

2. Methodology

Considering the objectives of this research, a precise research methodology was developed to specifically retrieve patent applications and granted patents with the subject matter related to RNA virus and their biotechnological implications with specific focus on important genes and proteins, biotechnology and genetic engineering. The research methodology of this study was further elaborated in specific steps below.

2.1. Designing search strategy

The initial phase of methodology included development of a search strategy with specific keywords that are related to RNA virus and 2019-nCoV. The range of year was from 1979 to 2020. Specifically, the keywords are selected to retrieve patent applications with subject matter related to diagnosis and treatment of RNA virus based infectious diseases appearing in the title, abstract and claims (TAC) of the patents. Search strategy increases the integrity of the patent analyses. The details of designed search strategy used to retrieve patent applications for patent intelligence analysis is provided in [Table 1](#).

Table 1

Details of search strategy designed to retrieve patent applications directed towards biotechnological and/or genetic engineering implications of RNA viruses.

Patent search strategy	TAC: (((Corona AND Virus) OR (COVID)) AND ((gene*) OR (RNA) OR (protein*) OR (spike protein) OR (ORF)))
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2.2. Conducting patent search

Patent data related to different patent applications and granted patents of different jurisdictions has been widely spread in different open access patent databases as well as subscription-based patent databases. Both the patent applications and granted patents that we have analysed in this study were retrieved from a combination of both the open access and subscription-based databases such as Google patents, Espacenet, Patentscope and PatSeer. The designed search strategy was then used to retrieve the most relevant patent applications and granted patents (in the above provided databases) with subject matter directed towards RNA virus and their biotechnological implications with specific focus on important genes and proteins.

2.3. Deduplication and refinement of search results

The next step in the methodology included deduplication and refinement of retrieved patent applications and granted patents. In light of this, the data that was retrieved using specific search strategy from above specified databases was deduplicated and manually analysed/curated to exclude irrelevant patent documents. The initial search strategy retrieved a total number of 453 patent applications and granted patents in which 131 patent documents have been identified as irrelevant to the scope of this study.

2.4. Manual curation of retrieved patent data

Manual curation was used for the analysis as and when required, to delete/remove irrelevant patents and to be assured that any important and significant patent is not screened out. Once the initial steps of deduplication, refinement and screening was completed, a total number of 322 patent applications and granted patents were selected for further analysis. These 322 patent applications and granted patents were further manually analysed to identify the genes and proteins that have been actively researched and are related to the diagnosis and treatment of RNA virus infections. Specifically, the manual patent analysis of 322 patent applications and granted patents were processed using spread sheets as in Supplementary Information 2.

2.5. Analysis and visualisation

In the later steps, the data retrieved from the manual patent analysis was analysed using Vantage point patent analysis software [19]. Vantage point is a data mining software application that offers a comprehensive set of powerful tools for refining, analysing, and reporting for scientific, technical, market, and patent information [19]. Vantage point was specifically used for this study to identify the percentage of patent applications and granted patents, types of claims, country coverage, most cited CPC classifications, patent filing trend, legal status, technology keywords and top assignees etc.

3. Results and discussion

3.1. Patent application and publication trends

The patent data retrieved has been analysed in multi-dimensions to make sure all-important aspects of the RNA virus related research with genes, proteins, and biotechnology terms were covered. Specifically, the patent application and publication trend analysis revealed the huge

increase of patent application filings during the years 2002 to 2004 and corresponding patent publications in the year 2007 (Figs. 1, 2). This increase of patent filings related to RNA virus research during the years 2002 to 2004 was due to the emergence of SARS infection around the globe in the same period [20]. The insights of patent application and publication trend analysis also indicate that the patent filing trend has been gradually reduced after 2004 and this may be due to the reduction of number of infected individuals around the world thereby shifting the focus of RNA virus related research. This information is an obvious reflection of less investment and decreased commercial interests in RNA virus related research [21]. The filing activity saw steep increase in the area of infectious diseases and cancer in the last few years, but patent applications related to infectious diseases outnumbered to those for cancer in last three years. The possible correlation for this focused patent filing in the arena of infectious diseases may be due to recent fatal infections by RNA viruses, thereby developing interest in vaccines [5].

Further patent analysis of retrieved patent data revealed that around 75 % of patent data include patent applications and 24 % includes granted patents applications (Supplementary Fig. 1). This indicates that the patent grant rate is only 1 in 4 patent applications. Geographical distribution analysis of patent data revealed that patent applications and granted patents related to RNA viruses were mostly filed in United States (15 %) and European Union (14 %). Similarly, Japan and Australia share a percentage of 12 % each followed by Canada and China sharing 11 % each (Fig. 3). Taking into account the results from geographical distribution analysis, it is pertinent to emphasise that the US and EU are more actively involved in RNA virus based research followed by patent filing reflecting the commercial interest due to the health care businesses in those jurisdictions in comparison with the other countries around the world.

3.2. Technological trends

Technological classification analysis of patent data using available cooperative patent classifications (CPC) codes identified that most of the patent applications and granted patents related to RNA virus are classified under “Medicinal preparations containing antigens or antibodies” (A61P31) and specifically related to antivirals and anti-infectives followed by “Peptides having more than 20 amino acids” (C07K14) and

“Genetic engineering inventions related to Viruses; Bacteriophages; Compositions thereof; Preparation or purification thereof” (C12N7) (Fig. 4). Insights from the CPC classification analysis indicates that most of the patents in specific period focus on different techniques and products related to vaccine development as products and methods claiming medicinal preparations containing antigens or antibodies are mostly related to vaccine development [22]. The CPC classification analysis also displayed that most of the patent applications and granted patents claim technologies related to peptides or proteins, indicates that most of the research is focused on peptide based vaccine development against different types of infections caused due to RNA viruses [23,24]. Additionally, the results also indicate that most of the patents disclose use of genetic engineering technologies to develop techniques for diagnosis and treatment of infections caused due to different types of RNA viruses [25].

The technological analysis of patent data was carried out by analysis of technological keywords contained in patent documents. The cluster analysis of technological keywords revealed terms having highest frequency of co-occurrence in most of the patent applications such as “Spike protein in 62 patents” distantly followed by other keywords such as “Nucleic acid”, “RNA virus”, “Expression vector”, “Viral infection”, “Corona virus” and “SARS Corona virus” (Fig. 5). Spike protein is one of the major proteins to diagnose and treat the infections of RNA viruses [26]. The Spike protein of the new variant of coronavirus “2019-nCoV” which is a RNA virus has also been majorly researched [27]. The insights from the technology cluster analysis has also supported that most of patent applications and granted patents filed, published and granted during specific period are focused towards Spike protein which strengthens the argument of Spike protein and its variants being one of the potential targets for vaccine development and will act as therapeutic advances for any emerging viral infections [26]. The technology cluster analysis revealed the terms such as “Viral infection”, “Corona virus”, “SARS Corona virus” and “RNA virus” which indicate that most of analysed patent documents are focused on infections caused due to Coronavirus. SARS in 2002, MERS in 2012, nCoV-19 in 2019 were reported during 21st century and are some of the major viral infections related to the class of Corona viruses (which are basically RNA viruses) [28]. The research on diagnosis, treatment and vaccine development related to any particular variants of RNA viruses, has been intense in the

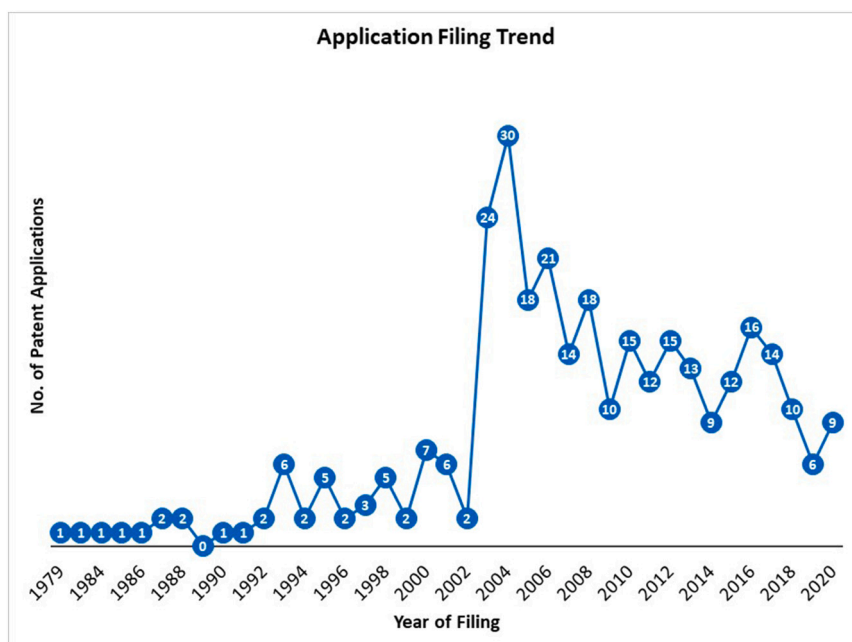


Fig. 1. Graphical visualisation illustrating the filing trend of patent applications related to RNA viruses.

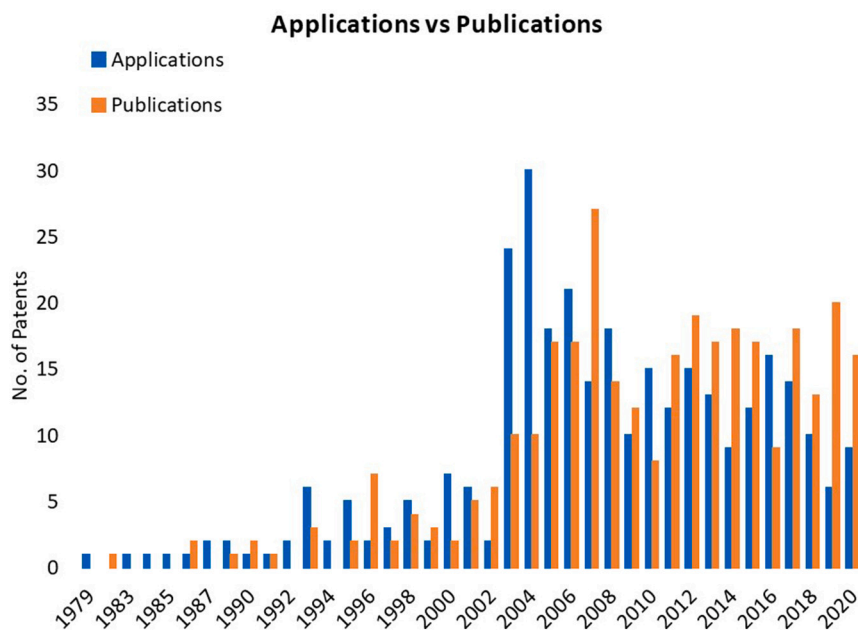


Fig. 2. Patent application and publication trend related to RNA virus patent applications and granted patents.

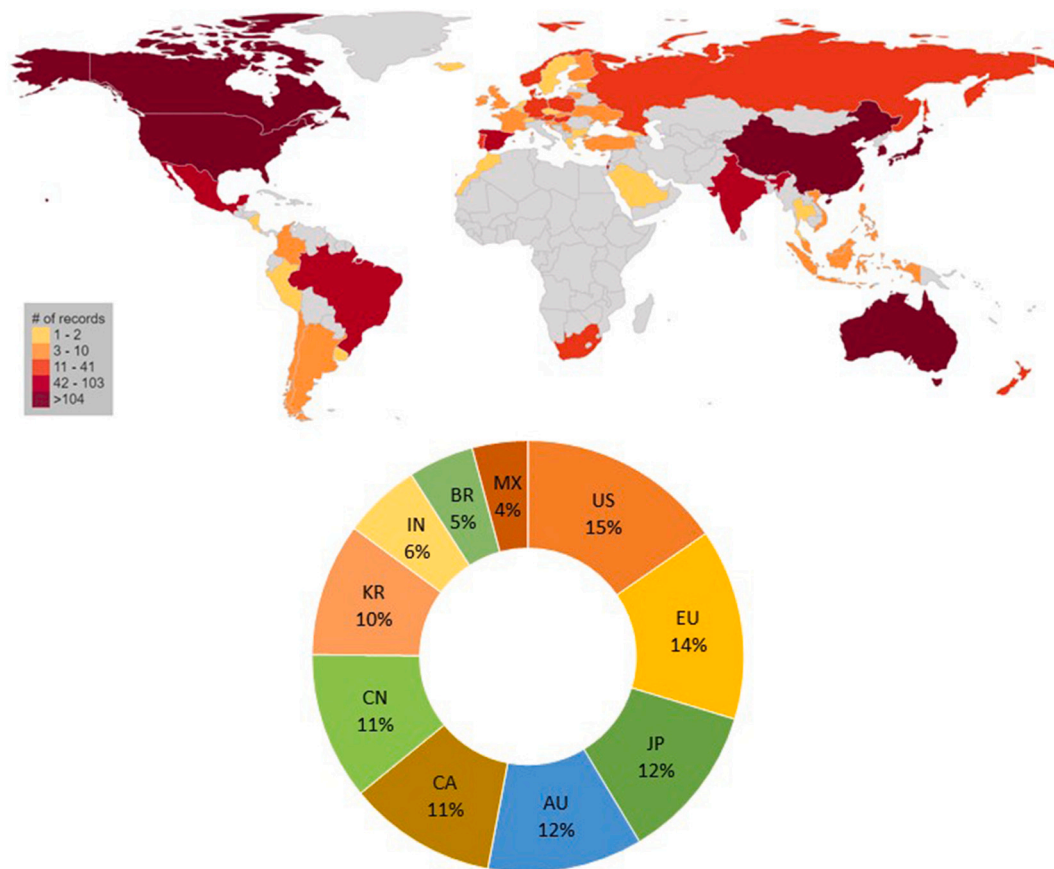


Fig. 3. Geo-distribution analysis of patent applications and granted patents related to RNA viruses.

past few decades [29]. In light of this, there is an increase in the commercial interests of major pharma companies, academic institutions in patenting relevant genetic engineering technologies with patent claims related to specific variants of RNA viruses [30].

3.2.1. Key genes and proteins

The technological analysis was also focused on identifying the key genes and proteins which were significant in this study. The results of patent analysis specific to the genes and proteins used in RNA virus research revealed that most of the biotechnology and/or genetic engineering research related to RNA viruses were conducted using Spike

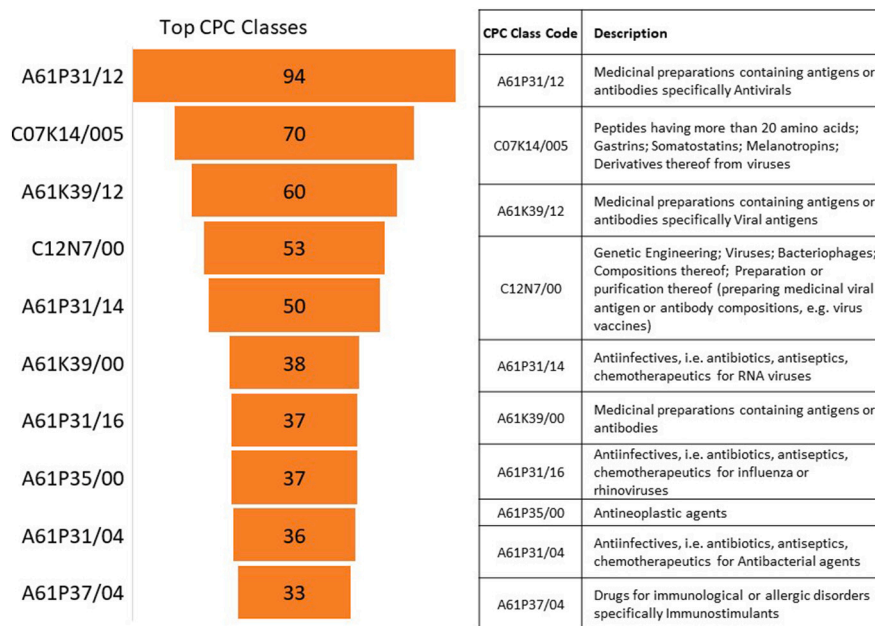


Fig. 4. A funnel representation illustrating the most cited CPC classification codes in the patent applications and granted patents related to RNA viruses.

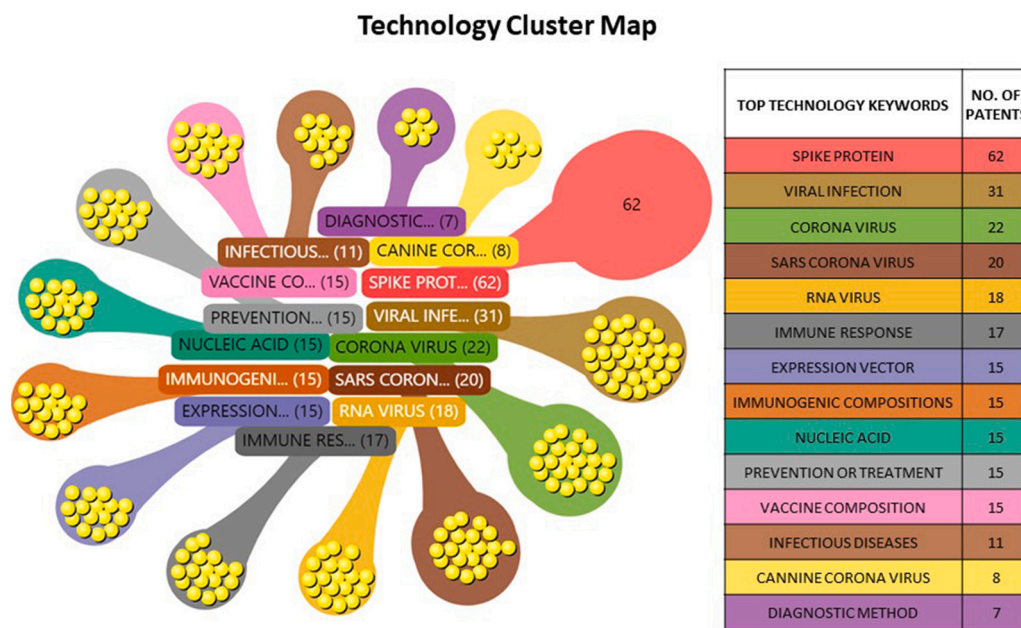


Fig. 5. Technological cluster map illustrating the top keywords used in the patent applications and granted patents related to RNA viruses.

protein (S gene), followed by Nucleocapsid protein (N gene), Membrane protein (M gene), Envelope protein (E gene) and variant capsid protein (VP gene) (Fig. 6). While the patent analysis directed towards relevant proteins indicated almost the same results similar to that of patent analysis of relevant genes, the results of relevant proteins indicate that protein research related to RNA viruses is focused on Glycoprotein after the Spike and Nucleocapsid proteins (Fig. 7).

The genome of RNA viruses of coronavirus family encodes four structural proteins comprising S, N, E, M proteins. A comparative analysis of patent publication year data with the top genes and proteins revealed that most of the research related to RNA virus was focused on Spike protein followed by N protein in the years 2001 to 2020 (Suppl. Figs. 2 to 5). This shows that R&D activity was more pivoted towards S and N genes as compared to other biological macromolecules. In

addition, during the year 2020, there is an upward trend visible for these genes due to COVID-19 pandemic [31]. The S gene, M gene, N gene and E gene are major genes that give rise to their respective proteins which are essential for the structural and functional properties of RNA viruses [32]. The vaccines having S-protein may induce more immunogenicity and it may be useful for vaccine development as it has the ability to neutralize antibodies and invokes strong T cell response [33]. Considering the results of our research, we believe that our patent landscaping study (highlighting major genes, proteins) would be stepping stone in advancement of biotechnology research related to the diagnosis and treatment of RNA virus related infections. Our analysis also indicates that comparatively the most important RNA virus proteins viz. S protein and N protein are a preferred choice for vaccine development [34]. The spike protein (S protein) is a key protein found on viral surface and

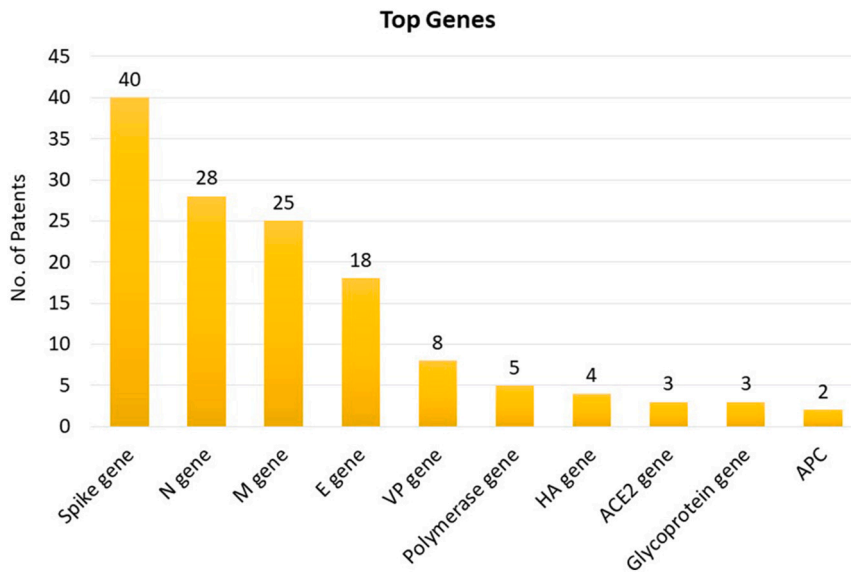


Fig. 6. Key genes which have been actively used in RNA viruses research.

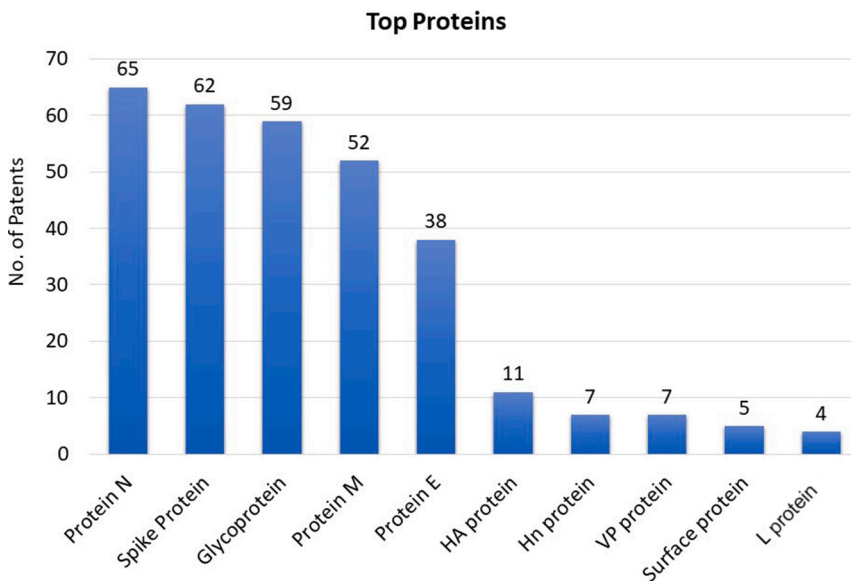


Fig. 7. A bar graphical visualisation illustrating the key proteins actively used in RNA virus research.

nucleocapsid proteins (N proteins) are involved in infection, thus a choice for getting targeted during vaccine development [35]. S proteins on the surface of SARS-CoV-2 gets bound to the host receptor angiotensin-converting enzyme 2 (ACE2) and help viral entry [36]. Recent studies related to the new variant of corona virus “2019-nCoV” also indicate that antibody to the N protein of “2019-nCoV” is more sensitive than S protein antibody for detecting early infection [37].

3.3. Analysis of patent claims

As patent claims provide legal boundaries to the scope of an invention and in light of the same, the further analysis of patent data has been focused to identify the type of patent claims [38]. The patent claim analysis revealed that 65 % of the patent claims were directed towards both products and process related to RNA virus, followed by 20 % of the patent applications and granted patents claiming only process and 15 % claiming only products related to RNA virus (Suppl. Fig. 6). The insights of patent claim analysis indicate that most of the patent applications and

granted patents have their claims directed towards products as well as processes or methods related to RNA virus study. The patent owners and/or inventors and/or respective companies have claimed both products and/or process patents related to RNA virus for harvesting commercial interests, as evident by the observation of this study. The claim analysis of the selected patent data revealed that the product related claims were directed towards RNA viral proteins, RNA genetic sequences, diagnostic kits etc. On the other hand, the method claims are directed towards different methods and processes of diagnosis and treatment of infections caused due to RNA viruses (Suppl. Fig. 7).

3.4. Assignee trends

The assignee analysis is used to identify and evaluate the innovation potential of different institutions having commercialisation interests. The key assignees were retrieved from the patent data to analyse and identify those who own patents related to RNA viruses. The assignee analysis revealed that most of the patent applications (7 patent

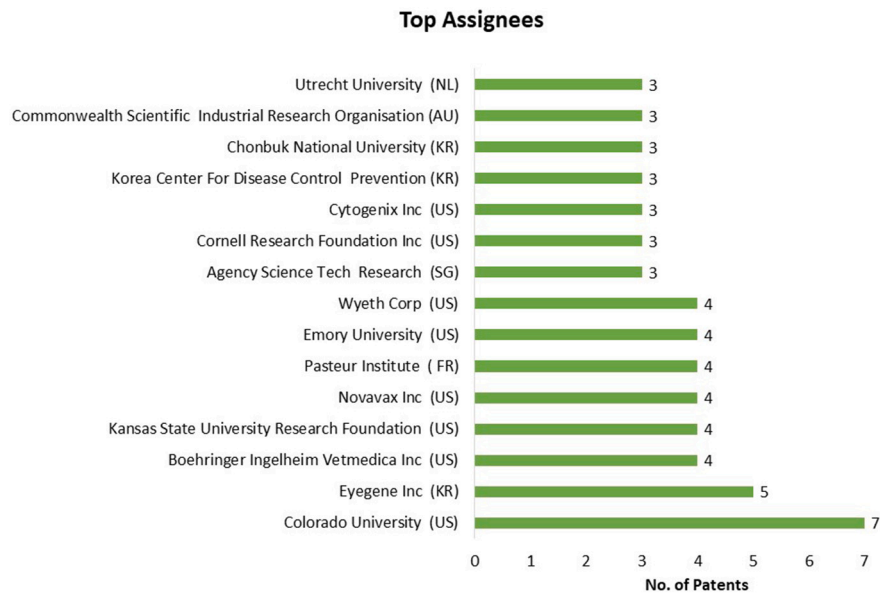


Fig. 8. Assignee analysis related to coronavirus research.

applications) were filed by Colorado University of United States of America followed by Eyegene Inc. of Korea and Boehringer Ingelheim Vetmedica Inc. of United States of America (Fig. 8). On the other hand, the active and inactive patent analysis reflected that the legal status and the information therein may be freely exploited mostly in case of inactive patents, and this paves way for investment in the development of generic technologies. The analysis of legal status of the patent applications and granted patents further revealed that almost 72 % of the patent applications and granted patents are active whereas 28 % of are inactive or dead (Suppl. Fig. 8).

4. Conclusions

Research on RNA viruses has been exceptionally increased in the past few decades owing to the SARS and MERS viral infections caused due to different variants of RNA viruses. The recent “2019-nCoV” corona virus variant is one of the RNA viruses that has led to SARS-CoV-2 infection outbreak and ranged warning bells around the globe that increased research activity related to diagnosis and treatment of RNA virus infections and still a sorrow state persists about its dangerous mutation rate, high transformation ability and immune escape. The insights from our research indicate that most of the patent applications and granted patents are directed towards different methods and products for diagnosis and treatment of RNA virus related infections. Specifically, the insights from gene, protein and technology cluster analysis indicated that most of the research related to RNA viruses has been specifically focused on S protein and N protein thus proving roles of molecular players in the spread of this disease. Additionally, a comparative analysis of the results with the recent research on RNA virus infections and particularly infections caused due to coronavirus also indicated that S protein and N protein are the most targeted macromolecules for efficient diagnosis and treatment of RNA related virus infections. Considering the insights and outcomes of our research, it is recommended that the future research for the diagnosis and treatment of the new SARS-CoV-2 infection may be focused on S protein and N protein to overcome the infections of RNA viruses. The results of our analysis also reflect the importance of patent research in identifying macromolecules for future research for vaccine or drug development and in light of this, the upcoming patent research can be focused on the recent outbreak of Monkeypox virus which is a species of double-stranded DNA virus but, that will set a whole new narrative.

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijbiomac.2022.08.169>.

CRedit authorship contribution statement

Saurabh Yadav: Conceptualization, Supervision, Methodology, Data curation, Validation, Writing, Reviewing and Editing.

Pratap Devarapalli: Methodology, Data curation, Validation, Software, Draft preparation, Writing, Reviewing and Editing.

Pragati Kumari: Data curation, Methodology, Writing, Reviewing and Editing,

Seema Soni: Data Curation, Writing, Draft preparation.

Vandana Mishra: Methodology, Data curation.

Declaration of competing interest

The authors declare that there are no conflicts of interest.

Data availability

Data will be made available on request.

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