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SARS COV, MERS COV, SARS COV-2 AND TREATMENTS: A BIBLIOMETRIC ANALYSIS

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ABSTRACT: As the incidences of Coronavirus (SARS CoV-2) infections have been increasing at a rapid pace, the need for its containment and treatment has taken center stage for numerous research institutions. The similarity of SARS CoV-2 with that of SARS CoV has led to a jumpstart in the research activities on corona-virus on the same. The number of research articles appearing since the time SARS CoV-2 was discovered has skyrocketed. While every research group has been busy in pushing the research information to the next level, hardly any convincing research has come up the effective treatments or therapeutics against the disease. In this study we conduct a bibliographic analysis for SARS CoV, MERS CoV and SARS CoV-2, and statistically compare the incidence of research articles combining along the "treatment" and 'therapies" as keywords. We attempt to draw trends and conclusions based on the data available on the databases mined.

INTRODUCTION: As the incidences of a previously unknown Coronavirus disease (Covid-19) rise around the world, the scare has progressively been spreading its sprawling wings. At the time of writing this article, there has been no cure or vaccine for the disease. As the disease moved from an epidemic to a pandemic stage, the research fraternity steered its focus towards the know-how and the therapies for handling and containing Covid-19 spread.

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The scarcity of epidemiological information, clinical data, genetic composition, or therapeutic know-how allowed the brazen spread of the Coronavirus (Cov) amongst the population at large.

In this study, we attempt to discuss a bibliometric analysis of the viruses (SARS CoV, MERS CoV, and SARS CoV-2) and existing therapies employed for the treatment of Covid-19. The data has been collected from European PMC, GigaDb, and PUBMED. Coronavirus is an RNA virus that contains a single strand of positive-sense RNA, of 29 ± 3 kilobases, enclosed in a protein envelope of size 100 ± 20 nm. The envelope is mainly spherical, with Club shaped glycoproteins protruding on the surface. The virus contains one of the largest reported genomes compared to its class. Cov uses its large genome to its advantage by

incorporating frequent recombination(s) resulting in vicious mutations that help the virus escape any kind of antiviral agents/treatment(s) frequently. Corona-virus has a remarkably high similarity with Severe Acute Respiratory Syndrome (SARS)-CoV. There have been several reports that indicate 7 strains of Cov, out of which 3 strains (SARS-Cov, MERS-Cov, and19-nCov) are reported to be highly pathogenic.

These three strains are essentially zoonotic, but the reservoir of these is still not confirmed. 19-nCov infects the upper respiratory tract initially and subsequently spreads to the lower respiratory tracts [1]. The symptoms of Covid-19 infections are fairly common and shared by pneumonia, common cold, pharyngitis, sinusitis, *etc.* As these symptoms are quite widespread and have been easily confused with the common cold, it becomes imperative to diagnose it carefully and ascertain to the highest level of accuracy.

But the reality is that the Covid-19 infections go viciously unnoticed and keep on propagating silently [2]. The clinicians and healthcare staff that are involved in the diagnosis are inclined towards traditional diagnosis systems and conventional treatments for the symptoms of Covid-19, generally miscalculated as common cold, fever or pneumonia.

A potent risk of undercover Covid-19 progression is the self-medication attitude of the people at large. Covid-19 transmission follows droplet infection *via* sneezing, coughing, or touching a Covid-19 positive patient. Several reports have indicated the transmission to happen through body fluids, such as urine, sweat, or even feces [3]. The conclusions in the case of Covid-19 infection is a result of misplaced/masked symptoms under commonly occurring seasonal infections [4, 5]. Our team mined PubMed, European PMC, GigaDB with the words “SARS CoV-2” “Treatments,” and “Therapies” till 23 April 2020. The search results were exported in “.xml” format from the PubMed, European PMC and GigaDB websites. The exported citations packaged as .xml files were imported into a web-based citation Rayyan QCRI program, which semi-automates the screening of title and abstract for quicker analysis. As a complementary search to SARS CoV-2, MERS-CoV and SARS CoV were also searched as keywords for calculating the total publications appearing in the searched databases.

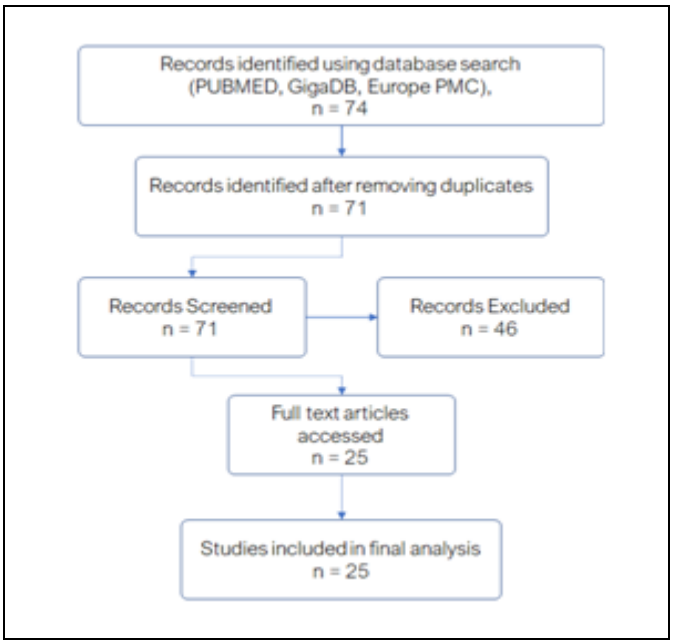

FIG. 1: PARETO CHART FOR THE STUDIES ON COVID-19 AND THERAPIES ACROSS COUNTRIES (N=72)

Initially, the number of articles found against SARS CoV-2 and Treatments and Therapies were screened and weeded out for duplicates. The initial number of articles found was 74, out of which 3 were duplicates. The remaining articles were further scanned for relevance, and 46 articles were excluded for not being relevant for the study undertaken. With the remaining 25 articles, full-text screening was done. All the articles were included for the final study as indicated in the ‘Pareto chart’ **Fig. 1**.

As a second stage of the study, the above-stated databases were searched discreetly for SARS CoV, MERS CoV, and SARS CoV-2. The data was collected from 2003 – April 2020. Search in the PUBMED database for SARS CoV yielded 4503 articles, MERS CoV resulted in 2162 articles, and SARS CoV-2 returned 1339 publications, compared to Europe PMC that returned 12660, 5169 and 1386 articles for SARS CoV, MERS CoV, and SARS-CoV-2 **Fig. 2A and B**. The total number of publications for SARS CoV-2 has the highest number amongst the three variants. The publications for SARS CoV-2 can be averaged out as 267 publications per month. This number does not include pre-prints and reviews.

The outbreak of SARS and MERS viruses were not as widespread as that of SARS CoV-2 in the past. This leads us to conclude the higher number of research laboratories working on SARS CoV-2. The trends for the publications over the years have been depicted in **Fig. 3**, where the highest slope is obtained for publications on SARS CoV-2 from Dec 2019 to April 2020 **Fig. 4**.

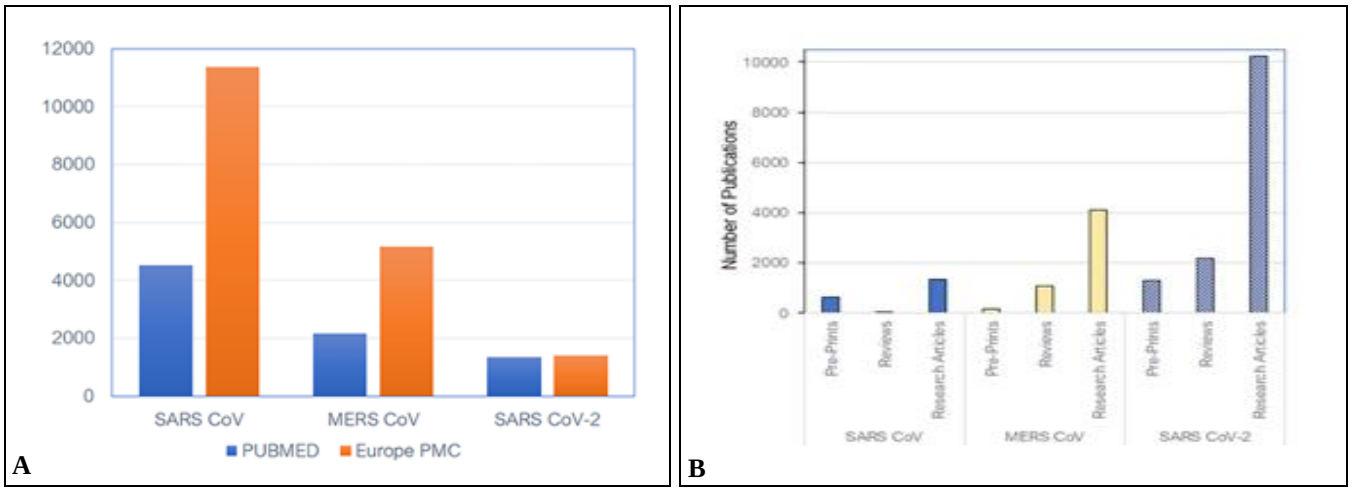

FIG. 2(A, B): NUMBER OF PUBLICATIONS TILL MAY 2020.

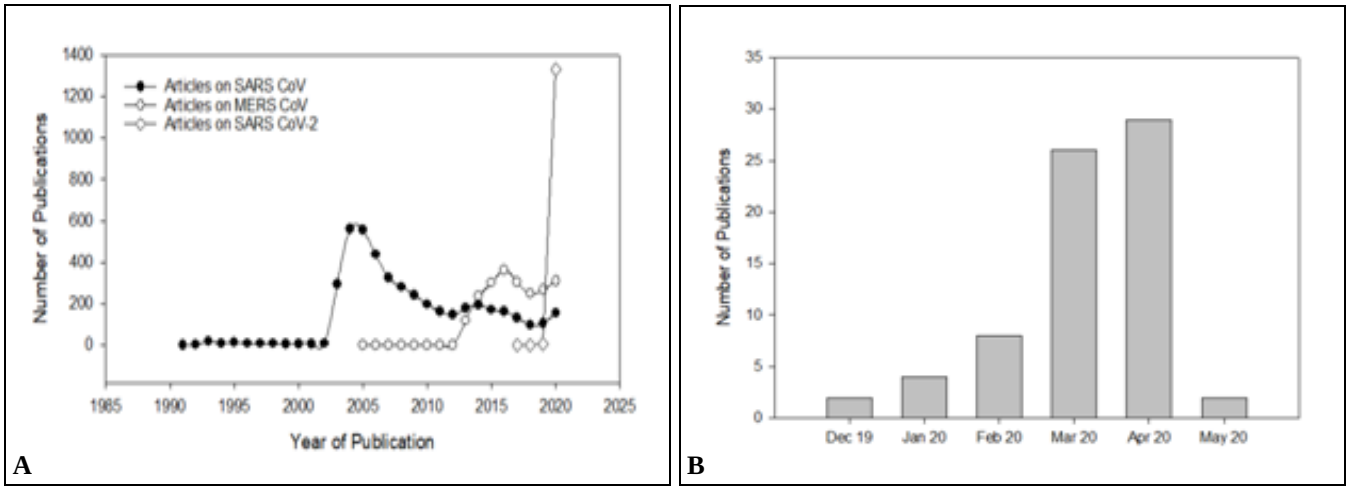

FIG. 3: A. NUMBER OF PUBLICATIONS PER YEAR (PUBMED) (B). PUBLICATIONS APPEARING FROM DEC 2019 TO MAY 2020

Nevertheless, there are a huge number of publications appearing on a daily basis, on SARS CoV-2, the number drastically reduces to 71 articles (excluding reviews and preprints) when the database is looked out for "SARS CoV-2" AND "Treatments" and "Therapies" in Europe PMC database and results in just 3 articles in PUBMED summing it to 74 **Fig. 1**.

The citations were exported to Rayyan QCRI for quickly sorting them into different categories and removal of duplicates. A total of 71 unique articles were found, and the records were screened for the aforesaid keywords. A full-text screening resulted in 25 articles that were considered relevant for the study. Approximately 32% of all the selected publications were from USA, followed by China at 16%, United Kingdom at 12% and Italy with 8% share of the selected articles. The remaining proportion was shared by countries, as shown in **Fig. 5**. From Dec 2019, the number of publications has been exponentially increasing, but those that discuss the therapies and treatment against SARS CoV-2 are still meager. **Fig. 2B** shows the number of publications segregated into 'Research articles', 'Reviews', and 'Preprints'.

The majority of the publications appear as reviews, systematic reviews, case reports, meta-analysis studies or suggestive therapies that summarize expected outcomes based on older treatments of SARS CoV and MERS CoV cases.

Table 1 indicates the therapies used by various research groups. 886709 positive cases of SARS CoV-2 are reported in USA with 50,243 deaths. America remains the worst affected country at the time of this study. (https://www.worldometers. info/coronavirus).

TABLE 1: THERAPEUTIC AGENTS REPORTED TO BE EMPLOYED FOR SARS COV-2 THERAPY ACROSS PUBLICATIONS

Country	Therapeutic agent against Covid-19
Belgium	Hydroxyquinone
Brazil	Bevacizumumab / Lopinavir / Arbidol / Redesivir
Canada	Remdesivir
China	Convalescent Plasma
China	Lianhuaqingwen (Traditional Chinese Medicine)
China	Lopinavir / Ritonavir
China	Papain like proteases
France	Remdesivir / Diltiazem
Germany	Ribavirin
Ireland	Broad Spectrum antiviral agents
Italy	Hydroxyquinone / Interleukin - 6
Italy	Interleukin -1
Spain	Baricitinib
Switzerland	Angiotensin Converting Enzyme (ACE - II)
United Kingdom	Interleukin-g
United Kingdom	Interferon-b
United Kingdom	Renin Angiotensin Aldostone System Inhibitor
USA	Interleukin - 6
USA	Angiotensin Converting Enzyme (ACE - II)
USA	Oseltamivir
USA	Chloroquine / Hydroxychloroquine
USA	Angiotensin Converting Enzyme (ACE - II)
USA	Chloroquine / Hydroxychloroquine
USA	Janus Kinase Inhibitor
USA	Angiotensin Converting Enzyme (ACE - II)

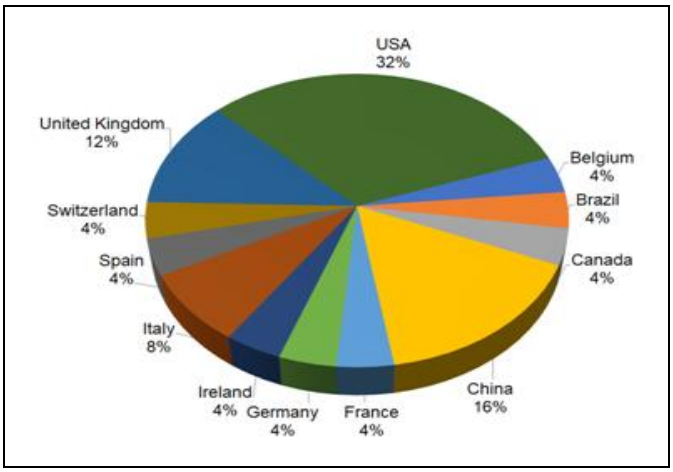

FIG. 4: COUNTRIES WITH HIGHEST NUMBER OF RESEARCH PUBLICATIONS ON COVID-19

As any outbreak occurs, its' obvious that the research laboratories will kick in to handle, contain, and defeat the outbreak as soon as possible. SARS CoV outbreak occurred in 2002, and we observe an increase in the number of research publications after 2002. Similar trends were observed after MERS CoV infections in 2012. The number of publications appearing after both the outbreaks were reasonably high as the outbreak was limited and the deaths from these outbreaks was less than 1,000 (~800 for SARS CoV and ~500 for MERS CoV). The number of publications for SARS CoV-2 has spiked to 1,200 in just over 4 months. This exponential rise may be due to the plethora of information obtained from the previous similar outbreak, advanced research facilities over the years, and the growth of the scientific fraternity.

Fig. 5 compares the trends and attempts curve fitting showing variable trends for SARS CoV research, while MERS CoV trends increase rapidly; none of both compare to the increase in the research papers published for SARS CoV-2. Comparison of the number of research publications on the year of an outbreak and preceding 4 years showed a significant correlation between the SARS and MERS outbreaks, while the high numbers of SARS CoV-2 publications do not correlate significantly **Table 2**. Arguably, the existing knowledge, the outbreak history, and enhancements in research avenues have contributed to such a high pace of research against SARS CoV-2. Of all the publications found and listed, only a handful discuss and attempt to counter the infection with real clinical data.

Even when the number of research publications is skyrocketing, convincing data for the use of therapeutic agents for the treatment of SARS CoV-2 infections remain appallingly low. A number of laboratories talk about Combination of anti-malarial drugs, Angiotensin Converting Enzyme (ACE) – II, Janus kinase inhibitor, Papain linke proteases, remdesivir, interferon β-1, Bevacizumab, Oseltamir, hydroxy-chloroquine, Retonavir, Azithromycin, Interleukin -I, Lopinavir, Convalescent plams, *etc.*, none of these have emerged convincingly effective in the treatment **Table 1**. Hospitals have been employing Hydroxy-chloroquie and Azithromycin, in combination with other drugs to treat and overcome the SARS CoV-2

infection; still the mode of action of these drugs on the virus and the recovery process remains a mystery. The availability of information of the virus genome, its size, capsid composition, protein coat, spike protein, binding sites are available, designing of a vaccine still has a long time before it can be effectively used for the treatment. In conclusion, the focus of research needs to be divided into scientists and clinicians. Where the clinicians generate infection and treatment data with recoveries and share that with scientists and virologists to provide them with the insight of the disease mechanisms. Researchers should focus on the conserved regions of the virus to develop antiviral agents; the virus can't escape quickly.

This would lead to quicker development of much effective, long-lasting therapeutic agents for the treatment and prevention of SARS CoV-2 infections.

TABLE 2: CORRELATION OF PUBLICATIONS APPEARING FROM 0 TO (-4) YEARS OF THE OUTBREAK

Pearson r	SARS CoV	MERS CoV	SARS CoV2
r	0.9481	0.9923	0.7765
90% confidence interval	0.1664 to 0.9980	0.8113 to 0.9997	-0.5429 to 0.9907
R squared	0.8989	0.9846	0.603
P value			
P (two-tailed)	0.0519	0.0077	0.2235
P value summary	ns	**	ns
Significant? (alpha = 0.1)	Yes	Yes	No

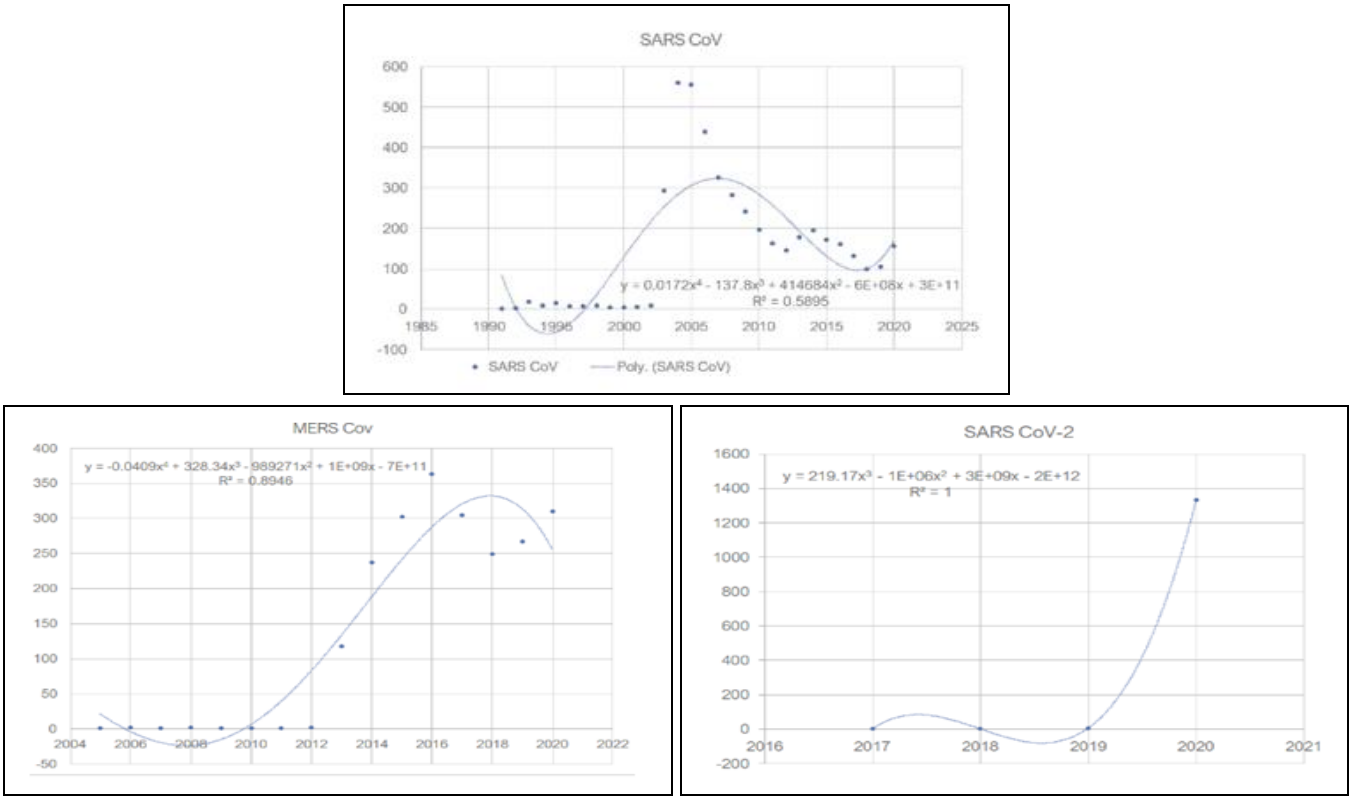

FIG. 5: PUBLICATION TRENDS FOR MERS, SARS, AND SARS COV-2

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Ekta Arya and Dr. Raju K Mandal compiled the information by screening the publications. Dr. Arshad and Dr. Shafi drafted the manuscript and critically reviewed and reshaped the article.

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