Publication trend of TMPRSS2 as SARS-CoV-2 receptor during the COVID-19 pandemic

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Publication trend of TMPRSS2 as SARS-CoV-2 receptor during the COVID-19 pandemic

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ABSTRACT

The Coronavirus Disease 2019 (COVID-19) pandemic has not yet been fully under public health control, which is still currently impacting a large number of people worldwide in 2023. Since the pandemic emerged, the growing number of publications related to TMPRSS2 as a SARS-CoV-2 receptor worldwide has increased rapidly with various findings and qualities. It is important to determine the trend of TMPRSS2 publication as no such studies currently exist that represent the publication trend related to this critical field of study. Here, we employed a bibliometric-based approach to evaluate the research trends of TMPRSS2 mechanistically as the SARS-CoV-2 receptor. We identified 1012 research documents published between 2020 and 2022 for this study. The most common document category was "Research Article" (646 articles, 63.84%) followed by "Review Article" (261 articles, 25.79%), and letters to editors (57 articles, 5.63%). Germany was the most cited country with a total of citations (9400 citations), followed by the USA (6409 citations) and China (1788 citations), respectively. In conclusion, given the impact of COVID-19, this study indicated TMPRSS2 as a SARS-CoV-2 receptor as a timely and highly relevant research topic.

Keywords: bibliometrics, COVID-19, SARS-CoV-2, TMPRSS2

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INTRODUCTION

Coronavirus Disease 2019 (COVID-19) was first emerged in Wuhan, China as the new infectious respiratory disease (Huang et al., 2020). The first wave of infections was traced back to a seafood market in Wuhan, where animal contact resulted in virus transmission to people and eventually human-to-human transmission (Chan et al., 2020). In February of 2020, the International Committee on Taxonomy of Viruses (ICTV) named the virus that causes COVID-19 as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Organization, 2020) based on its close homology to SARS-CoV (Zhu et al., 2020). The number of patients infected with SARS-CoV-2 has been gradually increasing in multiple countries including Asia, Australia, Europe, the Americas, and Africa. This condition has led the World Health Organization (WHO) to declare this disease a pandemic. As of January 1, 2022, over 281 million cases and over 5.4 million deaths have been reported worldwide (Wordometers, 2022). In response to the spread of the virus, many countries, particularly those with advanced economies, have implemented strict measures to limit people's movements and interactions. The goal of these measures is to slow the spread of the virus and ensure that hospitals do not become overwhelmed with critically ill patients. While these measures have been effective in reducing the number of infections and deaths, they have also come at a significant cost to the economy. Businesses have been forced to close or operate at reduced capacity, causing job losses and financial hardship for many people. Governments have had to spend large amounts of money to support businesses and individuals affected by the pandemic.

Effective vaccinations or preventive medicines that target SARS-CoV-2 cellular uptake would almost probably contribute to illness mitigation. In May 2020, the Hoffman group published a study revealing that successful infection of lung epithelial cells with SARS-CoV-2, the virus responsible for the COVID-19 pandemic, requires the presence of two key host factors: angiotensin-converting enzyme 2 (ACE-2) and transmembrane protease serine 2 (TMPRSS2) (Hoffmann et al., 2020). These factors are critical in the viral entry process, which is necessary for the virus to replicate and cause disease. The entry of coronaviruses into host cells requires the activation of the viral spike (S) protein by a protease from the host cell. TMPRSS2, a type II transmembrane serine protease, was found to be an essential host component in airway epithelial cells that facilitates access into the cells. The activation of the S protein by TMPRSS2 is a crucial step in the viral entry process, and targeting TMPRSS2 may represent a promising strategy for developing antiviral therapies for COVID-19 (Glowacka et al., 2011; Hoffmann et al., 2020; Li et al., 2003). The potential of TMPRSS2 inhibitors in preventing the virus from entering the cell by blocking the protease activity of TMPRSS2 was investigated in this work by Hoffman et al (Hoffmann et al., 2020). Since that publication was published on the *Cell* paper, it has been growing dramatically by citing these documents. Until now, TMPRSS2 was utilized as the drug target gene for fighting SARS-CoV-2. Several publications have investigated the role of TMPRSS2 as the molecular process of COVID-19.

The pandemic has not yet been under public health control, and researchers are still in the search for finding the best drug or cure for COVID-19. However, until now, it remains unclear the relative importance and relevance of TMPRSS2 as the SARS-CoV-2 receptor, as a biological mechanism for COVID-19. No studies thus far have represented the publication trend related to TMPRSS2 as SARS-CoV-2 receptors for COVID-19. Bibliometric analysis has a pivotal role in guiding research to prioritize future research. Therefore, the importance of bibliometric analysis of TMPRSS2-related studies as SARS-CoV-2 receptors for COVID-19 is to find relevant themes that need to be studied further by evaluating the explored areas and the highly cited relevant articles. Here, we used a bibliometric-based approach to assess the TMPRSS2 as SARS-CoV-2 receptors for COVID-19 publication since the pandemic situation emerged.

Bibliometric analyses have in general been a quantitative method for evaluation of research articles, including authors of each article, the journal where it was published, and the number of citations of these journals. The bibliometric analysis shed light on the research activity through quantitative bibliographic description (Jones, 2016). The results will allow future studies to assess several important points, including the publication trends related to the TMPRSS2 gene and the most

frequently used author keywords, citation analysis and the highly cited articles, top 10 most cited countries, top 10 most active journals and international collaboration. In a relatively short period, within two years since 2019-2020, the COVID-19 pandemic has impacted the entire world. Many scientists around the world have made various kinds of efforts to overcome this pandemic altogether. One of these efforts was to find out how the mechanism of the SARS-COV-2 virus enters the human body. Few studies were focused on evaluating the trend of publication of TMPRSS2. Therefore, the current study focused on evaluating the trend of publication of the TMPRSS2 gene as SARS-CoV-2 receptors for COVID-19. As proven on this bibliometric analysis, knowledge of existing papers on TMPRSS2 as SARS-CoV-2 receptors may aid researchers in better understanding the mechanism by which the COVID-19 virus enters the human body.

MATERIALS AND METHODS

Database

SciVerse Scopus is an online database used to retrieve relevant publications in this research (accessed on 28/12/2021). Scopus was chosen because of its advantages over other electronic databases (Falagas et al., 2008). First, its database provides the information of a number of features that make it easier to sort and rank, including the countries, authors, journals, and institutions. Second, it also gives the number of citations for any group of documents, which is used as a metric of scientific merit (Hirsch, 2005).

Indicators of bibliometrics

The following bibliometric criteria were investigated in this study: (1) Types of documents and languages; (2) Growth of publications; (3) Most frequently used author keyword; (4) Citation analysis and the highly cited articles; (5) Top 10 Most cited countries; (6) Top 10 Most active Journals, and (7) International collaboration. The data for the most cited publications came from Scopus, which counts the number of cited documents for each publication. Data on the most active and cited countries were also collected directly from Scopus, which counts each country's number of papers and citations annually. VOSViewer version 1.6.16 was utilized for the bibliometric analysis (Van Eck & Waltman, 2010) and the Biblioshiny R package (Aria & Cuccurullo, 2017). VOSViewer and Biblioshiny are two free software programs for creating and viewing bibliometric maps.

Keywords and search strategy

Several methodological approaches were used to retrieve the foremost number of documents possible. Supplementary File 1 represents a particular search method and all terms used. Research published from 2020 to 2022 was searched using the keywords "TMPRSS2" AND "COVID-19" AND "SARS-CoV-2" to discover all documents related to the study. Quote marks were used to find the exact phrase in Scopus, while asterisks were used as a wildcard to find all possible related keywords. We devised a title/abstract/keywords strategy that incorporated all potentially relevant terms and phrases.

RESULT AND DISCUSSION

Type of documents and languages for TMPRSS2 research

In total, 1012 documents were extracted from the Scopus database from 2020-2022. Around 7477 authors worldwide were involved in writing 1012 documents. The retrieved documents included 646 research pieces (63.84%) and 261 review articles (25.79%). In addition, other types of documents featured letters 57 (5.63%), notes 22 (2.17%), editorials 15 (1.48%), short surveys 7 (0.69%), book chapters 3 (0.30%), and a conference paper 1 (0.09%).

Growth of publications for TMPRSS2 research

In total, 1012 documents were extracted during the pandemic from 2020 to 2022. This study focuses on the utilized TMPRSS2 as SARS-CoV-2 receptors for COVID-19. The first documents

appeared in early 2020 and surprisingly, the annual number of publications has grown significantly since then, which hits its peak in 2021 (n=619) compared to 2020 (n=383). In addition, we highlighted that the total number of publications in 2022 was still 10 documents (as this article submitted). This relatively low number was presumably due to its being in early 2022 when this article was written. However, it does not rule out the possibility that it will continue to grow up in the middle until the end of 2022. The trend of growing up publication in TMPRSS2 studies indicated the increased interest in finding the solution for COVID-19, which started from identifying the target of the SARS-CoV-2 virus in humans. Further, the top 5 subject areas related to the publication of the TMPRSS2 gene were in the area of medicine (n=564), genetics and molecular biology and biochemistry (n=452), microbiology and immunology (n=185), pharmacology, toxicology and pharmaceutics (n=122), and chemistry (n=59).

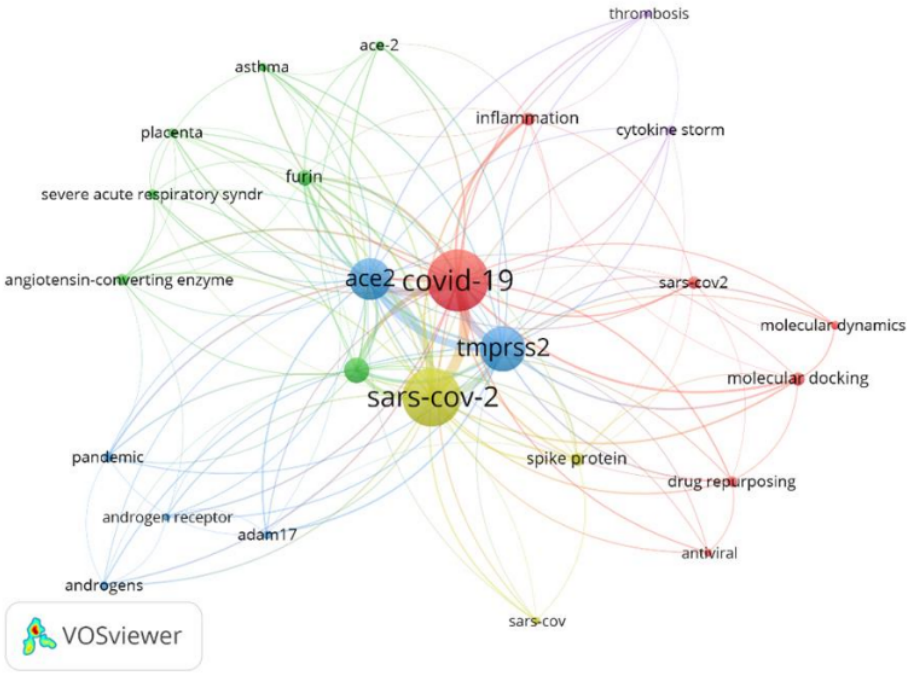

Figure 1. Visualization of the most frequent author keywords (minimum occurrences of 25 times) related to the TMPRSS2 gene as SARS-CoV-2 receptors for COVID-19

Most frequently used author keywords for TMPRSS2 research

Figure 1 depicts the network visualization map of most of the author's keywords appear in at least 25 occurrences. COVID-19 (534 occurrences) followed by SARS-CoV-2 (480 occurrences), 'TMPRSS2 (289 occurrences), and ACE-2 (246 occurrences) were the most frequently used keywords. Overlay visualization indicated the most author keywords related to TMPRSS2 gene as SARS-CoV-2

receptors during these two years (2020-2022), which were categorized into fourth-largest clusters, each with different colours including COVID-19 (red colour) and SARS-CoV-2 (yellow colour) and two genes that important was TMPRSS2 (dark blue colour) and ACE-2 (blue colour).

The highly cited articles and Citation analysis for TMPRSS2 research

The retrieved documents demonstrated that the average document citation was 28.69. A study published in the *Cell* in May 2020 received the highest number of citations and 7479 citations during two consecutive years (2020-2021); it was very surprising the citation of this article was almost 7-fold higher than that of the other top ten highe[60]ited articles. The trend of citations seems to be increased over time. The author of this article was Hoffman et al., 2020 title of his article "SARS-CoV-2 Cell Entry Depends on [38]MPRSS2 and ACE2 and is interupted by a Protease Inhibitor that has been clinically proven" (Hoffmann et al., 2020). Surprisingly, Hoffman et al., 2020 also published another published in *Molecular Science* (Hoffmann et al., 2020). The second highest citation of the document was published in March 2020 in *Nature Medicine* with the title "SARS-CoV-2 entry factors together with innate immune ge[17]s are highly expressed in nasal epithelial cells" (Sungnak et al., 2020); it has been cited 1072 times. The top 10 most cited articles related to the study of TMPRSS2 as SARS-CoV-2 receptors for COVID-19 were listed in Figure 2 and Table 1. From 10 journals that showed in Figure 2 and Table 1 was published in highly reputed journals. An interesting finding highlighted that among the ten journals with the highest citation we identified, the *Cell* was dominated as it ranked 1st, 3rd, and 7th.

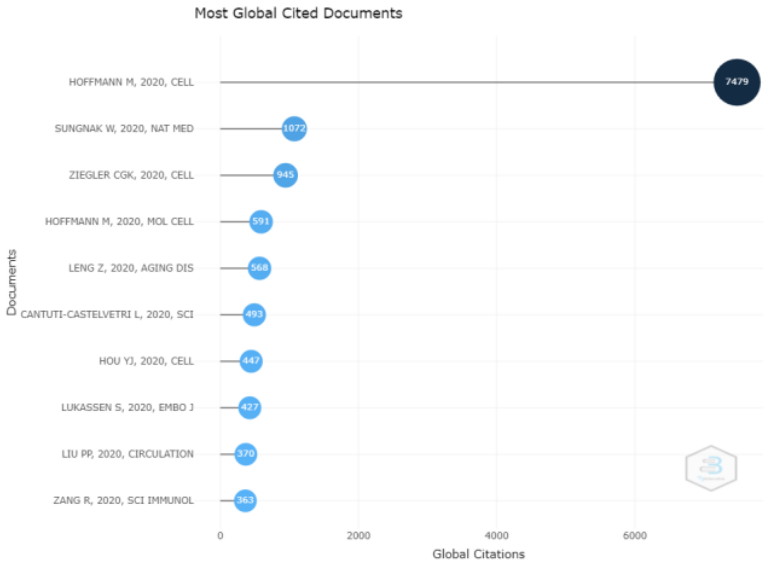

Figure 2. Top 10 cited country related the TMPRSS2 gene as SARS-CoV-2 receptors for COVID-19

Top 10 most cited countries for TMPRSS2 research

Figure 3 shows the top 10 countries cited for COVID-19 TMPRSS2 publication. Germany had 9400 citations, followed by the USA with 6409 and China with 1788. It is not surprising that the most cited countries were from Germany. This result was in line with the authors with the highest citation

associated with Germany and Hoffman Markus (Hoffmann et al., 2020). Authors from Germany have published an article in high-reputation journals. The top ten countries with the most citations related to the study of TMPRSS2 for COVID-19 are listed in Figure 3 and Table 1**.** Interestingly, most of the journals were open-access, which is implicated in citation advantage. As reported by several studies revealed that the Open Access Journal promotes citations (Basson & Prozesky, 2021; Sotudeh & Horri, 2007).

Top 10 most cited journals for TMPRSS2 research

The leading journal in publishing articles related to TMPRSS2 for COVID-19 was the *International Journal of Molecular Science,* with a total number of documents was 23. According to the analysis that we collected based on the names of journals, we herein emphasized that the *International Journal of Molecular Science* was the most productive in publishing the study of TMPRSS2 for COVID-19. In addition, the second most active journal was published in *Scientific Reports* which were published around 22 articles at the time this manuscript was written. The third leading journal was published in *frontiers in Immunology* and *Viruses* journals with a total number of around 17 articles. The top 10 most active journals related to publishing the study of TMPRSS2 for COVID-19 are listed in Figure 4.

International collaboration for TMPRSS2 research

International collaboration was very important in the scientific field. Through collaboration, scientists around the world enable to share/exchange information related to the field with one another. The strength of a two-country research collaboration is shown by how thick the line between them is (Figure 5). The USA was the country with a total link strength. Most countries worked together with the United States. So, it is in the middle of the map and has many lines going out to other countries. Thus, it fills the map's center with many connecting lines to other countries. In addition, the international collaboration also can be presented based on the corresponding author 30untry. Each author can collaborate with other countries based on the same field. Figure 6 depicts the single-country publication (SCP) and multiple-country publicati31(MCP) related to TMPRSS2 gene publication during the pandemic. According to our findings, the USA has the highest number of collaborating countries, followed by China and Germany in second and third places, respectively. Figure 6 visually represents international cooperation between countries that have produced at least 25 documents.

The present study found that the USA had the greatest number of countries working together on research on the TMPRSS2 gene as the SARS-CoV-2 receptor. The collaboration allows scientists around the globe to share /exchange information and stay updated about the field. This result could be attributed to a number of variables, including its huge population, high-income countries, status as COVID-19's most affected nation, affordable medical research resources, and highly reliable data management systems. During the pandemic, China, Germany, India, and the USA all contributed significantly to the worldwide network of COVID-19 evaluating TMPRSS2 as SARS-C50-2 receptors, leading to an increase in bilateral research articles (Figure 5). Evidence showed that each country's per capita gross national product greatly affects biomedical research productivity worldwide (Rahman & Fukui, 2003). 59

Most publications were in medicine and biochemistry, genetics and molecular biology, and less were associated with chemistry. Since the beginning of the pandemic, health sciences papers have accounted for the majority of publications, as well as the most cited literature (Malekpour et al., 2021). This finding indicates that this is a topic of interest, thus, more research is required. Our findings also revealed that extensive collaboration research had been carried out from the b36nning of the COVID-19 outbreak. Such collaborations undoubtedly improve our understanding of the SARS-CoV-2 virus's nature (Shang et al., 2020). International collaboration can also greatly accelerate, support, and develop effective vaccine research (Smith et al., 2020).

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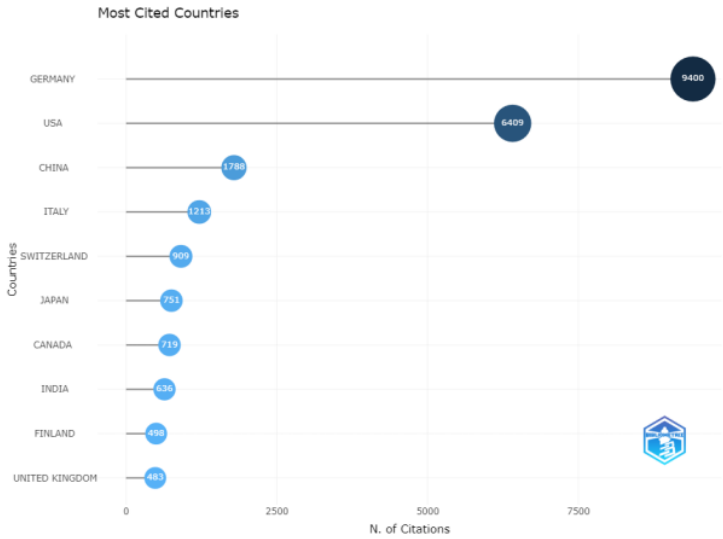

Figure 3. Top 10 cited country related the TMPRSS2 gene as SARS-CoV-2 receptors for COVID-19

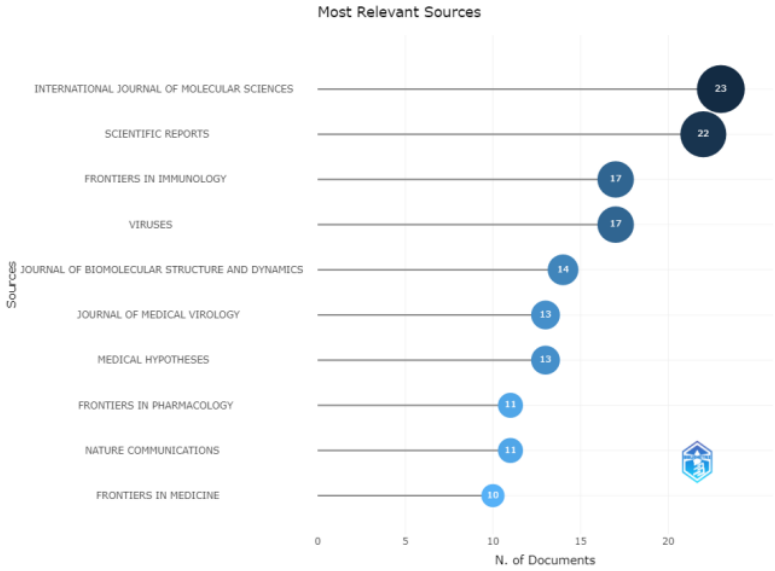

Figure 4. Top 10 journals in publishing TMPRSS2 gene as SARS-CoV-2 receptors for COVID-19

Table 1. Top 10 cited articles related to the TMPRSS2 gene as SARS-CoV-2 receptors for COVID-19

Paper	Year of Publication	Title	Journals	Total Citations	TC per Year	IF*	Ref
Hoffmann M	2020	SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor	Cell	7479	3739,5	41.58	(Hoffmann et al., 2020)
Sungnak W	2020	SARS-CoV-2 entry factors are highly expressed in nasal epithelial cells together with innate immune genes	Nature Medicine	1072	536	53.44	(Sungnak et al., 2020)
Ziegler C	2020	SARS-CoV-2 Receptor ACE2 Is an Interferon-Stimulated Gene in Human Airway Epithelial Cells and Is Detected in Specific Cell Subsets across Tissues	Cell	945	472,5	41.58	(Ziegler et al., 2020)
Hoffmann M	2020	A Multibasic Cleavage Site in the Spike Protein of SARS-CoV-2 Is Essential for Infection of Human Lung Cells	Molecular Cell	591	295,5	17.97	(Hoffmann et al., 2020)
Leng Z	2020	Transplantation of ACE2- Mesenchymal Stem Cells Improves the Outcome of Patients with COVID-19 Pneumonia	Aging and Disease	568	284	6.74	(Leng et al., 2020)
Cantuti-CL	2020	Neuropilin-1 facilitates SARS-CoV-2 cell entry and infectivity	Science	493	246,5	41.84	(Cantuti-Castelvetri et al., 2020)
Hou Yj	2020	SARS-CoV-2 Reverse Genetics Reveals a Variable Infection Gradient in the Respiratory Tract	Cell	447	223,5	41.58	(Hou et al., 2020)
Lukassen S	2020	SARS-CoV-2 receptor ACE2 and TMPRSS2 are primarily expressed in bronchial transient secretory cells	Embo Journal	427	213,5	11.60	(Lukassen et al., 2020)
Liu P	2020	The Science Underlying COVID-19: Implications for the Cardiovascular System	Circulation	370	185	29.69	(Liu et al., 2020)
Zang R	2020	TMPRSS2 and TMPRSS4 promote SARS-CoV-2 infection of human small intestinal enterocytes	Science Immunology	363	181,5	13.44	(Zang et al., 2020)

***Impact Factor in 2020**

The most cited papers among the top 10 cited publications of TMPRSS2 as SARS-COV-2 receptors for COVID-19 patients were original articles/ research articles. The Journal from Germany, namely the *Cell* with a high impact factor (IF 2020: 41.58), had the highest number of citations on TMPRSS-2 as SARS-CoV-2 receptors for COVID-19, the total number of citations was 7479 citations. The article was written by Hoffman et al. since the early of pandemic in May 2020. This article focused on the factor associated with SARS-CoV-2 infection of lung epithelial cells that requires ACE-2 and TMPRSS2. Recently, TMPRSS2 was found to be an essential host in airway epithelial cells that helps SARS-COV-2 get into the cells (Hoffmann et al., 2020). Surprisingly, among the top 10 articles with the highest number of citations, three were published in the High Impact

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journal the *Cell*. Among these publications, Germany was the non-English-speaking country with the most citations. Interestingly, Hoffman et al. are from a German institution with Hoffman himself is a German, thereby no won Germany is the country with the highest citations with regard to articles discussing TMPRSS2 as one of the receptors for SARS-CoV- 2. This suggests that the impact factor, not research methodology or quality, was the best predictor of citations each year (Callaham et al., 2002).

The present study has both merits and drawbacks. The study's merits include providing sy access to the evidence and research trend on a topic and identifying papers focused on TMPRSS2 as a SARS-CoV-2 receptor for COVID-19. The drawbacks of the current study were that it only comes from one single database (Scopus). Therefore, it may not collect all relevant evidence available. Furthermore, another noteworthy limitation of our research is limited to English articles, which implies we may be missing out on valuable information from the articles provided in other languages. Besides, citation analysis for article impact has some drawbacks. Citation analysis counts how many researchers have cited an article. However, it is limited by factors that affect article citation rates. Limitations include self-citation, incomplete citation, and omission bias. When an author cites their own work in their articles, self-citation can boost their citation count. When a researcher cites only part of an article, it may receive fewer citations. Due to language, access, or personal biases, some articles are not cited. Citation timing also affects citation rates. After becoming popular, some articles may be cited more often. Citation rates don't always indicate an article's impact. Thus, citation analysis's limitations must be considered when assessing an article's impact (Brandt et al., 2019). We only included articles from 2020 – 2022, which implies the trend of research in the future may change over time. Future investigations could re-evaluate more included scientific databases to identify more comprehensive findings, such as Web of Science or PubMe and assess articles' quality based on their study design. The requirement for research on TMPRSS2 as a SARS-CoV-2 receptor is likely to grow as long as the pandemic continues. Consequently, this could be a significant research issue in the future. Besides, the genomic variant of TMPRSS2 as SARS-CoV-2 receptor also is important information to influence the susceptibility of COVID-19 among multiple continents (Irham et al. 20 20; Shen et al., 2017). It has been shown that a transmembrane protease, serine 2 (TMPRSS2), a type II transmembrane serine protease (TTSP), plays a crucial role in SARS and MERS coro viruses (CoV), as well as Asian H7N9 flu and several H1N1 subtype influenza A viruses, in 2013. Infections caused by Coronav uses and some low pathogenic influenza viruses can be treated by targeting TMPRSS2 (Matsuyama et al., 2010; She et al., 2017; Tarnow et al., 2014; Zumla et al., 2016). Clinically proven protease inhibitors can block SARS-CoV-2 cell entry by blocking ACE2 and TMPRSS2 (Figure 7).

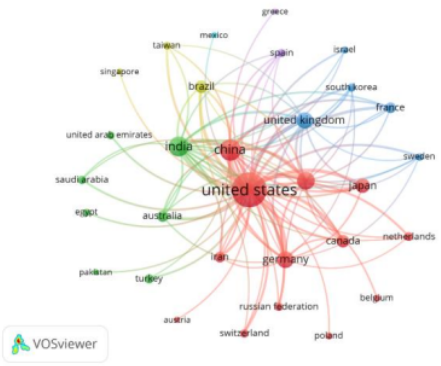

Figure 5. Research collaboration among countries with minimum research output of 32 documents for TMPRSS2 publication

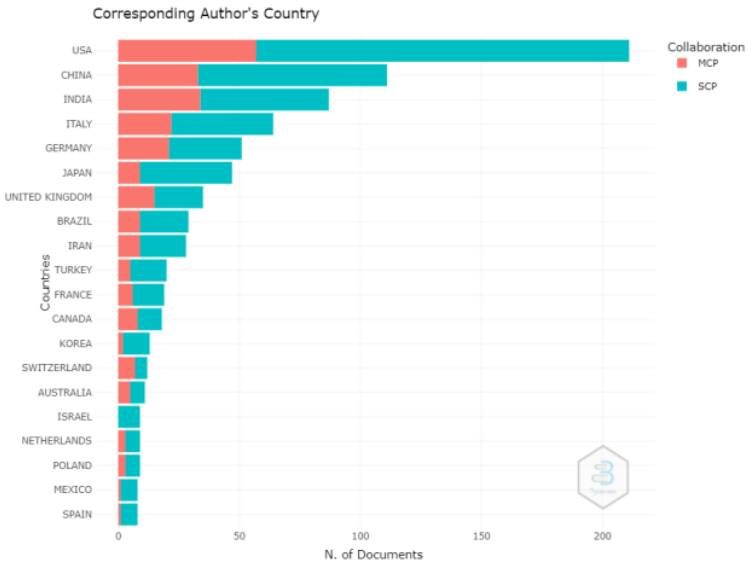

Figure 6. Research collaboration among countries with minimum research output of 32 documents for TMPRSS2 publication

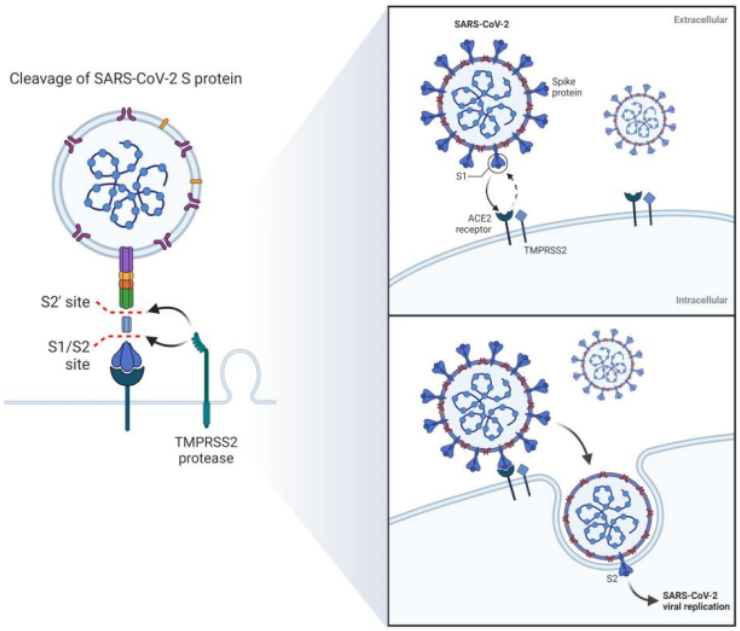

Figure 7. SARS-CoV-2 Entry through Host TMPRSS2 and ACE2 (by Biorender.com under license number *GS24Y4YZSS*)

Implications of this study

To the best of our knowledge, this study could be the first report on the most-cited papers in TMPRSS2 and SARS-COV-2 receptors. As collaborative work and network are essential to lead research in the new emerging disease, researchers worldwide may have opportunities to contribute to a research team, especially in genomics, medicinal chemistry, molecular biology, biochemistry and related sciences such as cell biology and biophysics.

CONCLUSION

A large number of publications related to TMPRSS2 as SARS-CoV-2 receptors have been published rapidly in many journals in the past two consecutive years since the outbreak of COVID-19. Knowledge of existing findings on TMPRSS2 as SARS-CoV-2 receptors is not only helped researchers to further understand the mechanism of SARS-CoV-2 entering the human body of COVID-19 facilitated by TMPRSS2 gene, but it also can help researchers to find the drug target gene for COVID-19 (genomic driven drug discovery) and highlight the importance of exploring research on SARS-COV-2 receptors. Our current study concluded the TMPRSS2 publication trend. The annual number of publications grew significantly starting in early 2020 with a total number of fluctuations in 2021. Besides, Germany was the most cited country with total citations, followed by USA and China, respectively. In conclusion, this study indicated an important topic for alleviating COVID-19 was the TMPRSS2 as a receptor for SARS-CoV-2.

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