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Judul artikel:

**Trend of Publication of TMPRSS2 as the SARS-CoV-2 Receptor:
Bibliometric Analysis During the COVID-19 Pandemic**

Lalu Muhammad Irham*, Dyah Aryani Perwitasari, Yudha Rizky Nuari, Wirawan Adikusuma, Haafizah Dania, Rita Maliza, Made Ary Sarasmita, Rocky Cheung, Adi Wira Septama. **Publication trend of TMPRSS2 as SARS-CoV-2 receptor during the COVID-19 pandemic.** Pharmaciana. Vol.13, No.1, March 2023, Page. 58-70. ISSN: 2088 4559; e-ISSN: 2477 0256 DOI: 10.12928/pharmaciana.v13i1.24052

50 **Trend of Publication of TMPRSS2 as the SARS-CoV-2 Receptor:**
51 **Bibliometric Analysis During the COVID-19 Pandemic**

52
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63 **Submitted :..... Reviewed :..... Accepted:.....**

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65
66 **ABSTRACT**

67
68 The pandemic of coronavirus disease 2019 (COVID-19) has not yet been fully controlled
69 until now, which is still impacting a large number of people worldwide. Since the pandemic
70 emerged, the growing number of publications related to TMPRSS2 as SARS-CoV-2 receptor
71 around the world increased rapidly with various findings and qualities. It is important to
72 determine the trend of TMPRSS2 publication as no such studies currently exist that represent
73 the trend of publication related to this field. Here, we employed a bibliometric analysis-based
74 approach to evaluate the relevant research of TMPRSS2 as the receptor of SARS-CoV-2.
75 Research published from 2020 to 2022 was identified. A total of 1012 relevant documents were
76 selected. The most common type of documents was research article 646 (63.84%) followed by
77 review article 261 (25.79%), and letters to editors 57 (5.63%). The annual number of
78 publications growth significantly started from early 2020 with the total number of fluctuations
79 in 2021 (n=619). Germany was the most cited country with total citations 9400, followed by
80 USA (6409) and China (1788), respectively. In conclusion, given the urgency of this situation,
81 this study indicated that the TMPRSS2 as SARS-CoV-2 receptor was an important topic for
82 alleviating the COVID-19.

83
84 **Keywords:** Bibliometrics, COVID-19, SARS-CoV-2, TMPRSS2.

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101 INTRODUCTION

102 Coronavirus disease 2019 (COVID-19) was first emerged in Wuhan, China, as the new
103 infectious respiratory disease (Huang et al., 2020). The first wave of infections was traced back
104 to a seafood market in Wuhan, where animal contact resulted in virus transmission to people
105 and eventually human-to-human transmission (Chan et al., 2020). In February of 2020, the
106 ICTV named the virus that causes COVID-19 as severe acute respiratory syndrome coronavirus
107 2 (SARS-CoV-2) (Organization, 2020) based on its close homology to SARS-CoV (Zhu et al.,
108 2020). The number of patients infected with SARS-CoV-2 has been gradually increasing in
109 multiple countries including Asia, Australia, Europe, the Americas, and Africa. This condition
110 has led the World Health Organization (WHO) to declare this disease a pandemic. As of January
111 1, 2022, over 281 million cases and over 5.4 million deaths have been reported worldwide
112 (Wordometers, 2022). In order to slow the spread of the virus and keep the number of critical
113 patients within hospital capacity, almost all developed countries have imposed strong
114 restrictions on residents' movement, which has come at a high cost in terms of money.

115 Effective vaccinations or preventive medicines that target SARS-CoV-2 cellular uptake
116 would almost probably contribute in illness mitigation. In May 2020, the Hoffman group was
117 reperforated that infection of lung epithelial cells with SARS-CoV-2 requires angiotensin-
118 converting enzyme 2 (ACE-2) and transmembrane protease serine 2 (encoded by TMPRSS2)
119 (M. Hoffmann, H. Kleine-Weber, S. Schroeder, et al., 2020). Coronaviruses must employ a
120 protease from the host cell to activate the viral spike (S) protein for successful infection, and
121 TMPRSS2 has recently been identified as an important host component in airway epithelial
122 cells that facilitates access into the cells (Glowacka et al., 2011; M. Hoffmann, H. Kleine-Weber,
123 S. Schroeder, et al., 2020; Li et al., 2003). The potential of TMPRSS2 inhibitors in preventing
124 the virus from entering the cell by blocking the protease activity of TMPRSS2 was investigated
125 in this work by Hoffman et al (M. Hoffmann, H. Kleine-Weber, S. Schroeder, et al., 2020).
126 Since that publication was published on the *Cell* paper, it has been growing dramatically by
127 citing these documents. Until now, TMPRSS2 was utilized as the drug target gene for fighting
128 SARS-CoV-2. Several publications have investigated the role of TMPRSS2 as the molecular
129 process of COVID-19.

130 The pandemic has not yet been controlled, and researchers still find the best drug for
131 COVID-19. However, until now, it remains unclear how many publications related to the
132 TMPRSS2 for COVID-19. Up to now, no studies has represented the trend of publication
133 related to TMPRSS2 as SARS-CoV-2 receptors for COVID-19 have been published.
134 Bibliometric analysis has a pivotal role in guiding research to prioritize future research.
135 Therefore, the importance of bibliometric analysis of TMPRSS2-related studies as SARS-CoV-
136 2 receptors for COVID-19 is to find relevant themes that require more research by evaluating
137 which areas have been explored and which have been highly cited.. Here, we used a
138 bibliometric-based approach to assess the TMPRSS2 as SARS-CoV-2 receptors for COVID-19
139 publication since the pandemic situation began.

140 Bibliometric analyses have been a well-known method for quantitative evaluation of
141 research articles, including authors of each article, the journal where it was published, and the
142 number of citations of these journals. The bibliometric analysis shed light on the research
143 activity through quantitative bibliographic description (Jones, 2016). The results will allow
144 future studies to assess several important points, including the publication trends related to the
145 TMPRSS2 gene and the most frequently used author keywords, citation analysis and the highly
146 cited articles, top 10 most cited countries, top 10 most active journals, and international
147 collaboration.

149 MATERIALS AND METHOD (11pt)

151 Database

152 SciVerse Scopus is an online database used to retrieve relevant publications in this
153 research (accessed on 28/12/2021). Scopus was chosen because of its advantages over other
154 electronic databases (Matthew E. Falagas, Eleni I. Pitsouni, George A. Malietzis, & Georgios
155 Pappas, 2008). First, its database provide the information of a number of features that make it

156 easier to sort and rank, including the countries, authors, journals, and institutions. Second, it
157 also gives the number of citations for any group of documents, which is used as a metric of
158 scientific merit(Hirsch, 2005).

159

160 **Indicators of bibliometrics**

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

172

173 **Keywords and search strategy**

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

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182 **RESULT AND DISCUSSION**

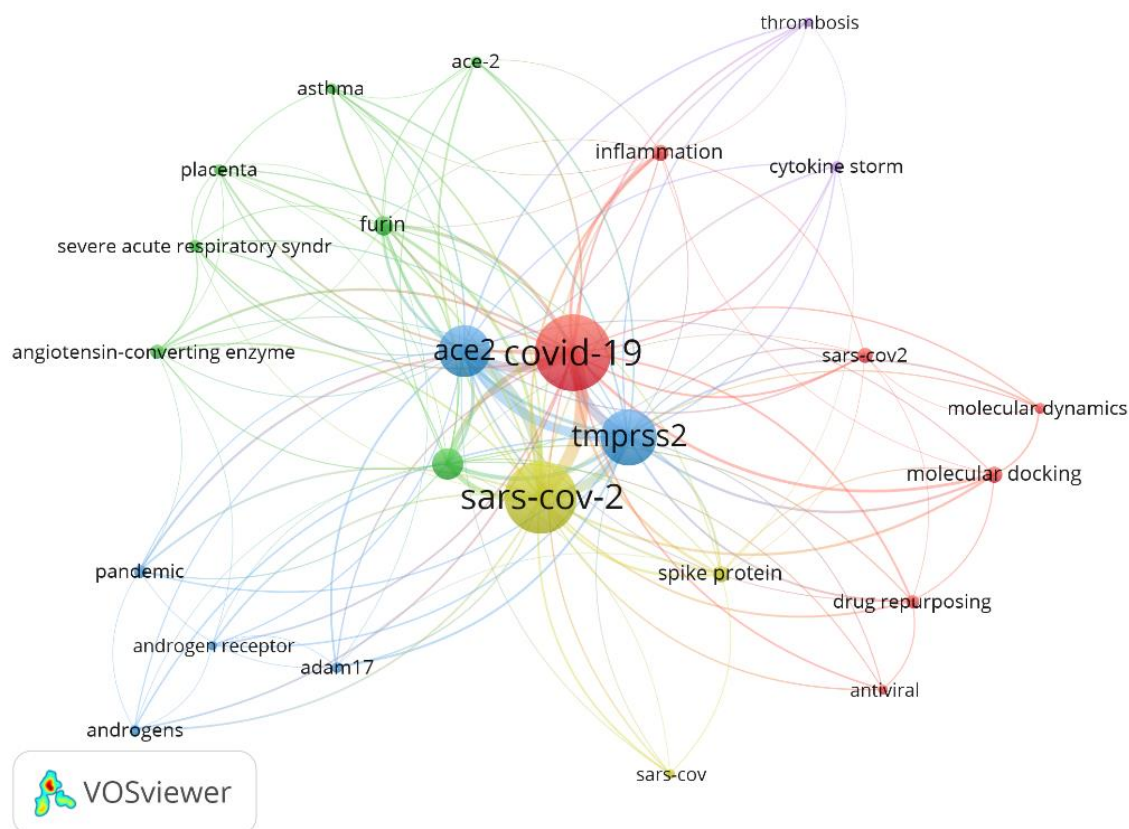
183 **Type of documents and languages**

184 In total, 1012 documents were retrieved from the Scopus database from 2020-2021. Around
185 7477 authors worldwide were involved in writing 1012 documents. Analysis of the retrieved
186 documents showed that 646 (63.84%) were research articles, and 261 (25.79%) were review
187 articles. In addition, other types of documents featured letters 57 (5.63%), notes 22 (2.17%),
188 editorials 15 (1.48%), short survey 7 (0.69%), book chapters 3 (0.30%), and a conference paper
189 1 (0.09%). Herein, only documents in English were selected. The comprehensive data of the
190 retrieved documents are available in Excel format in **Supplementary file 1**.

191

192 **Growth of publications**

193 In total, 1012 documents were extracted during the pandemic from 2020 to 2022. This study
194 focuses on the utilized TMPRSS2 as SARS-CoV-2 receptors for COVID-19. The first
195 documents appeared in early 2020 and surprisingly, the annual number of publications has
196 grown significantly since then, which hits its peak in 2021 (n=619) compared to 2020 (n=383).
197 In addition, we highlighted that the total number of publications in 2022 was still 10 documents
198 (as this article submitted). This relatively low number was presumably due to its being in early
199 2022 when this article was written. However, it does not rule out the possibility that it will
200 continue to grow up in the middle until the end of 2022. The trend of growing up publication
201 in TMPRSS2 studies indicated the increased interest in finding the solution for COVID-19,
202 which started from identifying the target of the SARS-CoV-2 virus in humans. Further, the top
203 5 subject areas related to the publication of the TMPRSS2 gene were in the area of medicine
204 (n=564), biochemistry, genetics and molecular biology (n=452), immunology and
205 microbiology (n=185), pharmacology, toxicology and pharmaceutics (n=122), and chemistry
206 (n=59).



207
208 **Figure 1. Visualization of most frequent author keywords (minimum occurrences of 25**
209 **times) related to the TMPRSS2 gene as SARS-CoV-2 receptors for COVID-19.**

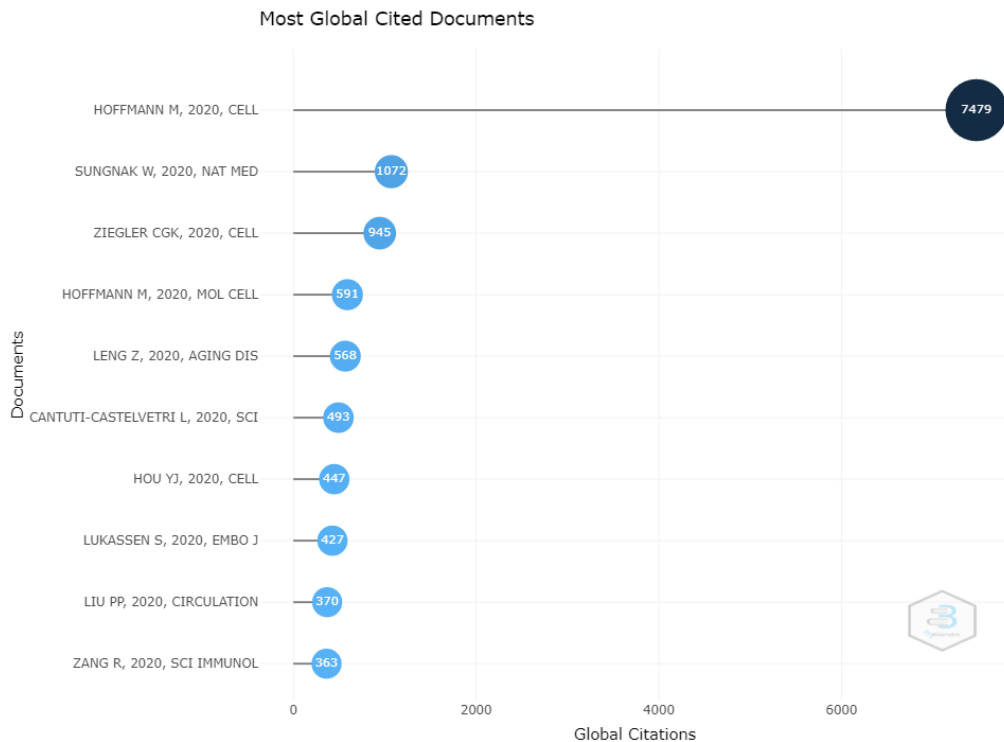
210 **Most frequently used author keywords**

211 **Figure 1** depicts the network visualization map of most of the author keywords with minimum
212 occurrences of 25. Author keywords with the highest number of occurrences were ‘COVID-19
213 (534 occurrences)’ followed by ‘SARS-CoV-2 (480 occurrences), ‘TMPRSS2 (289
214 occurrences), and ACE-2 (246 occurrences)’. Overlay visualization indicated the most author
215 keywords related to TMPRSS2 gene as SARS-CoV-2 receptors during these two years (2020-
216 2022), which were categorized into fourth-largest clusters, each with different colours including
217 COVID-19 (red colour) and SARS-CoV-2 (yellow colour) and two genes that important was
218 TMPRSS2 (dark blue colour) and ACE-2 (blue colour).
219

220 **Citation analysis and the highly cited articles**

221 The retrieved documents demonstrated that the average of citations per document was 28.69.
222 The study that received the highest number of citations was published in the *Cell* in May 2020
223 and received 7479 citations during two consecutive years (2020-2021); it was very surprising
224 the citation of this article was almost 7-fold higher citation than that the other top ten highest
225 cited articles. The trend of citation seems to be increased over time. The author of this article
226 was Hoffman et al., 2020 with the title of his article “SARS-CoV-2 Cell Entry Depends on
227 ACE2 and TMPRSS2 and is Blocked by a Clinically Proven Protease Inhibitor”(Markus
228 Hoffmann et al., 2020). Surprisingly, Hoffman et al., 2020 also published another published in
229 *Molecular Science* (Hoffmann, Kleine-Weber, & Pöhlmann, 2020). The second highest citation
230 of the document was published in March 2020 in *Nature Medicine* with the title “SARS-CoV-
231 2 entry factors are highly expressed in nasal epithelial cells together with innate immune
232 genes”(Sungnak et al., 2020), the total number of citations of this article was 1072. The top 10
233 most cited articles related to the study of TMPRSS2 as SARS-CoV-2 receptors for COVID-19
234 were listed in **Figure 2** and **Table 1**. From 10 journals that showed in **Figure 2** and **Table 1**

235 was published in high reputed journals. An interesting finding highlighted that among ten
 236 journals with the highest citation we identified, the *Cell* was dominated as it ranked in 1st, 3rd,
 237 and 7th.



238
 239 **Figure 2. Top 10 cited documents related the TMPRSS2 gene as SARS-CoV-2**
 240 **receptors for COVID-19.**

241
 242 **Top 10 most cited countries**

243 **Figure 3** shows the top 10 most cited countries related to the publication of TMPRSS2 for
 244 COVID-19. Our analysis highlighted that Germany was the most cited country with a total
 245 number of citations of 9400, followed by the USA with a total number of citations around 6409,
 246 and China with a total number of citations around 1788. It is not surprising that the most cited
 247 countries were from Germany. This result was in line with authors with the highest citation was
 248 associated with Germany as well, Hoffman Markus (Markus Hoffmann et al., 2020). Authors
 249 from Germany has published an article in high reputation journals. The top 10 most cited
 250 countries related to the study of TMPRSS2 for COVID-19 are listed in **Figure 3** and **Table 1**.

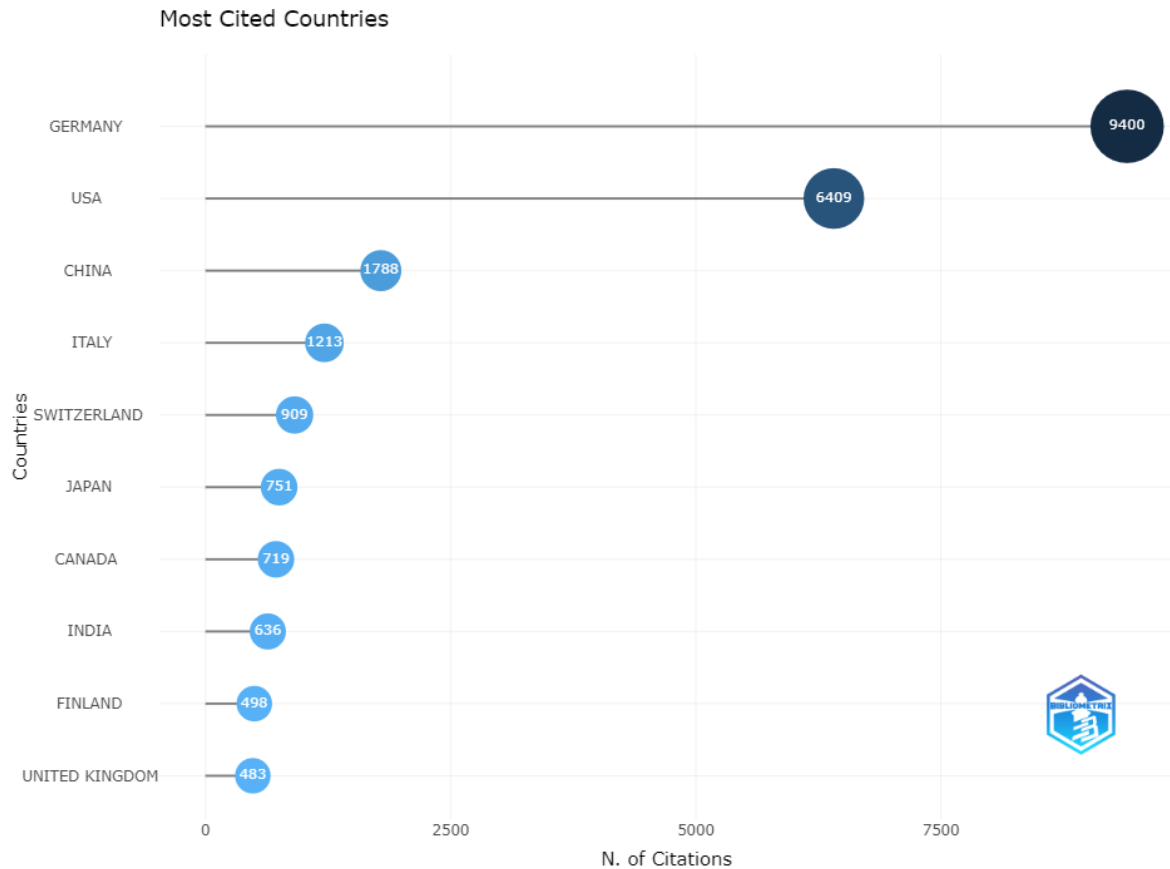
251
 252 **Top 10 most active Journals**

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

262
 263 **International collaboration**

264 International collaboration was very important in the scientific field. Through collaboration,
 265 scientists around the world enable to share/exchange information related to the field with one
 266 another. The thickness of the connecting line between any two countries represents the relative
 267 strength of research collaboration. The country with the greatest total link strength was the USA.

268 The USA had the largest number of collaborating countries. Therefore, it occupies the center of
 269 the map with many connecting lines with different countries (**Figure 5**). In addition, the
 270 international collaboration also can be presented based on the corresponding author country.
 271 Each of the authors can collaborate with other countries based on the same field. **Figure 6**
 272 depicted the single country publication (SCP) and multiple country publication (MCP) related
 273 to TMPRSS2 gene publication during the pandemic situation. According to our findings, USA
 274 is the country with the highest number of collaborating countries, followed by China and
 275 Germany in second and third places, respectively. Visualization of international collaboration
 276 among countries with minimum productivity of 25 documents is shown in **Figure 6**.



277
 278 **Figure 3. Top 10 cited country related the TMPRSS2 gene as SARS-CoV-2 receptors for**
 279 **COVID-19.**
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 283
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 286
 287 **Table 1. Top 10 cited articles related to the TMPRSS2 gene as SARS-CoV-2 receptors for**
 288 **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	(Markus Hoffmann et al., 2020)
Sungnak W	2020	SARS-CoV-2 entry factors are highly expressed in nasal	Nature Medicine	1072	536	53.44	(Sungnak et al., 2020)

			epithelial cells together with innate immune genes					
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	(M. Hoffmann, H. Kleine-Weber, & S. Pöhlmann, 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, Blet, Smyth, & Li, 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)	

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***Impact Factor in 2020**

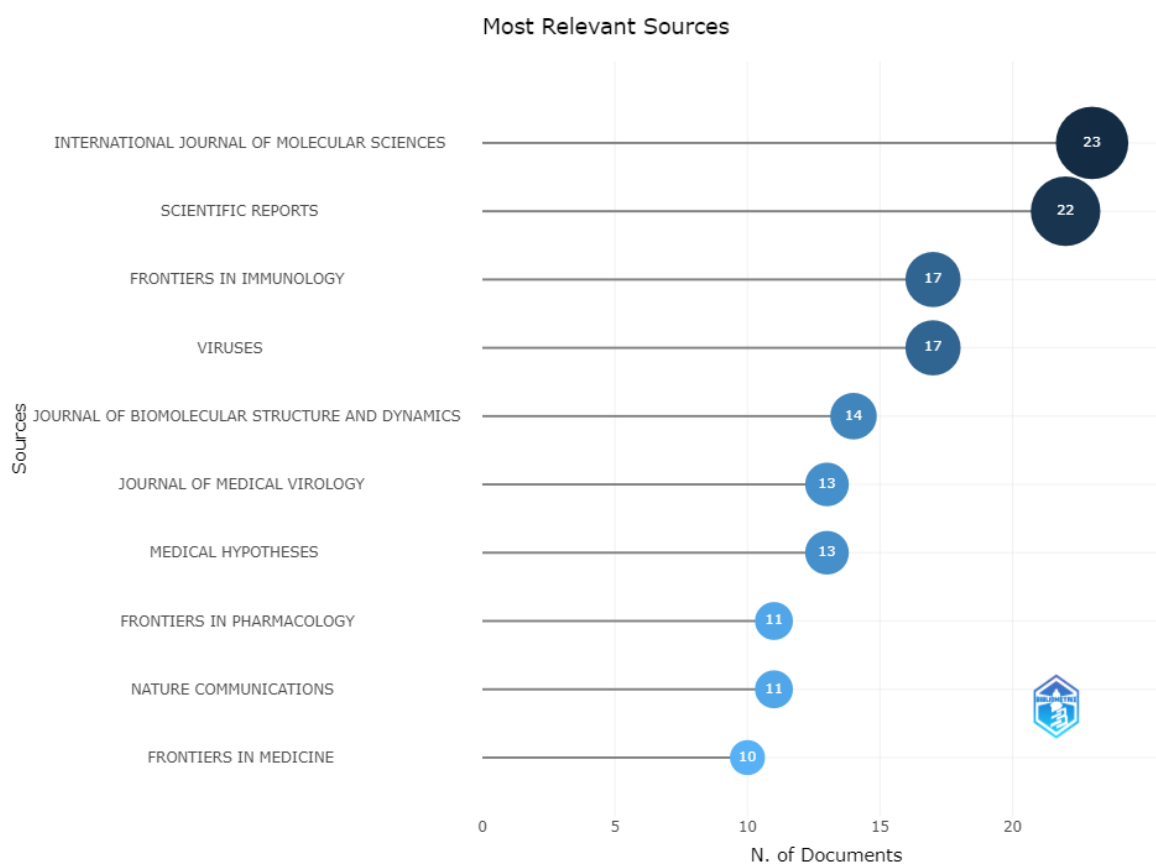


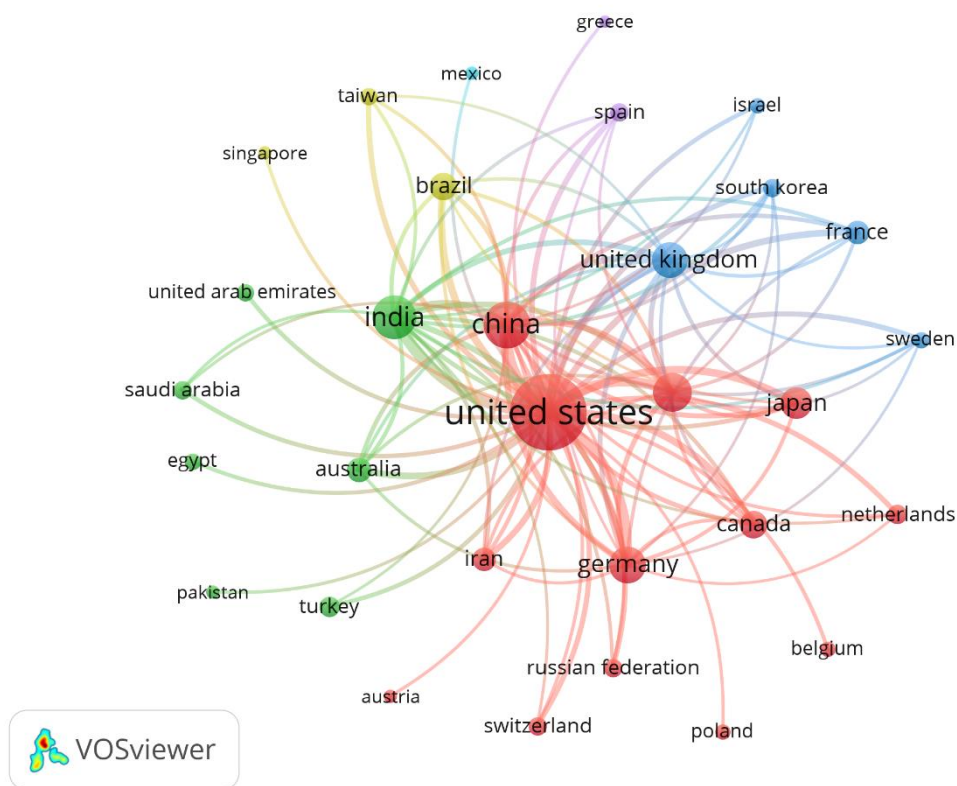
Figure 4. Top 10 journals in publishing TMPRSS2 gene as SARS-CoV-2 receptors for COVID-19.

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In a relatively short period, within two years, 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.

The results of the current study showed that the USA had the highest number of collaborating countries related to the TMPRSS2 gene as SARS-CoV-2 receptor. The collaboration allows scientists around the globe to share /exchange information and to stay updated about the field. This result could be attributed to a number of variables, including its huge population, high income countries, status as one of the countries most affected by COVID-19, 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-CoV-2 receptors, leading to an increase in bilateral research articles (**Figure 5**). An evidence showed that biomedical research productivity around the world is largely dependent on each country's per capita gross national product(Rahman & Fukui, 2003). Most publications were in the fields of medicine and biochemistry, genetics and molecular biology, and less number 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 beginning of the COVID-19 outbreak. Such collaborations

321 undoubtedly improve our understanding of the SARS-CoV-2 virus's nature(Shang et al., 2020).
 322 International collaboration can also greatly accelerate, support, and develop effective vaccine
 323 research (Smith et al., 2020).

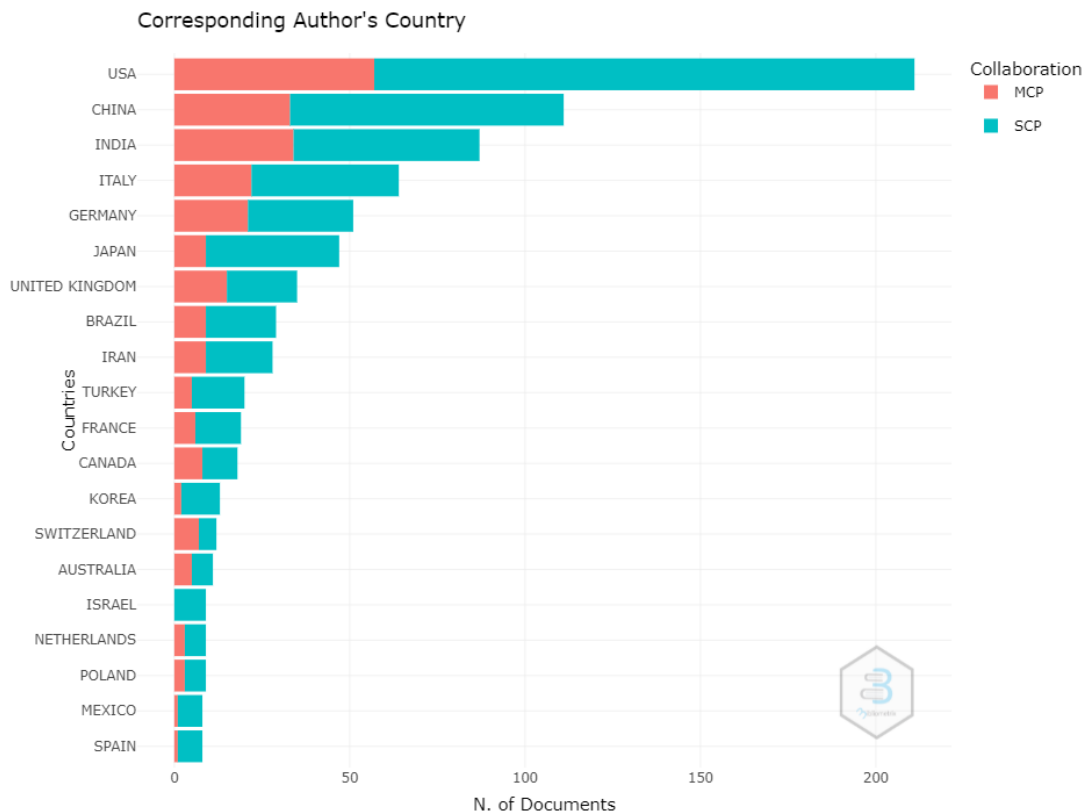


324 **Figure 5. Research collaboration among countries with minimum research output of 32**
 325 **documents in TMPRSS2 publication.**
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328 The most cited papers among the top 10 cited publications of TMPRSS2 as SARS-
 329 CoV-2 receptors for COVID-19 patients were research articles/original articles. The Journal
 330 from Germany, namely the *Cells*, one of the journals with a high impact factor (IF 2020: 41.58),
 331 had the highest number of citations on TMPRSS-2 as SARS-CoV-2 receptors for COVID-19,
 332 the total number of citations was 7479 citations. The article was written by Hoffman et al. since
 333 the early of the pandemic in May 2020. This article focused on the factor associated with SARS-
 334 CoV-2 infection of lung epithelial cells requires ACE-2 and TMPRSS2. TMPRSS2 has recently
 335 been identified as an important host component in airway epithelial cells that facilitate SARS-
 336 CoV-2 entering the cells (Markus Hoffmann et al., 2020). It is surprising that among the top
 337 10 articles with the highest number of citations, three were published in the High Impact journal
 338 the *Cell*. Among these publications, Germany was the non-English-speaking country with the
 339 highest number of citations. Interestingly, Hoffman et al. are from a German institution with
 340 Hoffman himself is a German, thereby no wonder Germany is the country with the highest
 341 citations with regards to articles discussing TMPRSS2 as one of the receptors for SARS-CoV-
 342 2. This finding seems leading that the impact factor was the widely effective predictor of
 343 citations each year, rather than methodology or quality of the research (Callaham, Wears, &
 344 Weber, 2002).

345 The present study has both merits and drawbacks. The study's merits include providing easy
 346 access to the core of evidence and research trend on a topic and identifying papers focused on
 347 TMPRSS2 as a SARS-CoV-2 receptor for COVID-19. The drawbacks of the current study were
 348 that it only comes from one single database (Scopus), therefore it may not collect all relevant
 349 evidence available. Furthermore, another noteworthy limitation of our research is limited to
 350 English articles, which implies we may be missing out on valuable information from the articles

351 provided in other languages. Besides, citation analysis, which is based on the number of
 352 citations per article contributed to our limitation. Many factors affect citation rate, including
 353 journal and author self-citations, incomplete citing, and omission bias. Some influential articles
 354 are cited a limited number of times until their research become popular (Brandt et al., 2019).
 355 We only included articles from 2020 – 2022, which implies the trend of research in the future
 356 may change overtime. Future investigations could re-evaluate more included scientific
 357 databases to identify more comprehensive findings, such as Web of Science or PubMed, and
 358 assessed the quality of articles based on their study design. The requirement for research on
 359 TMPRSS2 as a SARS-CoV-2 receptor is likely to grow as long as the pandemic continues.
 360 Consequently, this could be a significant research issue in the future.
 361



362 **Figure 6. Single country publications (SCP) and multiple country publications (MCP)**
 363 **the TMPRSS2 gene as SARS-CoV-2 receptors for COVID-19.**
 364

365 **Table 2. Top 10 corresponding author countries publishing article of TMPRSS2 gene as**
 366 **SARS-CoV-2 receptors for COVID-19.**
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Country	Articles	Freq	SCP	MCP	MCP Ratio
USA	211	0,23392	154	57	0,27
CHINA	111	0,12306	78	33	0,297
INDIA	87	0,09645	53	34	0,391
ITALY	64	0,07095	42	22	0,344
GERMANY	51	0,05654	30	21	0,412
JAPAN	47	0,05211	38	9	0,191
UNITED KINGDOM	35	0,0388	20	15	0,429
BRAZIL	29	0,03215	20	9	0,31
IRAN	28	0,03104	19	9	0,321
TURKEY	20	0,02217	15	5	0,25

368 Single country publications (SCP) and multiple country publications (MCP)

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Implications of the study for practice

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

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 years since the outbreak of COVID-19. Knowledge of existing findings on TMPRSS2 as SARS-CoV-2 receptors is not only helped researchers in better understanding 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.

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521 ORIGINAL RESEARCH

522 **Trend of Publication of TMPRSS2 as the SARS-CoV-2 Receptor:**
523 **Bibliometric Analysis During the COVID-19 Pandemic**

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Abstract

554 The pandemic of coronavirus disease 2019 (COVID-19) has not yet been fully
555 controlled until now, which is still impacting a large number of people worldwide. Since
556 the pandemic emerged, the growing number of publications related to TMPRSS2 as
557 SARS-CoV-2 receptor around the world increased rapidly with various findings and
558 qualities. It is important to determine the trend of TMPRSS2 publication as no such
559 studies currently exist that represent the trend of publication related to this field. Here,
560 we employed a bibliometric analysis-based approach to evaluate the relevant research
561 of TMPRSS2 as the receptor of SARS-CoV-2. Research published from 2020 to 2022
562 was identified. A total of 1012 relevant documents were selected. The most common
563 type of documents was research article 646 (63.84%) followed by review article 261
564 (25.79%), and letters to editors 57 (5.63%). The annual number of publications growth
565 significantly started from early 2020 with the total number of fluctuations in 2021
566 (n=619). Germany was the most cited country with total citations 9400, followed by
567 USA (6409) and China (1788), respectively. In conclusion, given the urgency of this
568 situation, this study indicated that the TMPRSS2 as SARS-CoV-2 receptor was an
569 important topic for alleviating the COVID-19.

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571 **Keywords:** Bibliometrics, COVID-19, SARS-CoV-2, TMPRSS2.

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Introduction

588 Coronavirus disease 2019 (COVID-19) was first emerged in Wuhan, China, as the new
589 infectious respiratory disease (Huang et al., 2020). The first wave of infections was
590 traced back to a seafood market in Wuhan, where animal contact resulted in virus
591 transmission to people and eventually human-to-human transmission (Chan et al.,
592 2020). In February of 2020, the ICTV named the virus that causes COVID-19 as severe
593 acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Organization, 2020) based
594 on its close homology to SARS-CoV (Zhu et al., 2020). The number of patients infected
595 with SARS-CoV-2 has been gradually increasing in multiple countries including Asia,
596 Australia, Europe, the Americas, and Africa. This condition has led the World Health
597 Organization (WHO) to declare this disease a pandemic. As of January 1, 2022, over

598 281 million cases and over 5.4 million deaths have been reported worldwide
599 (Wordometers, 2022). In order to slow the spread of the virus and keep the number of
600 critical patients within hospital capacity, almost all developed countries have imposed
601 strong restrictions on residents' movement, which has come at a high cost in terms of
602 money.

603 Effective vaccinations or preventive medicines that target SARS-CoV-2 cellular
604 uptake would almost probably contribute in illness mitigation. In May 2020, the
605 Hoffman group was reperforated that infection of lung epithelial cells with SARS-CoV-
606 2 requires angiotensin-converting enzyme 2 (ACE-2) and transmembrane protease
607 serine 2 (encoded by TMPRSS2) (M. Hoffmann, H. Kleine-Weber, S. Schroeder, et al.,
608 2020). Coronaviruses must employ a protease from the host cell to activate the viral
609 spike (S) protein for successful infection, and TMPRSS2 has recently been identified
610 as an important host component in airway epithelial cells that facilitates access into the
611 cells (Glowacka et al., 2011; M. Hoffmann, H. Kleine-Weber, S. Schroeder, et al., 2020;
612 Li et al., 2003). The potential of TMPRSS2 inhibitors in preventing the virus from
613 entering the cell by blocking the protease activity of TMPRSS2 was investigated in this
614 work by Hoffman et al (M. Hoffmann, H. Kleine-Weber, S. Schroeder, et al., 2020).
615 Since that publication was published on the *Cell* paper, it has been growing dramatically
616 by citing these documents. Until now, TMPRSS2 was utilized as the drug target gene
617 for fighting SARS-CoV-2. Several publications have investigated the role of TMPRSS2
618 as the molecular process of COVID-19. The pandemic has not yet been controlled, and
619 researchers still find the best drug for COVID-19. However, until now, it remains
620 unclear how many publications related to the TMPRSS2 for COVID-19. Up to now,
621 no studies has represented the trend of publication related to TMPRSS2 as SARS-CoV-
622 2 receptors for COVID-19 have been published. Bibliometric analysis has a pivotal role
623 in guiding research to prioritize future research. Therefore, the importance of
624 bibliometric analysis of TMPRSS2-related studies as SARS-CoV-2 receptors for
625 COVID-19 is to find relevant themes that require more research by evaluating which
626 areas have been explored and which have been highly cited.. Here, we used a
627 bibliometric-based approach to assess the TMPRSS2 as SARS-CoV-2 receptors for
628 COVID-19 publication since the pandemic situation began.

629 Bibliometric analyses have been a well-known method for quantitative evaluation
630 of research articles, including authors of each article, the journal where it was published,
631 and the number of citations of these journals. The bibliometric analysis shed light on
632 the research activity through quantitative bibliographic description (Jones, 2016). The
633 results will allow future studies to assess several important points, including the
634 publication trends related to the TMPRSS2 gene and the most frequently used author
635 keywords, citation analysis and the highly cited articles, top 10 most cited countries,
636 top 10 most active journals, and international collaboration.

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Methods

640 Database

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

647 merit(Hirsch, 2005).

648

649 Indicators of bibliometrics

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

661

662 Keywords and search strategy

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

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Results

674 Type of documents and languages

675 In total, 1012 documents were retrieved from the Scopus database from 2020-2021.
676 Around 7477 authors worldwide were involved in writing 1012 documents. Analysis
677 of the retrieved documents showed that 646 (63.84%) were research articles, and 261
678 (25.79%) were review articles. In addition, other types of documents featured letters 57
679 (5.63%), notes 22 (2.17%), editorials 15 (1.48%), short survey 7 (0.69%), book chapters
680 3 (0.30%), and a conference paper 1 (0.09%). Herein, only documents in English were
681 selected. The comprehensive data of the retrieved documents are available in Excel
682 format in **Supplementary file 1**.

683

684 Growth of publications

685 In total, 1012 documents were extracted during the pandemic from 2020 to 2022. This
686 study focuses on the utilized TMPRSS2 as SARS-CoV-2 receptors for COVID-19. The
687 first documents appeared in early 2020 and surprisingly, the annual number of
688 publications has grown significantly since then, which hits its peak in 2021 (n=619)
689 compared to 2020 (n=383). In addition, we highlighted that the total number of
690 publications in 2022 was still 10 documents (as this article submitted). This relatively
691 low number was presumably due to its being in early 2022 when this article was written.
692 However, it does not rule out the possibility that it will continue to grow up in the
693 middle until the end of 2022. The trend of growing up publication in TMPRSS2 studies
694 indicated the increased interest in finding the solution for COVID-19, which started
695 from identifying the target of the SARS-CoV-2 virus in humans. Further, the top 5

696 subject areas related to the publication of the TMPRSS2 gene were in the area of
697 medicine (n=564), biochemistry, genetics and molecular biology (n=452), immunology
698 and microbiology (n=185), pharmacology, toxicology and pharmaceuticals (n=122), and
699 chemistry (n=59).

700

701 Most frequently used author keywords

702 **Figure 1** depicts the network visualization map of most of the author keywords with
703 minimum occurrences of 25. Author keywords with the highest number of occurrences
704 were ‘COVID-19 (534 occurrences)’ followed by ‘SARS-CoV-2 (480 occurrences),
705 ‘TMPRSS2 (289 occurrences), and ACE-2 (246 occurrences)’. Overlay visualization
706 indicated the most author keywords related to TMPRSS2 gene as SARS-CoV-2
707 receptors during these two years (2020-2022), which were categorized into fourth-
708 largest clusters, each with different colours including COVID-19 (red colour) and
709 SARS-CoV-2 (yellow colour) and two genes that important was TMPRSS2 (dark blue
710 colour) and ACE-2 (blue colour).

711

712 Citation analysis and the highly cited articles

713 The retrieved documents demonstrated that the average of citations per document was
714 28.69. The study that received the highest number of citations was published in the *Cell*
715 in May 2020 and received 7479 citations during two consecutive years (2020-2021); it
716 was very surprising the citation of this article was almost 7-fold higher citation than
717 that the other top ten highest cited articles. The trend of citation seems to be increased
718 over time. The author of this article was Hoffman et al., 2020 with the title of his article
719 “SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and is Blocked by a
720 Clinically Proven Protease Inhibitor”(Markus Hoffmann et al., 2020). Surprisingly,
721 Hoffman et al., 2020 also published another published in *Molecular Science* (M.
722 Hoffmann, H. Kleine-Weber, & S. Pöhlmann, 2020). The second highest citation of the
723 document was published in March 2020 in *Nature Medicine* with the title “SARS-CoV-
724 2 entry factors are highly expressed in nasal epithelial cells together with innate immune
725 genes”(Sungnak et al., 2020), the total number of citations of this article was 1072. The
726 top 10 most cited articles related to the study of TMPRSS2 as SARS-CoV-2 receptors
727 for COVID-19 were listed in **Figure 2** and **Table 1**. From 10 journals that showed in
728 **Figure 2** and **Table 1** was published in high reputed journals. An interesting finding
729 highlighted that among ten journals with the highest citation we identified, the *Cell* was
730 dominated as it ranked in 1st, 3rd, and 7th.

731

732 Top 10 most cited countries

733 **Figure 3** shows the top 10 most cited countries related to the publication of TMPRSS2
734 for COVID-19. Our analysis highlighted that Germany was the most cited country with
735 a total number of citations of 9400, followed by the USA with a total number of citations
736 around 6409, and China with a total number of citations around 1788. It is not surprising
737 that the most cited countries were from Germany. This result was in line with authors
738 with the highest citation was associated with Germany as well, Hoffman Markus
739 (Markus Hoffmann et al., 2020). Authors from Germany has published an article in
740 high reputation journals. The top 10 most cited countries related to the study of
741 TMPRSS2 for COVID-19 are listed in **Figure 3** and **Table 1**.

742 Top 10 most active Journals

743 The leading journal in publishing articles related to TMPRSS2 for COVID-19 was the
744 *International Journal of Molecular Science*, with a total number of documents was 23.
745 According to the analysis that we collected based on the names of journals, we herein

746 emphasized that the *International Journal of Molecular Science* was the most
747 productive in publishing the study of TMPRSS2 for COVID-19. In addition, the second
748 most active journals were published in *Scientific Reports* which were published around
749 22 articles at the time of this manuscript written. The third leading journal was
750 published in *frontiers in Immunology* and *Viruses* journals with a total number of around
751 17 articles. The top 10 most active journals related to publishing the study of TMPRSS2
752 for COVID-19 are listed in **Figure 4**.

753

754 International collaboration

755 International collaboration was very important in the scientific field. Through
756 collaboration, scientists around the world enable to share/exchange information related
757 to the field with one another. The thickness of the connecting line between any two
758 countries represents the relative strength of research collaboration. The country with
759 the greatest total link strength was the USA. The USA had the largest number of
760 collaborating countries. Therefore, it occupies the center of the map with many
761 connecting lines with different countries (**Figure 5**). In addition, the international
762 collaboration also can be presented based on the corresponding author country. Each of
763 the authors can collaborate with other countries based on the same field. Figure 6
764 depicted the single country publication (SCP) and multiple country publication (MCP)
765 related to TMPRSS2 gene publication during the pandemic situation. According to our
766 findings, USA is the country with the highest number of collaborating countries,
767 followed by China and Germany in second and third places, respectively. Visualization
768 of international collaboration among countries with minimum productivity of 25
769 documents is shown in **Figure 6**.

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Discussion

773 In a relatively short period, within two years, the COVID-19 pandemic has impacted
774 the entire world. Many scientists around the world have made various kinds of efforts
775 to overcome this pandemic altogether. One of these efforts was to find out how the
776 mechanism of the SARS-CoV-2 virus enters the human body. Few studies were
777 focused on evaluating the trend of publication of TMPRSS2. Therefore, the current
778 study focused on evaluating the trend of publication of the TMPRSS2 gene as SARS-
779 CoV-2 receptors for COVID-19. As proven on this bibliometric analysis, knowledge of
780 existing papers on TMPRSS2 as SARS-CoV-2 receptors may aid researchers in better
781 understanding the mechanism by which the COVID-19 virus enters the human body.

782 The results of the current study showed that the USA had the highest number of
783 collaborating countries related to the TMPRSS2 gene as SARS-CoV-2 receptor. The
784 collaboration allows scientists around the globe to share /exchange information and to
785 stay updated about the field. This result could be attributed to a number of variables,
786 including its huge population, high income countries, status as one of the countries most
787 affected by COVID-19, affordable medical research resources, and highly reliable data
788 management systems. During the pandemic, China, Germany, India, and the USA all
789 contributed significantly to the worldwide network of COVID-19 evaluating
790 TMPRSS2 as SARS-CoV-2 receptors, leading to an increase in bilateral research
791 articles (**Figure 5**). An evidence showed that biomedical research productivity around
792 the world is largely dependent on each country's per capita gross national
793 product (Rahman & Fukui, 2003).

794

Most publications were in the fields of medicine and biochemistry, genetics and

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

804 The most cited papers among the top 10 cited publications of TMPRSS2 as
805 SARS-COV-2 receptors for COVID-19 patients were research articles/original articles.
806 The Journal from Germany, namely the *Cells*, one of the journals with a high impact
807 factor (IF 2020: 41.58), had the highest number of citations on TMPRSS-2 as SARS-
808 CoV-2 receptors for COVID-19, the total number of citations was 7479 citations. The
809 article was written by Hoffman et al. since the early of the pandemic in May 2020. This
810 article focused on the factor associated with SARS-CoV-2 infection of lung epithelial
811 cells requires ACE-2 and TMPRSS2. TMPRSS2 has recently been identified as an
812 important host component in airway epithelial cells that facilitate SARS-COV-2
813 entering the cells (Markus Hoffmann et al., 2020). It is surprising that among the top
814 10 articles with the highest number of citations, three were published in the High Impact
815 journal the *Cell*. Among these publications, Germany was the non-English-speaking
816 country with the highest number of citations. Interestingly, Hoffman et al. are from a
817 German institution with Hoffman himself is a German, thereby no wonder Germany is
818 the country with the highest citations with regards to articles discussing TMPRSS2 as
819 one of the receptors for SARS-CoV- 2. This finding seems leading that the impact factor
820 was the widely effective predictor of citations each year, rather than methodology or
821 quality of the research (Callaham et al., 2002).

822 The present study has both merits and drawbacks. The study's merits include
823 providing easy access to the core of evidence and research trend on a topic and
824 identifying papers focused on TMPRSS2 as a SARS-CoV-2 receptor for COVID-19.
825 The drawbacks of the current study were that it only comes from one single database
826 (Scopus), therefore it may not collect all relevant evidence available. Furthermore,
827 another noteworthy limitation of our research is limited to English articles, which
828 implies we may be missing out on valuable information from the articles provided in
829 other languages. Besides, citation analysis, which is based on the number of citations
830 per article contributed to our limitation. Many factors affect citation rate, including
831 journal and author self-citations, incomplete citing, and omission bias. Some influential
832 articles are cited a limited number of times until their research become popular (Brandt
833 et al., 2019). We only included articles from 2020 – 2022, which implies the trend of
834 research in the future may change overtime. Future investigations could re-evaluate
835 more included scientific databases to identify more comprehensive findings, such as
836 Web of Science or Pubmed, and assessed the quality of articles based on their study
837 design. The requirement for research on TMPRSS2 as a SARS-CoV-2 receptor is likely
838 to grow as long as the pandemic continues. Consequently, this could be a significant
839 research issue in the future.

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843 Implications of the study for practice

844 To our knowledge, this study might be considered as the first report on the most cited

845 papers in TMPRSS2 and SARS-COV-2 receptor. As the collaborative work and
846 network are essential to lead research in the new emerging disease, researchers around
847 the world may have opportunities to contribute in to a research team, especially in the
848 expert of genomics, medicinal chemistry, biochemistry, molecular biology, and related
849 sciences such as biophysics and cell biology.

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Conclusion

852 A large number of publications related to TMPRSS2 as SARS-CoV-2 receptors have
853 been published rapidly in many journals in the past two years since the outbreak of
854 COVID-19. Knowledge of existing findings on TMPRSS2 as SARS-CoV-2 receptors
855 is not only helped researchers in better understanding the mechanism of SARS-CoV-2
856 entering the human body of COVID-19 facilitated by TMPRSS2 gene, but it also can
857 help researchers to find the drug target gene for COVID-19 (genomic driven drug
858 discovery) and highlight the importance of exploring research on SARS-COV-2
859 receptors.

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862 Disclosure

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Ethical Approval and Consent to participate

864 No ethical approval was required, as this was a bibliometric review for the existing
865 literature.

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Consent for publication

868 Not applicable.

869

Availability of data and materials

870 This study analyzed the dataset from the publicly available dataset. The source of this
871 study can be accessed here <https://www.scopus.com/results>

872
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Competing interests

874 The authors disclose no conflict.

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Funding

877 This research did not receive any specific grant from funding agencies in the public,
878 commercial, or not-for-profit sectors.

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Authors' contributions

882 LMI, DAP conceived and designed the study. LMI performed all data analyses. LMI,
883 DAP, YRN, WA, HD, RM, MAS and RC interpreted the results and revised the paper.
884 LMI wrote the manuscript. All authors read and approved the final manuscript.

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Acknowledgment:

887 The author would like to thank Universitas Ahmad Dahlan for giving the opportunities
888 to this study.

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Additional File

891 Supplementary Figure 1

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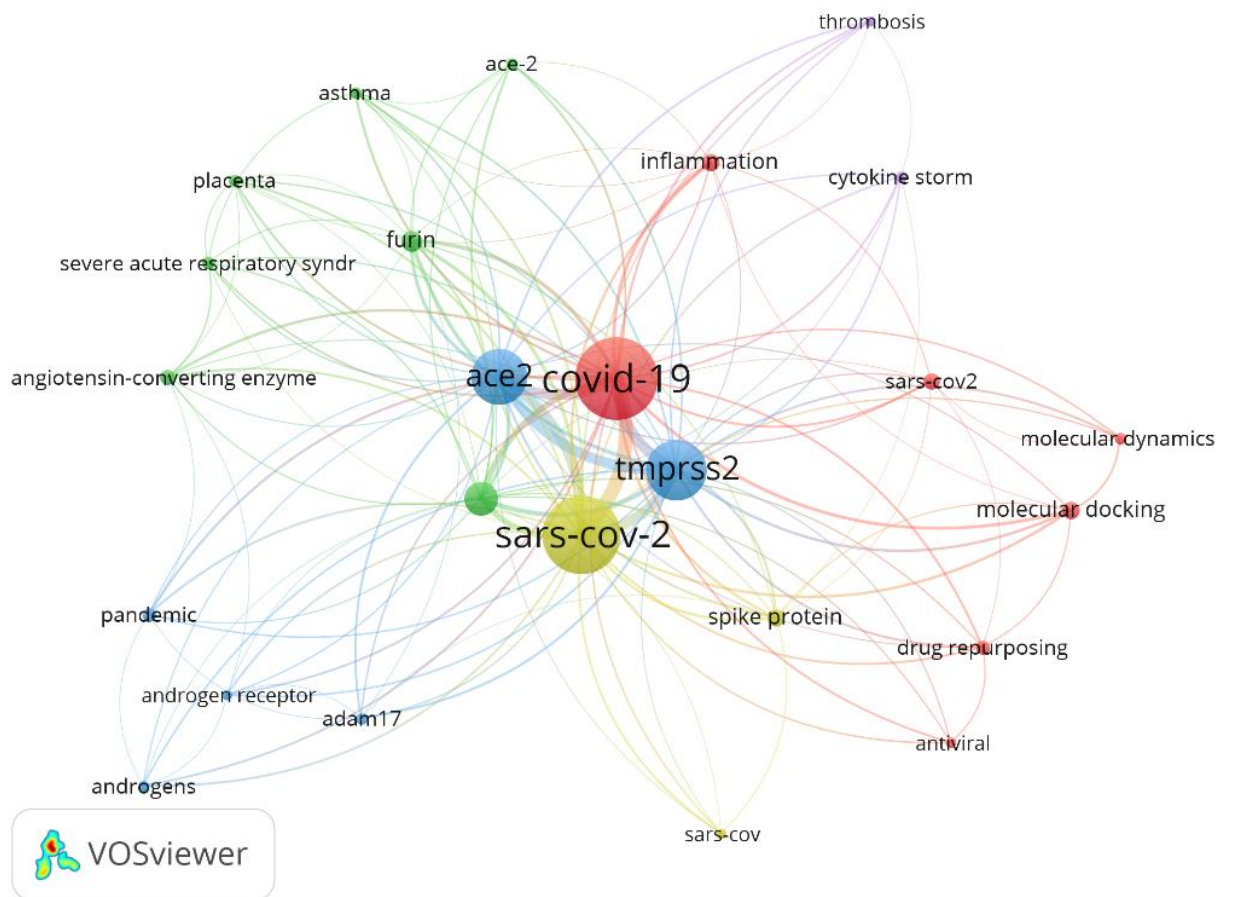
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913 **Figures:**



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

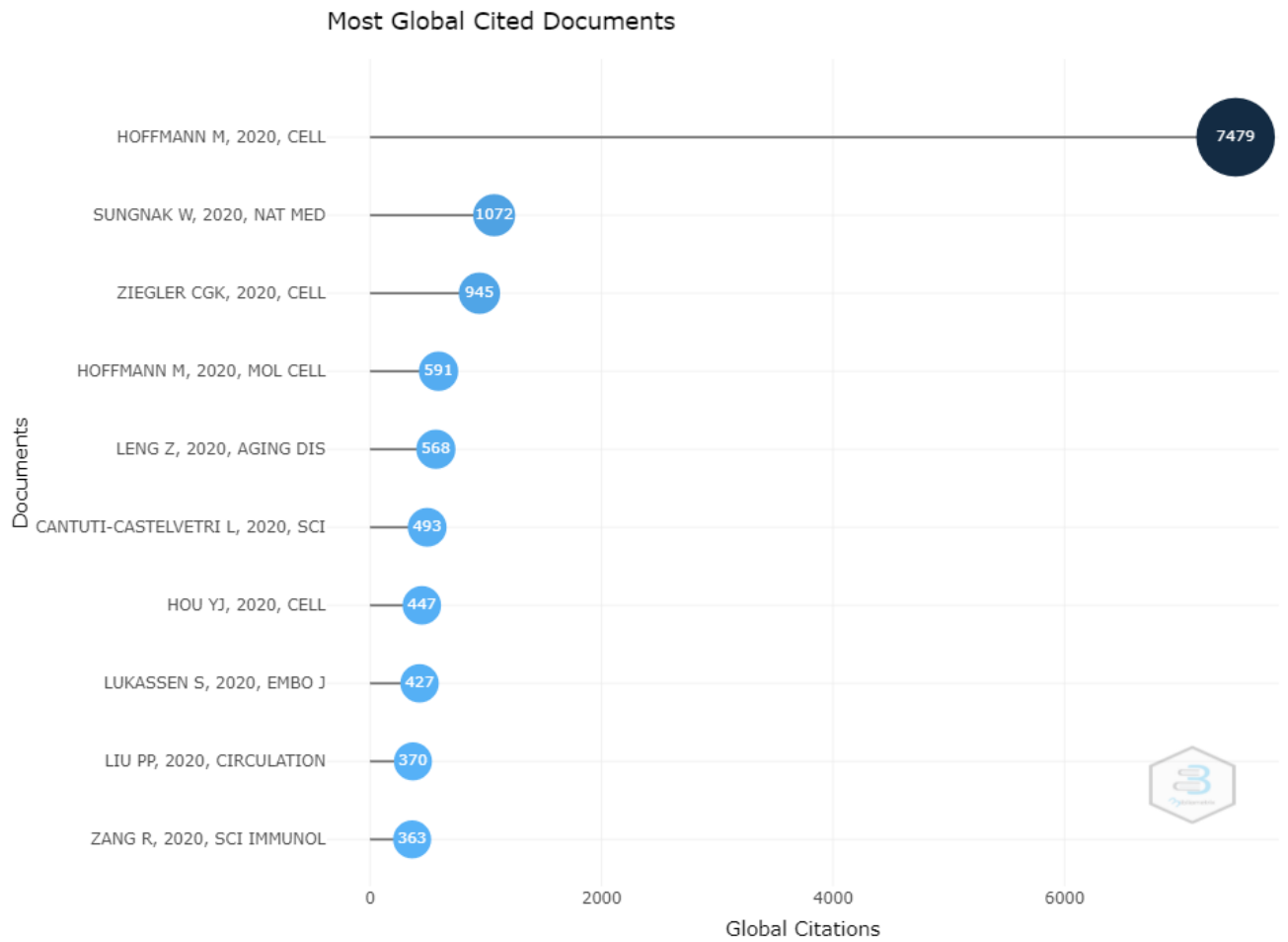
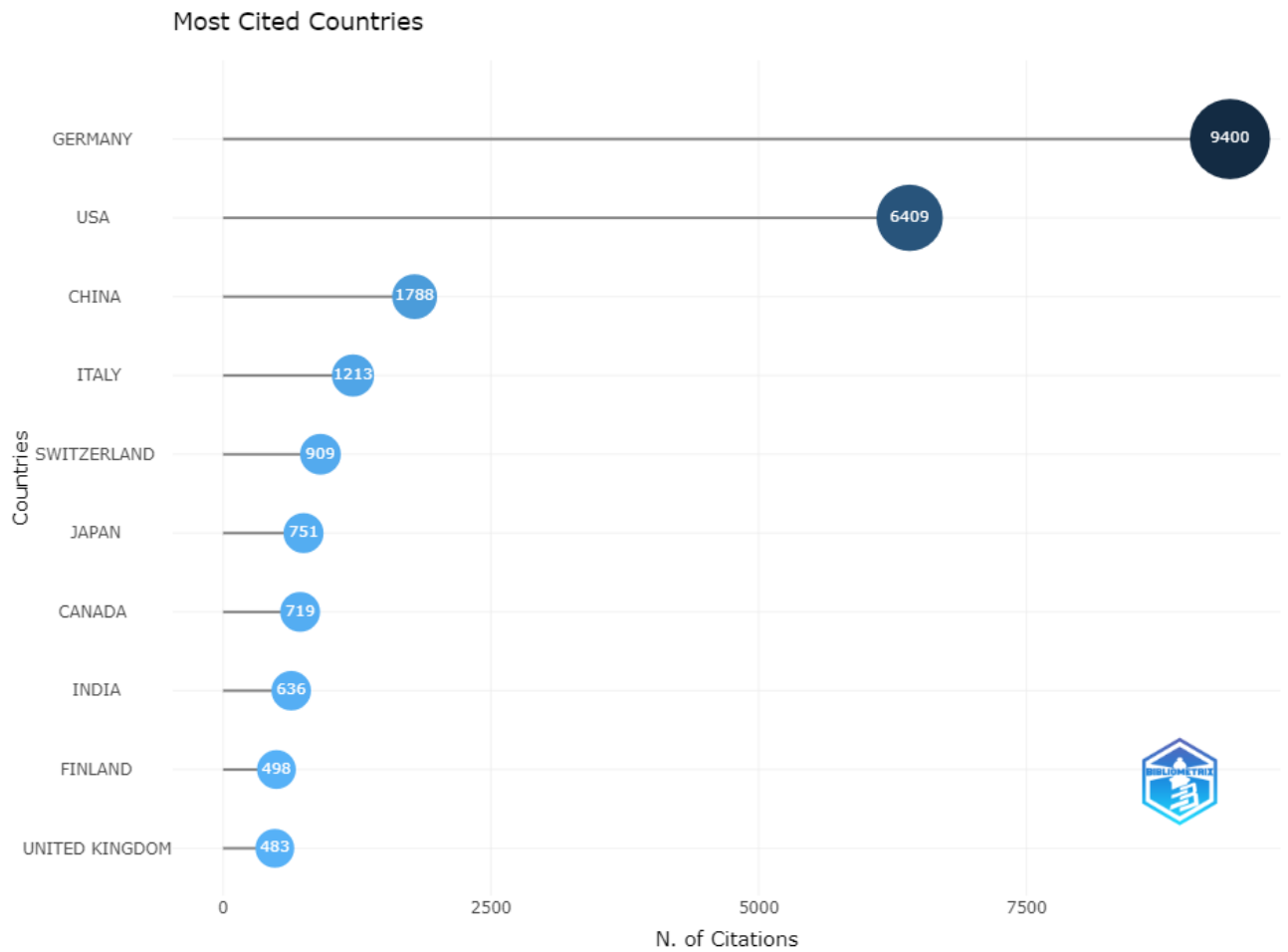


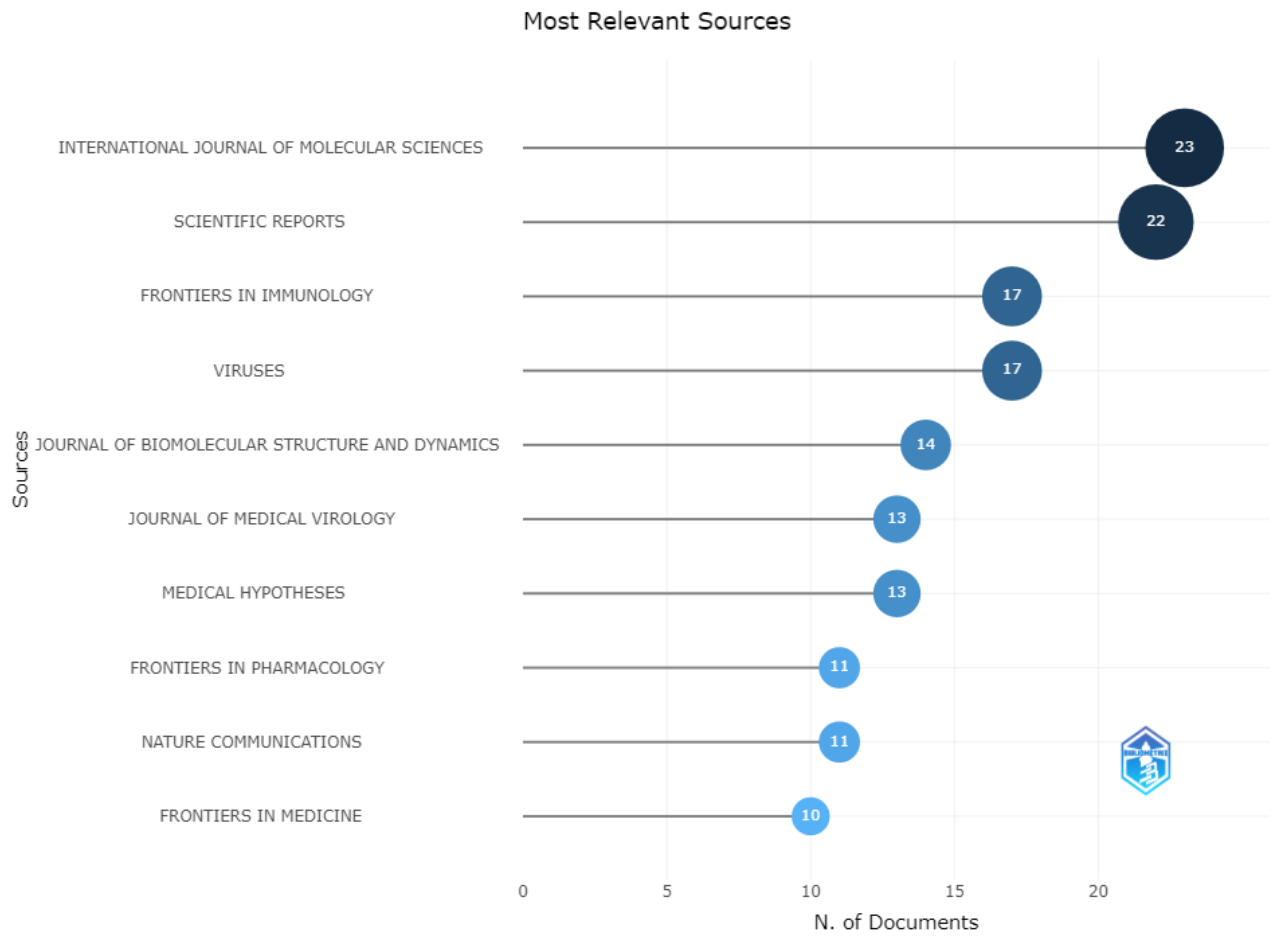
Figure 2. Top 10 cited documents related the TMPRSS2 gene as SARS-CoV-2 receptors for COVID-19.

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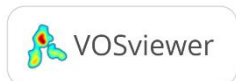
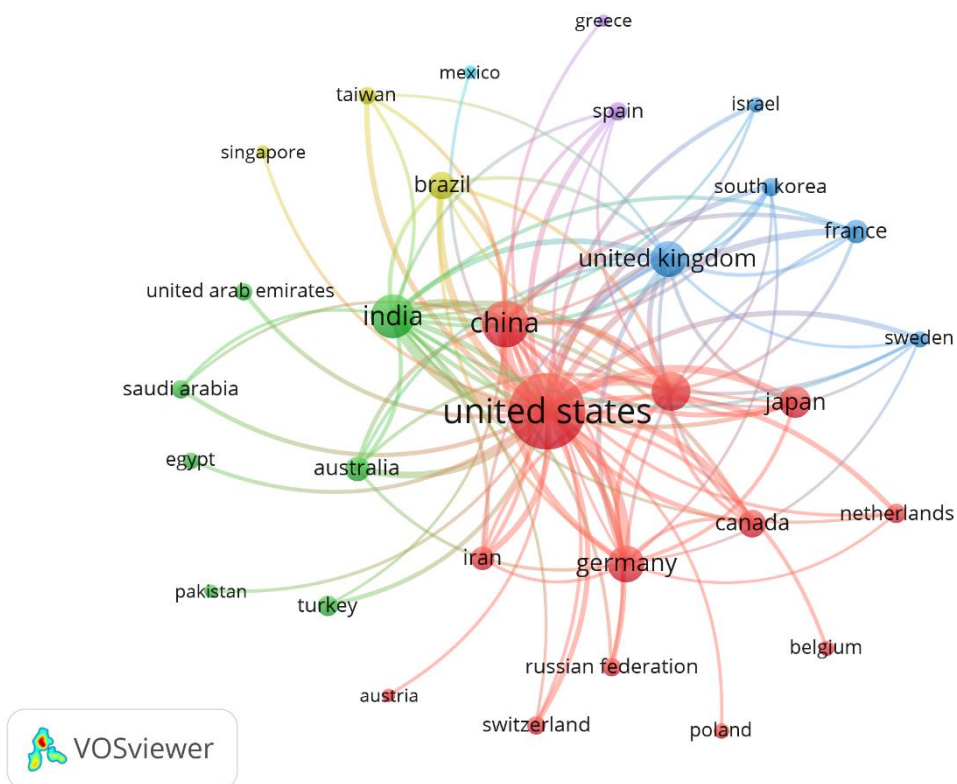
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Figure 3. Top 10 cited country related the TMPRSS2 gene as SARS-CoV-2 receptors for COVID-19.



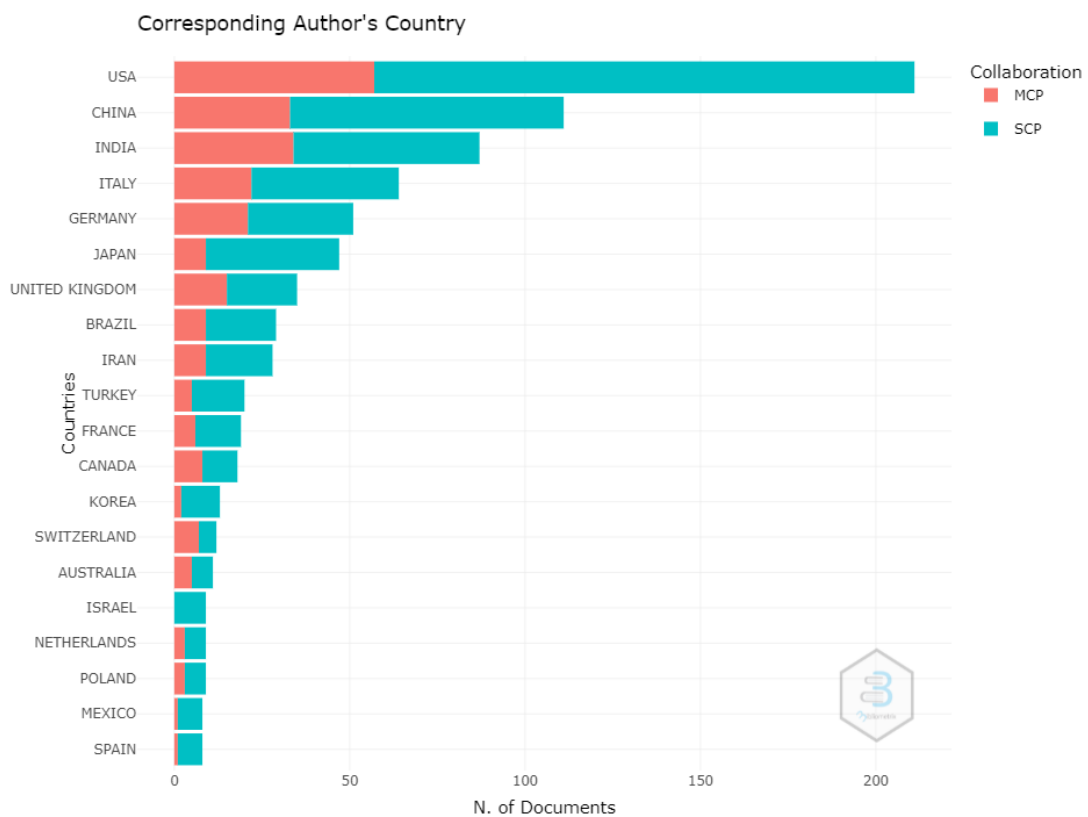
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Figure 4. Top 10 journals in publishing TMPRSS2 gene as SARS-CoV-2 receptors for COVID-19.



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Figure 5. Research collaboration among countries with minimum research output of 32 documents in TMRSS2 publication.



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Figure 6. Single country publications (SCP) and multiple country publications (MCP)

956 the TMPRSS2 gene as SARS-CoV-2 receptors for COVID-19.

Tables:**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	(Markus 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	(M. Hoffmann, H. Kleine-Weber, & S. Pöhlmann, 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**

Table 2. Top 10 corresponding author countries publishing article of TMPRSS2 gene as SARS-CoV-2 receptors for COVID-19.

Country	Articles	Freq	SCP	MCP	MCP Ratio
USA	211	0,23392	154	57	0,27
CHINA	111	0,12306	78	33	0,297
INDIA	87	0,09645	53	34	0,391
ITALY	64	0,07095	42	22	0,344
GERMANY	51	0,05654	30	21	0,412
JAPAN	47	0,05211	38	9	0,191
UNITED KINGDOM	35	0,0388	20	15	0,429
BRAZIL	29	0,03215	20	9	0,31
IRAN	28	0,03104	19	9	0,321
TURKEY	20	0,02217	15	5	0,25

Single country publications (SCP) and multiple country publications (MCP)

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3. **Naming the coronavirus disease (COVID-19) and the virus that causes it** [[https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/naming-the-coronavirus-disease-\(covid-2019\)-and-the-virus-that-causes-it](https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/naming-the-coronavirus-disease-(covid-2019)-and-the-virus-that-causes-it)]
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Januari 29, 2023

Dear Editors,

Please find our attached manuscript entitled “**Trend of Publication of TMPRSS2 as the SARS-CoV-2 Receptor: Bibliometric Analysis During the COVID-19 Pandemic**,” which we are submitting for consideration for publication as an Original Research article in *Pharmaciana*. We are thankful for your kind suggestions regarding our manuscript. Here, we are sending our revised manuscript in accordance with the comments given by the three reviewers. We have read through all the reviewers’ suggestions very carefully, and made the necessary revisions based on these comments, as detailed below in a point-by-point format. The revised sections are highlighted in yellow. Finally, we would like to thank you once again for giving us the opportunity to improve our manuscript. We very much hope that these revisions are adequate. We appreciate your assistance and are looking forward to hearing from you.

Sincerely yours,

Lalu Muhammad Irham M.Farm.,Ph.D Apt
Address: Faculty of Pharmacy,
Kampus 3 Universitas Ahmad Dahlan,
Jl Prof Dr Soepomo, Janturan, Yogyakarta
Yogyakarta 55166

We have reached a decision regarding your submission to Pharmacia, "Trend of Publication of TMPRSS2 as the SARS-CoV-2 Receptor: Bibliometric Analysis During the COVID-19 Pandemic".

Our decision is to:

Revision Required

Reviewer A:

Does the paper contain an original contribution to the field?:

Yes

Is the paper technically sound?:

Yes

Does the title of the paper accurately reflect the major focus contribution of this paper?:

Yes

Please suggest change of the title as appropriate (if any):

Is the abstract a clear description of the paper?:

Yes

Is the paper well written (clear, concise, and well organized)?:

Yes

Are the equations, figures and tables in this journal style, clear, relevant, and are the captions adequate?:

Yes

Please score the paper on a scale of 0 - 10 as per the directions below:

:

7-8 Good

Please write down your suggestion to improve this manuscript:

Find the comment in the attached file

Answer: We are grateful to the Reviewer for the positive assessment of our study.

Reviewer B:

Does the paper contain an original contribution to the field?:

Yes

Is the paper technically sound?:

Yes

Does the title of the paper accurately reflect the major focus contribution of this paper?:

Yes

Please suggest change of the title as appropriate (if any):

TMPRSS2 as a Receptor for SARS-CoV-2: Bibliometric Analysis During the COVID-19 Pandemic

Is the abstract a clear description of the paper?:

Yes

Is the paper well written (clear, concise, and well organized)?:

Yes

Are the equations, figures and tables in this journal style, clear, relevant, and are the captions adequate?:

No

Please score the paper on a scale of 0 - 10 as per the directions below:

:

7-8 Good

Answer: We are grateful to the Reviewer for this comment.

Please write down your suggestion to improve this manuscript:

In this manuscript (24052-63614-1-RV), the authors performed a bibliometric analysis to evaluate studies related to TMPRSS2 as a receptor for SARS-CoV-2. This well-structured and rationally organized manuscript contains an important discussion of TMPRSS2 as a gene of interest. I suggest it be accepted into the Pharmacia Journal after addressing the following issues.

Answer: We are grateful to the Reviewer for the positive assessment of our study.

1. It is not scientifically rigorous to ascribe the manuscript to title "Trend of Publication of TMPRSS2 as the SARS-CoV-2 Receptor: Bibliometric Analysis During the COVID-19 Pandemic". Bibliometric analysis already represents the trend of publication. It is suggested to shorten the manuscript title to be more accurate and precise.

Answer: We are grateful to the reviewer for this suggestion. We changed the title in to “Trend of Publication of TMPRSS2 as the SARS-CoV-2 Receptor During the COVID-19 Pandemic”.

2. There are some grammatical errors in the text such as conclusion in Abstract (line 30), COVID-19 in line 184 and 191, etc. The English quality and grammar need to be improved.

Answer: We are grateful to the Reviewer for this comment. The typho has been corrected in line 184“Figure 3 shows the top 10 most cited countries related to the publication of TMPRSS2 for COVID-19. Line 191” The top 10 most cited countries related to the study of TMPRSS2 for COVID-19 are listed in **Figure 3** and **Table 1**.

3. First mentioned abbreviation should be described what it stands for, such as ICTV (line 55).

Answer: Many thanks for the reviewer’s comments. We have made ascertain every abbreviation and describe it.

4. What is the biological role of TMPRSS2 in association with COVID-19 severity? Why is TMPRSS2 more important as compared the other identified genes responsible for COVID-19 such as ACE1 and ACE2? The genes comparison can be elaborated in the manuscript.

Answer: We are grateful to the Reviewer for noticing that. To made it more clear mechanism we added one figure (Figure 7) regarding the mechanism of action of SARS-CoV-2 Entry through Host ACE2 and TMPRSS2

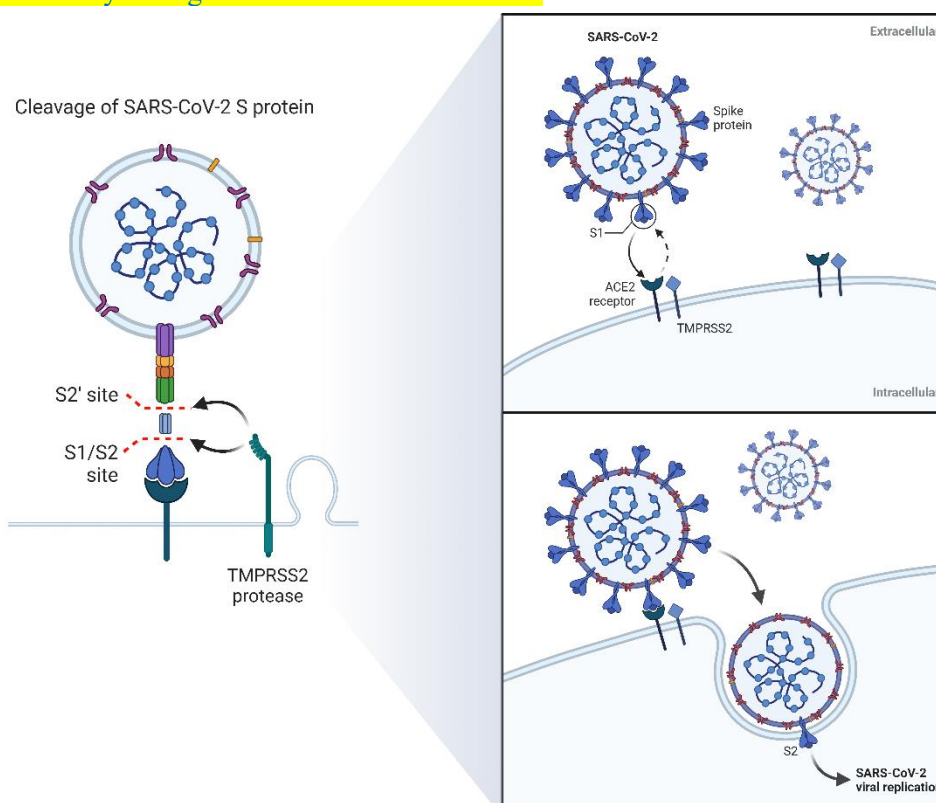


Figure 7. SARS-CoV-2 Entry through Host ACE2 and TMPRSS2. This figure was created by Biorender.com under license number GS24Y4YZSS.

5. In the methodology, why did authors not include other databases as data sources such as Web of Science, PubMed, or pre-print platforms?

Answer: We are grateful to the Reviewer for this comment. In the current study, Scopus was used because it is 100% inclusive of MEDLINE. Secondly, Scopus has a larger number of indexed journals (approximately 23,000 journals) than Web of Knowledge. Therefore, the volume of literature retrieved from Scopus will be larger than that obtained from Web of Science (M. E. Falagas, E. I. Pitsouni, G. A. Malietzis, & G. Pappas, 2008) . Thirdly, Scopus has many functions that facilitate citation analysis, counting research collaboration, and data export to Microsoft Excel for further tabulation and mapping. Indeed, many published bibliometric studies have used Scopus as the tool to retrieve the required data.

6. Please make sure the indentation consistency throughout the manuscript.

Answer: We are grateful to the Reviewer for this comment.

7. There two different year ranges under Result and Discussion section i.e., 2020-2021 and 2020-2022. Which is correct?

Answer: We are grateful to the Reviewer for this comment. We fixed already, we analyzed the publication during 2020-2022.

8. The results in Figs. 2 and 3 highlight the total citation number related the TMPRSS2 gene as SARS-CoV-2 receptors. Did authors consider the number and impact of self-citation?

Answer: We are grateful to the Reviewer for this comment. We could not concern about the impact of self-citation in this bibliometric study.

9. In Fig. 4, the top 4 journals (out of 10) that published articles related to TMPRSS2 for COVID-19 are from fully open access journals. In addition, 70% of the most active journals demonstrated in Fig. 4 are also open access. Does the journal platform have an impact on the bibliometric trend?

Answer: : We are grateful to the Reviewer for this comment. We added the information regarding the studies have been conducted to examine whether OA leads to a citation advantage. Interestingly, most of the journal were open access journal which is implicate to citation advantage. As reported by several studies revealed that the Open Access Journal promotes citations(Basson, Blanckenberg, & Prozesky, 2021; Sotudeh & Horri, 2007). (Line 191-194)

10. In the subsection of International collaboration (line 204), Figure 5 should be mentioned in advance to improve the clarity of the discussion.

Answer : We are grateful to the Reviewer for this comment. Figure 5 position has been corrected.

11. In Fig. 6, Switzerland is the only country that has a higher MCP than SCP while other countries show more SCP than that of MCP. Do authors have an explanation on this finding?

Answer : We are grateful to the Reviewer for this comment. Yes we agree that the Switzerland among based researchers was strong growth in current period. it is clear that collaboration with Asia has increased significantly. although Europe remains switzerland most important partner by far [https://issuu.com/sbfi_sefri_seri/docs/bibliometrie_sefri_2008_2018_en].

12. Table 2 has not been mentioned somewhere in the text.

Answer : We are grateful to the Reviewer for this comment. We fixed already (line 214). Thank you

13. The paragraph in line 236-243 of the Result and Discussion seems not quite relevant with the discussion and should be part of Introduction i.e., In a relatively short period, within two years...

Answer: We are grateful to the Reviewer for this comment. We already put the

paragraph in the introduction part. Line 94-102

14. Should the subsection of Implications of the study for practice (line 306) be in bold?

Answer: We are grateful to the Reviewer for this comment. We fixed already. Thank you

15. Conclusion part is too short. Please extend this section accordingly.

We are grateful to the Reviewer for this comment. We fixed already. Thank you

“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 in better understanding 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 trend of publication related to TMPRSS2 publication. The annual number of publications growth significantly started from early 2020 with the 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”.

16. All references should be in a consistent style and format.

We are grateful to the Reviewer for this comment. We fixed already. Thank you

Reference:

- Aria, M., & Cuccurullo, C. (2017). bibliometrix: An R-tool for comprehensive science mapping analysis. *Journal of Informetrics*, *11*(4), 959-975.
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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 METHOD

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

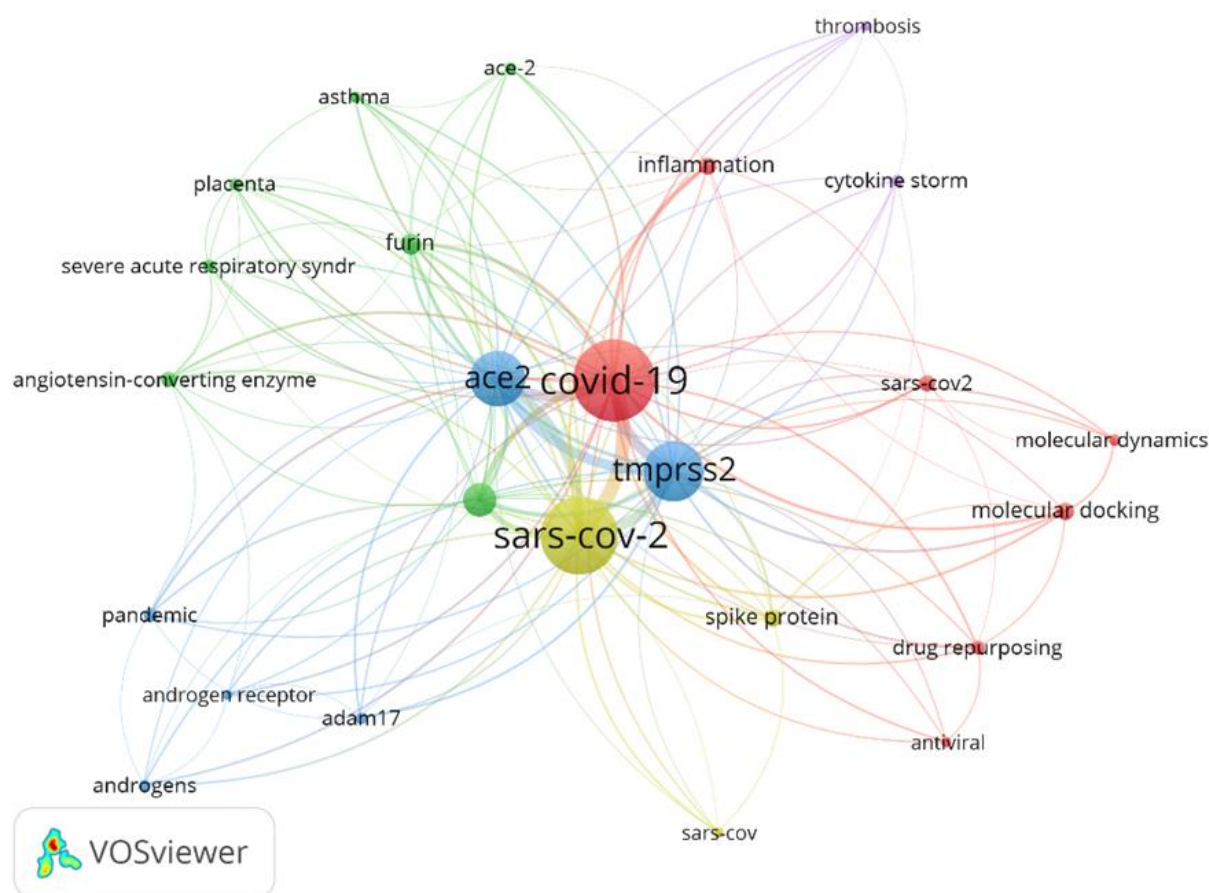
Type of documents and languages for TMPRSS2 research

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%). Herein, only documents in English were selected. The comprehensive data of the retrieved documents are presented in Excel format in **Supplementary File 1**.

153 **Growth of publications for TMPRSS2 research**

154 In total, 1012 documents were extracted during the pandemic from 2020 to 2022. This study
 155 focuses on the utilized TMPRSS2 as SARS-CoV-2 receptors for COVID-19. The first documents
 156 appeared in early 2020 and surprisingly, the annual number of publications has grown significantly
 157 since then, which hits its peak in 2021 (n=619) compared to 2020 (n=383). In addition, we highlighted
 158 that the total number of publications in 2022 was still 10 documents (as this article submitted). This
 159 relatively low number was presumably due to its being in early 2022 when this article was written.
 160 However, it does not rule out the possibility that it will continue to grow up in the middle until the end
 161 of 2022. The trend of growing up publication in TMPRSS2 studies indicated the increased interest in
 162 finding the solution for COVID-19, which started from identifying the target of the SARS-CoV-2
 163 virus in humans. Further, the top 5 subject areas related to the publication of the TMPRSS2 gene were
 164 in the area of medicine (n=564), genetics and molecular biology and biochemistry (n=452),
 165 microbiology and immunology (n=185), pharmacology, toxicology and pharmaceuticals (n=122), and
 166 chemistry (n=59).

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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

175 Most frequently used author keywords for TMPRSS2 research

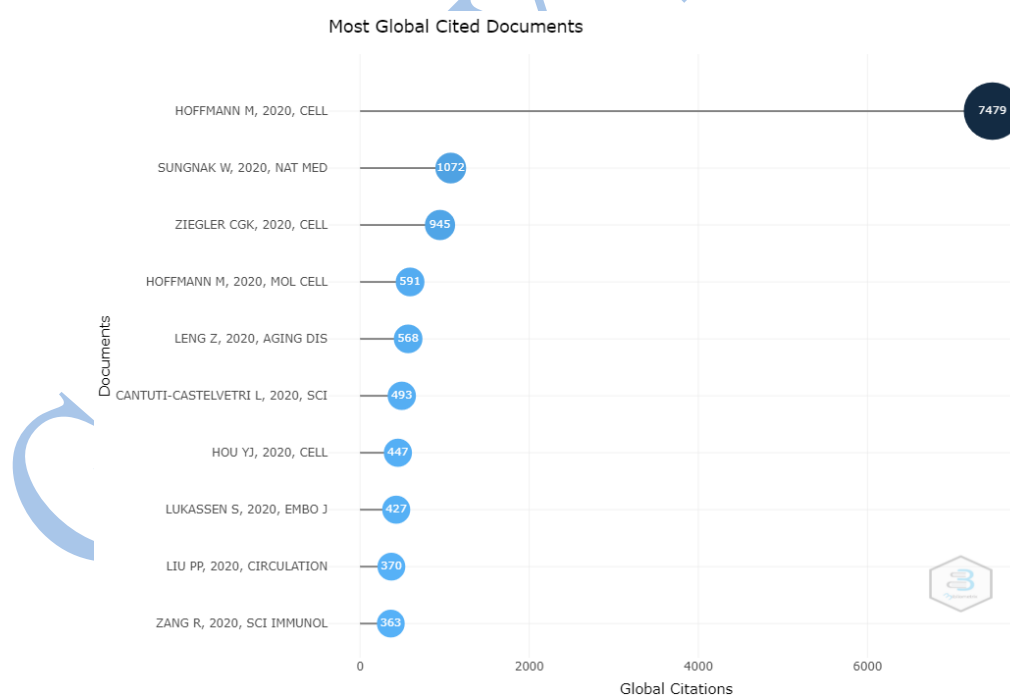
176 **Figure 1** depicts the network visualization map of most of the author's keywords appear in at least
 177 25 occurrences. COVID-19 (534 occurrences) followed by SARS-CoV-2 (480 occurrences),
 178 "TMPRSS2 (289 occurrences), and ACE-2 (246 occurrences) were the most frequently used keywords.
 179 Overlay visualization indicated the most author keywords related to TMPRSS2 gene as SARS-CoV-2
 180 receptors during these two years (2020-2022), which were categorized into fourth-largest clusters,
 181 each with different colours including COVID-19 (red colour) and SARS-CoV-2 (yellow colour) and
 182 two genes that important was TMPRSS2 (dark blue colour) and ACE-2 (blue colour).

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184 The highly cited articles and Citation analysis for TMPRSS2 research

185 The retrieved documents demonstrated that the average document citation was 28.69. A study
 186 published in the *Cell* in May 2020 received the highest number of citations and 7479 citations during
 187 two consecutive years (2020-2021); it was very surprising the citation of this article was almost 7-fold
 188 higher than that of the other top ten highest cited articles. The trend of citations seems to be increased
 189 over time. The author of this article was [Hoffman et al., 2020](#) title of his article "SARS-CoV-2 Cell
 190 Entry Depends on TMPRSS2 and ACE2 and is interrupted by a Protease Inhibitor that has been
 191 clinically proven" ([Hoffmann et al., 2020](#)). Surprisingly, Hoffman et al., 2020 also published another
 192 published in *Molecular Science* ([Hoffmann et al., 2020](#)). The second highest citation of the document
 193 was published in March 2020 in *Nature Medicine* with the title "SARS-CoV-2 entry factors together
 194 with innate immune genes are highly expressed in nasal epithelial cells" ([Sungnak et al., 2020](#)); it has
 195 been cited 1072 times. The top 10 most cited articles related to the study of TMPRSS2 as SARS-CoV-
 196 2 receptors for COVID-19 were listed in **Figure 2** and **Table 1**. From 10 journals that showed in **Figure**
 197 **2** and **Table 1** was published in highly reputed journals. An interesting finding highlighted that among
 198 the ten journals with the highest citation we identified, the *Cell* was dominated as it ranked 1st, 3rd, and
 199 7th.

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

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207 **Top 10 most cited countries for TMPRSS2 research**

208 **Figure 3** shows the top 10 countries cited for COVID-19 TMPRSS2 publication. Germany had
209 9400 citations, followed by the USA with 6409 and China with 1788. It is not surprising that the most
210 cited countries were from Germany. This result was in line with the authors with the highest citation
211 associated with Germany and Hoffman Markus ([Hoffmann et al., 2020](#)). Authors from Germany have
212 published an article in high-reputation journals. The top ten countries with the most citations related to
213 the study of TMPRSS2 for COVID-19 are listed in [Figure 3](#) and [Table 1](#). Interestingly, most of the
214 journals were open-access, which is implicated in citation advantage. As reported by several studies
215 revealed that the Open Access Journal promotes citations ([Basson & Prozesky, 2021](#); [Sotudeh &](#)
216 [Horri, 2007](#)).

217 **Top 10 most cited journals for TMPRSS2 research**

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

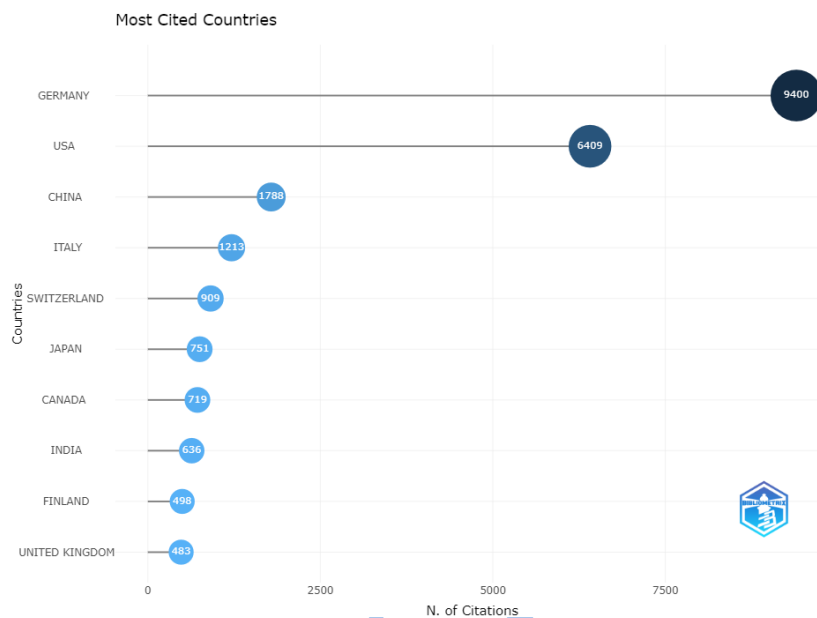
227 **International collaboration for TMPRSS2 research**

228 International collaboration was very important in the scientific field. Through collaboration,
229 scientists around the world enable to share/exchange information related to the field with one another.
230 The strength of a two-country research collaboration is shown by how thick the line between them is
231 ([Figure 5](#)). The USA was the country with a total link strength. Most countries worked together with
232 the United States. So, it is in the middle of the map and has many lines going out to other countries.
233 Thus, it fills the map's center with many connecting lines to other countries. In addition, the
234 international collaboration also can be presented based on the corresponding author country ([Table 2](#)).
235 Each author can collaborate with other countries based on the same field. [Figure 6](#) depicts the single-
236 country publication (SCP) and multiple-country publication (MCP) related to TMPRSS2 gene
237 publication during the pandemic. According to our findings, the USA has the highest number of
238 collaborating countries, followed by China and Germany in second and third places, respectively.
239 [Figure 6](#) visually represents international cooperation between countries that have produced at least 25
240 documents.

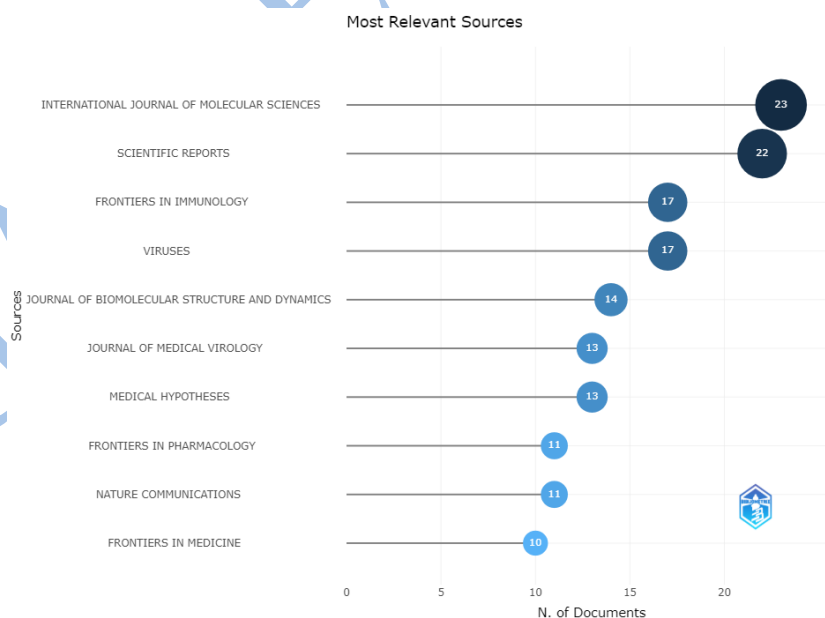
241 The present study found that the USA had the greatest number of countries working together on
242 research on the TMPRSS2 gene as the SARS-CoV-2 receptor. The collaboration allows scientists
243 around the globe to share /exchange information and stay updated about the field. This result could be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

251 Most publications were in medicine and biochemistry, genetics and molecular biology, and less
252 were associated with chemistry. Since the beginning of the pandemic, health sciences papers have
253 accounted for the majority of publications, as well as the most cited literature ([Malekpour et al., 2021](#)).
254 This finding indicates that this is a topic of interest, thus, more research is required. Our findings also
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257 revealed that extensive collaboration research had been carried out from the beginning of the COVID-
 258 19 outbreak. Such collaborations undoubtedly improve our understanding of the SARS-CoV-2 virus's
 259 nature (Shang et al., 2020). International collaboration can also greatly accelerate, support, and
 260 develop effective vaccine research (Smith et al., 2020).
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 266 **Figure 3. Top 10 cited country related the TMPRSS2 gene as SARS-CoV-2 receptors for**
 267 **COVID-19**
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 272 **Figure 4. Top 10 journals in publishing TMPRSS2 gene as SARS-CoV-2 receptors for COVID-**
 273 **19**

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

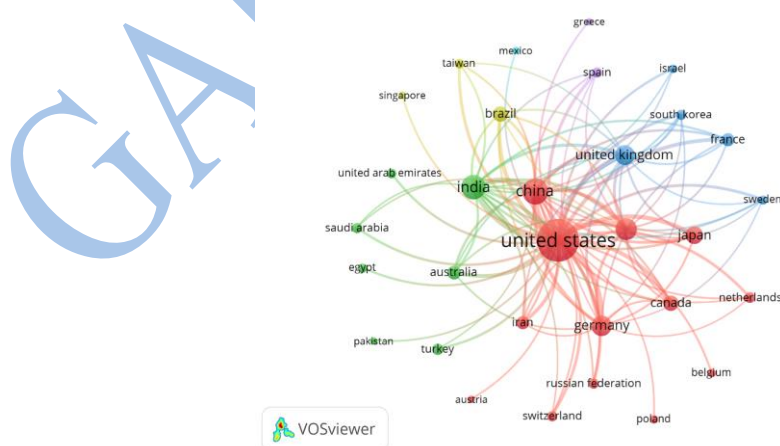
Paper	Year of Publication	Title	Journals	Total Citations	TC per Year	IF*	Ref
Hoffmann M	2020	SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor	Cell	7479	3739,5	41.58	(Hoffmann et al., 2020)
Sungnak W	2020	SARS-CoV-2 entry factors are highly expressed 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)

276 ***Impact Factor in 2020**

277
 278 The most cited papers among the top 10 cited publications of TMPRSS2 as SARS-COV-2
 279 receptors for COVID-19 patients were original articles/ research articles. The Journal from Germany,
 280 namely the *Cells* with a high impact factor (IF 2020: 41.58), had the highest number of citations on
 281 TMPRSS-2 as SARS-CoV-2 receptors for COVID-19, the total number of citations was 7479
 282 citations. The article was written by Hoffman et al. since the early of pandemic in May 2020. This
 283 article focused on the factor associated with SARS-CoV-2 infection of lung epithelial cells that
 284 requires ACE-2 and TMPRSS2. Recently, TMPRSS2 was found to be an essential host in airway
 285 epithelial cells that helps SARS-COV-2 get into the cells (Hoffmann et al., 2020). Surprisingly, among

286 the top 10 articles with the highest number of citations, three were published in the High Impact
287 journal the *Cell*. Among these publications, Germany was the non-English-speaking country with the
288 most citations. Interestingly, Hoffman et al. are from a German institution with Hoffman himself is a
289 German, thereby no wonder Germany is the country with the highest citations with regard to articles
290 discussing TMPRSS2 as one of the receptors for SARS-CoV-2. This suggests that the impact factor,
291 not research methodology or quality, was the best predictor of citations each year (Callaham et al.,
292 2002).

293 The present study has both merits and drawbacks. The study's merits include providing easy access
294 to the evidence and research trend on a topic and identifying papers focused on TMPRSS2 as a SARS-
295 CoV-2 receptor for COVID-19. The drawbacks of the current study were that it only comes from one
296 single database (Scopus). Therefore, it may not collect all relevant evidence available. Furthermore,
297 another noteworthy limitation of our research is limited to English articles, which implies we may be
298 missing out on valuable information from the articles provided in other languages. Besides, citation
299 analysis for article impact has some drawbacks. Citation analysis counts how many researchers have
300 cited an article. However, it is limited by factors that affect article citation rates. Limitations include
301 self-citation, incomplete citation, and omission bias. When an author cites their own work in their
302 articles, self-citation can boost their citation count. When a researcher cites only part of an article, it
303 may receive fewer citations. Due to language, access, or personal biases, some articles are not cited.
304 Citation timing also affects citation rates. After becoming popular, some articles may be cited more
305 often. Citation rates don't always indicate an article's impact. Thus, citation analysis's limitations must
306 be considered when assessing an article's impact (Brandt et al., 2019). We only included articles from
307 2020 – 2022, which implies the trend of research in the future may change over time. Future
308 investigations could re-evaluate more included scientific databases to identify more comprehensive
309 findings, such as Web of Science or PubMed, and assess articles' quality based on their study design.
310 The requirement for research on TMPRSS2 as a SARS-CoV-2 receptor is likely to grow as long as the
311 pandemic continues. Consequently, this could be a significant research issue in the future. Besides, the
312 genomic variant of TMPRSS2 as SARS-CoV-2 receptor also is important information to influence the
313 susceptibility of COVID-19 among multiple continents (Irham et al., 2020; Shen et al., 2017). It has
314 been shown that a transmembrane protease, serine 2 (TMPRSS2), a type II transmembrane serine
315 protease (TTSP), plays a crucial role in SARS and MERS coronaviruses (CoV), as well as Asian
316 H7N9 flu and several H1N1 subtype influenza A viruses, in 2013. Infections caused by Coronaviruses
317 and some low pathogenic influenza viruses can be treated by targeting TMPRSS2 (Matsuyama et al.,
318 2010; Shen et al., 2017; Tarnow et al., 2014; Zumla et al., 2016). Clinically proven protease inhibitors
319 can block SARS-CoV-2 cell entry by blocking ACE2 and TMPRSS2 (Figure 7).



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

324 **Implications of this study**

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

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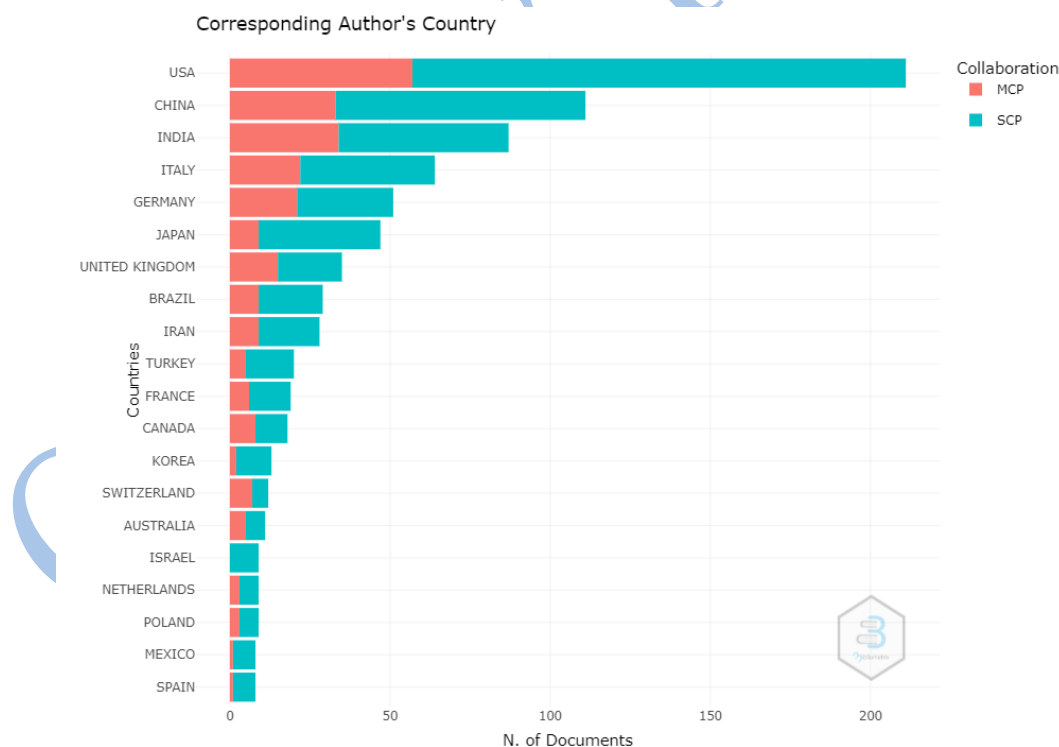
331 **Table 2. Top 10 corresponding author countries publishing article of TMPRSS2 gene as SARS-CoV-2**
 332 **receptors for COVID-19**

Country	Articles	Freq	SCP	MCP	MCP_Ratio
USA	211	0,23392	154	57	0,27
CHINA	111	0,12306	78	33	0,297
INDIA	87	0,09645	53	34	0,391
ITALY	64	0,07095	42	22	0,344
GERMANY	51	0,05654	30	21	0,412
JAPAN	47	0,05211	38	9	0,191
UNITED KINGDOM	35	0,0388	20	15	0,429
BRAZIL	29	0,03215	20	9	0,31
IRAN	28	0,03104	19	9	0,321
TURKEY	20	0,02217	15	5	0,25

333 Single country publications (SCP) and multiple country publications (MCP)

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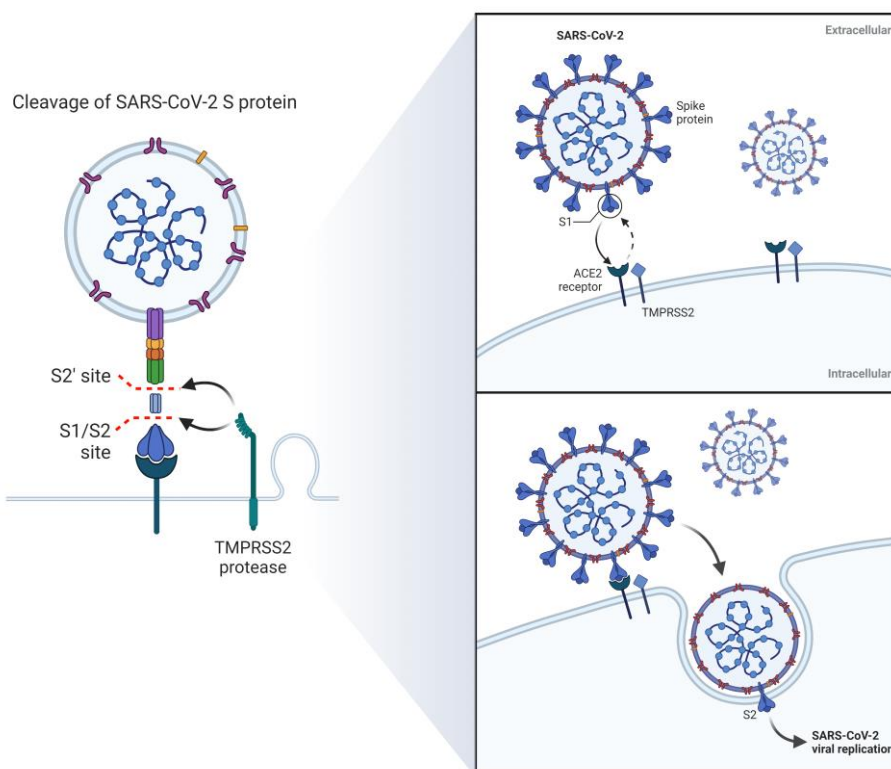


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338 **Figure 6. Research collaboration among countries with minimum research output of 32**
 339 **documents for TMPRSS2 publication**

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

348 A large number of publications related to TMPRSS2 as SARS-CoV-2 receptors have been
349 published rapidly in many journals in the past two consecutive years since the outbreak of COVID-19.
350 Knowledge of existing findings on TMPRSS2 as SARS-CoV-2 receptors is not only helped
351 researchers to further understand the mechanism of SARS-CoV-2 entering the human body of
352 COVID-19 facilitated by TMPRSS2 gene, but it also can help researchers to find the drug target gene
353 for COVID-19 (genomic driven drug discovery) and highlight the importance of exploring research on
354 SARS-COV-2 receptors. Our current study concluded the TMPRSS2 publication trend. The annual
355 number of publications grew significantly starting in early 2020 with a total number of fluctuations in
356 2021. Besides, Germany was the most cited country with total citations, followed by USA and China,
357 respectively. In conclusion, this study indicated an important topic for alleviating COVID-19 was the
358 TMPRSS2 as a receptor for SARS-CoV-2.
359

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363

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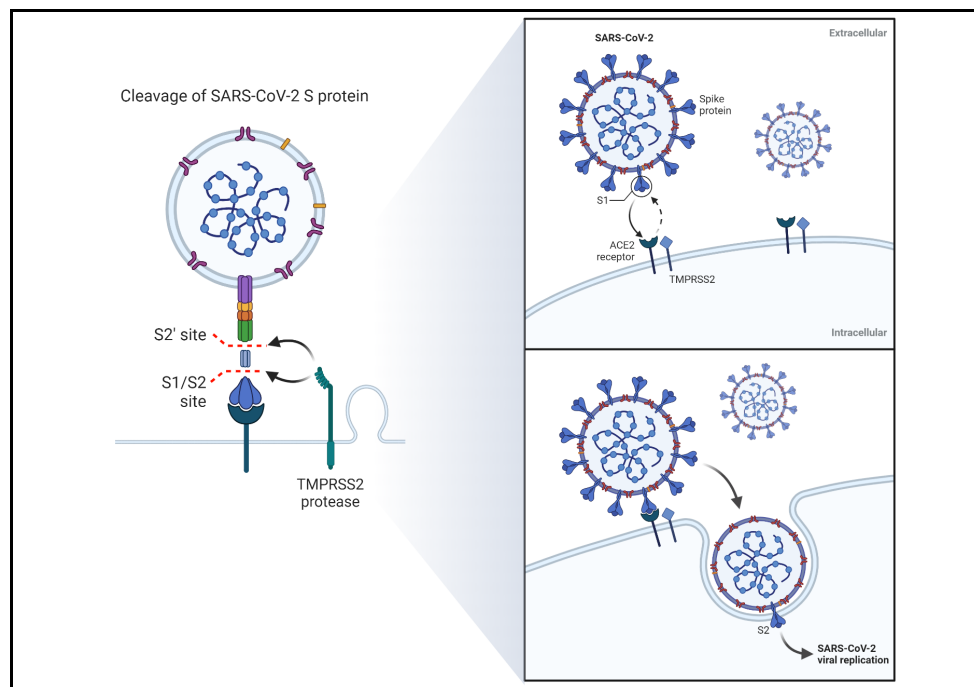
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Publication trend of TMPRSS2 as SARS-CoV-2 receptor during the COVID-19 pandemic

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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 pharmaceuticals (n=122), and chemistry (n=59).

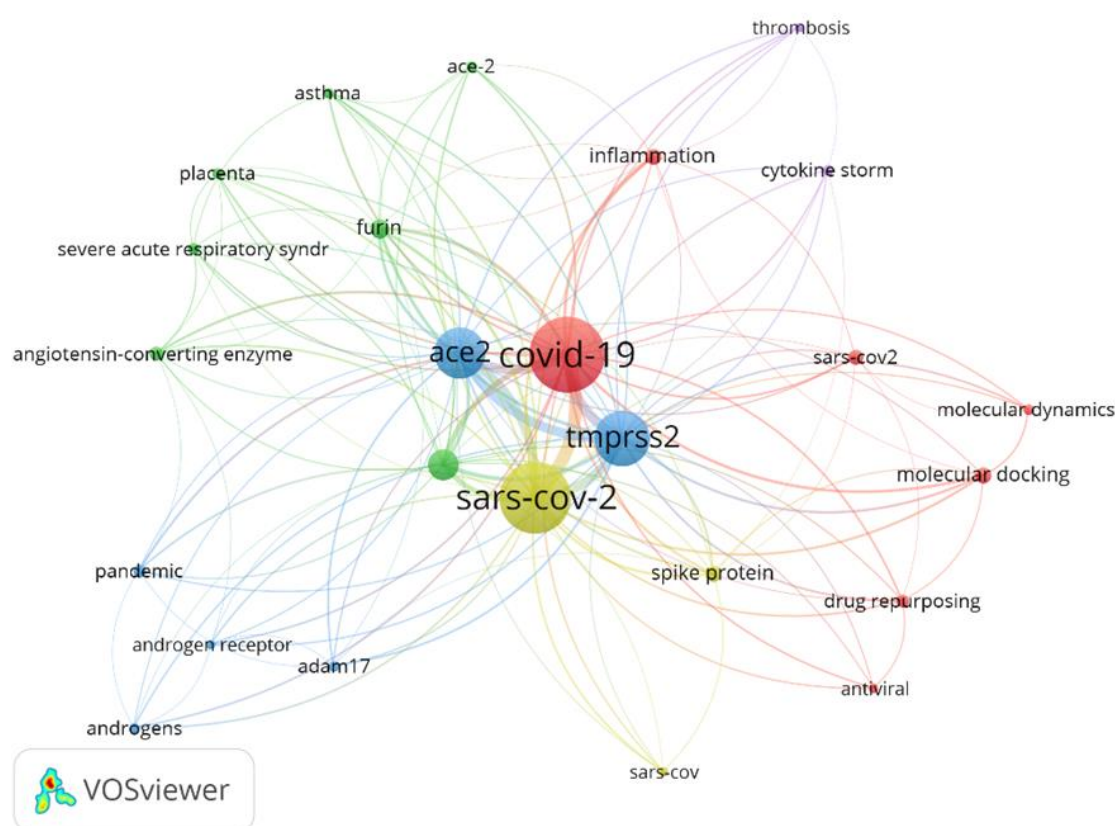


Figure 1. Visualization of the most frequent author keywords (minimum occurrences of 25 times) related to the TMPRSS2 gene as SARS-CoV-2 receptors for COVID-19

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 highest cited 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 TMPRSS2 and ACE2 and is interrupted 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 genes 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.

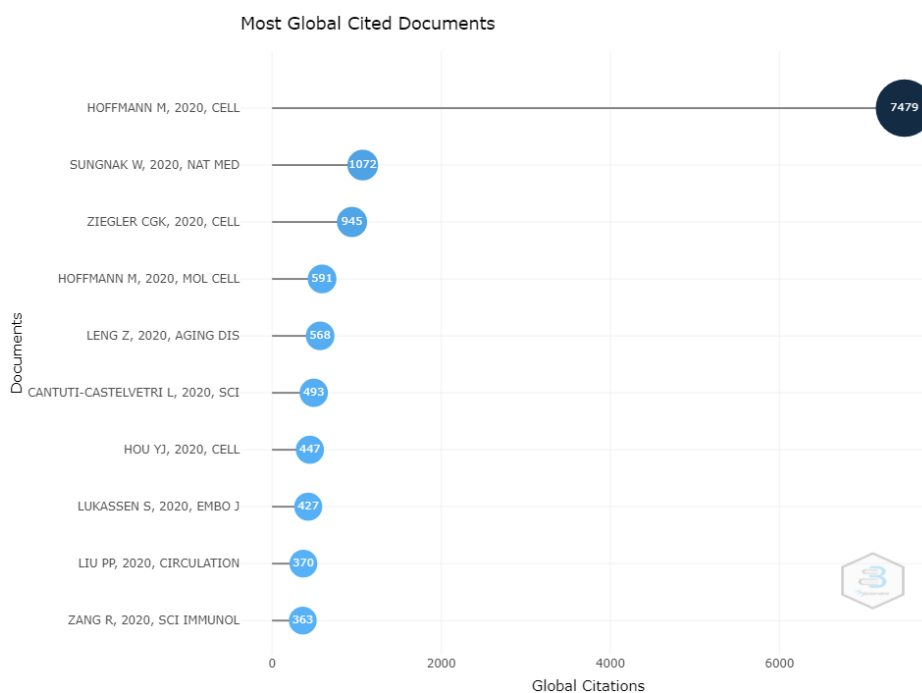


Figure 2. Top 10 cited country related the TMPRSS2 gene as SARS-CoV-2 receptors for COVID-19

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 country. Each author can collaborate with other countries based on the same field. Figure 6 depicts the single-country publication (SCP) and multiple-country publication (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-CoV-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).

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 beginning 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).

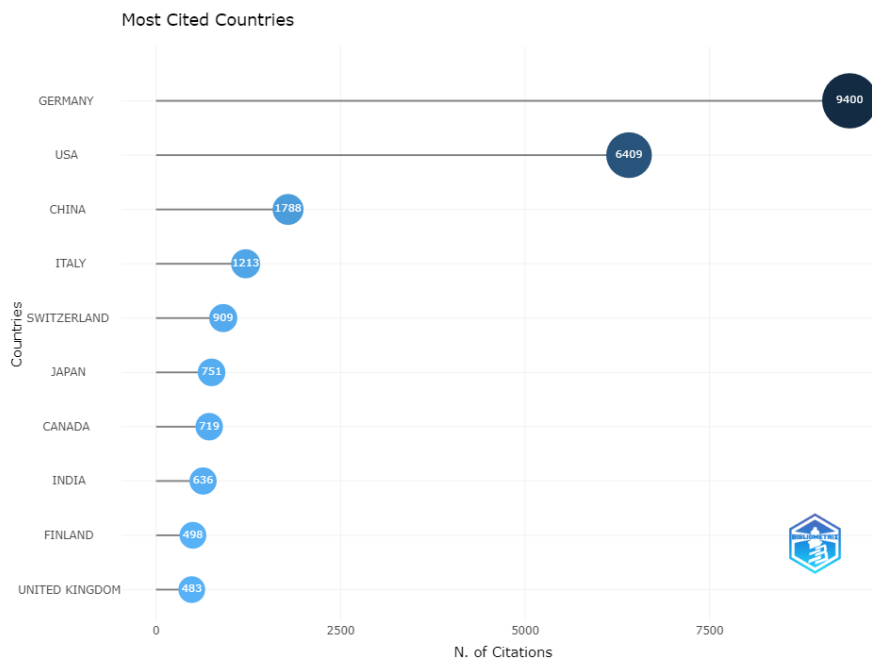


Figure 3. Top 10 cited country related the TMPRSS2 gene as SARS-CoV-2 receptors for COVID-19

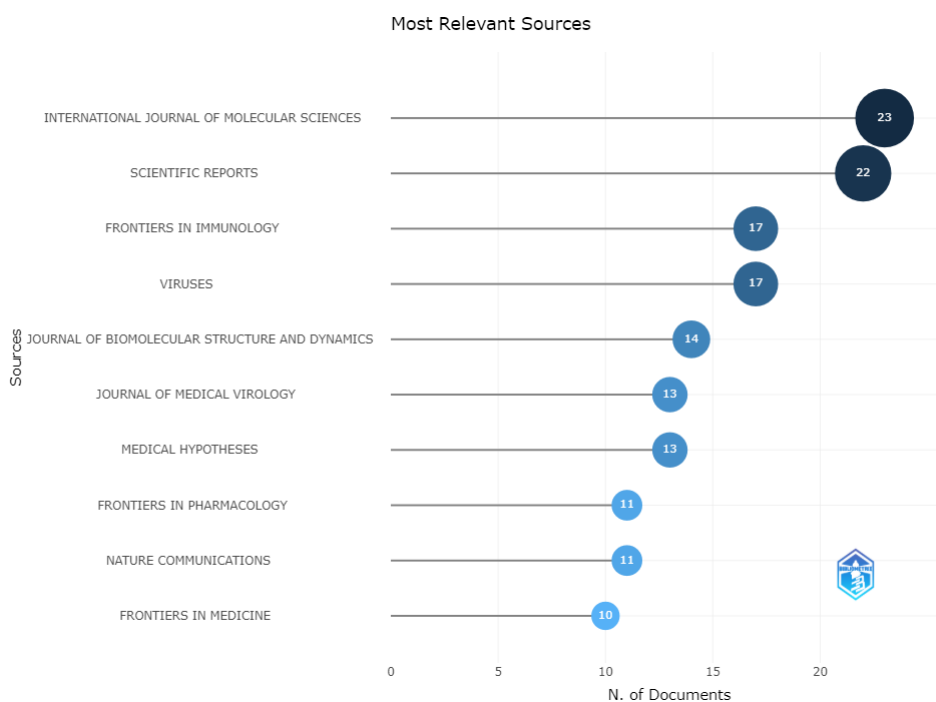


Figure 4. Top 10 journals in publishing TMPRSS2 gene as SARS-CoV-2 receptors for COVID-19

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 *Cells* 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

Publication trend of... (Irham et al.,)

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 wonder 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 easy 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 PubMed, 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., 2020; 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 coronaviruses (CoV), as well as Asian H7N9 flu and several H1N1 subtype influenza A viruses, in 2013. Infections caused by Coronaviruses and some low pathogenic influenza viruses can be treated by targeting TMPRSS2 (Matsuyama et al., 2010; Shen 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).

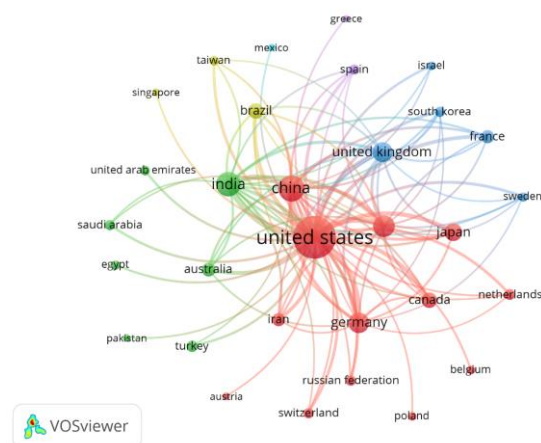


Figure 5. Research collaboration among countries with minimum research output of 32 documents for TMPRSS2 publication

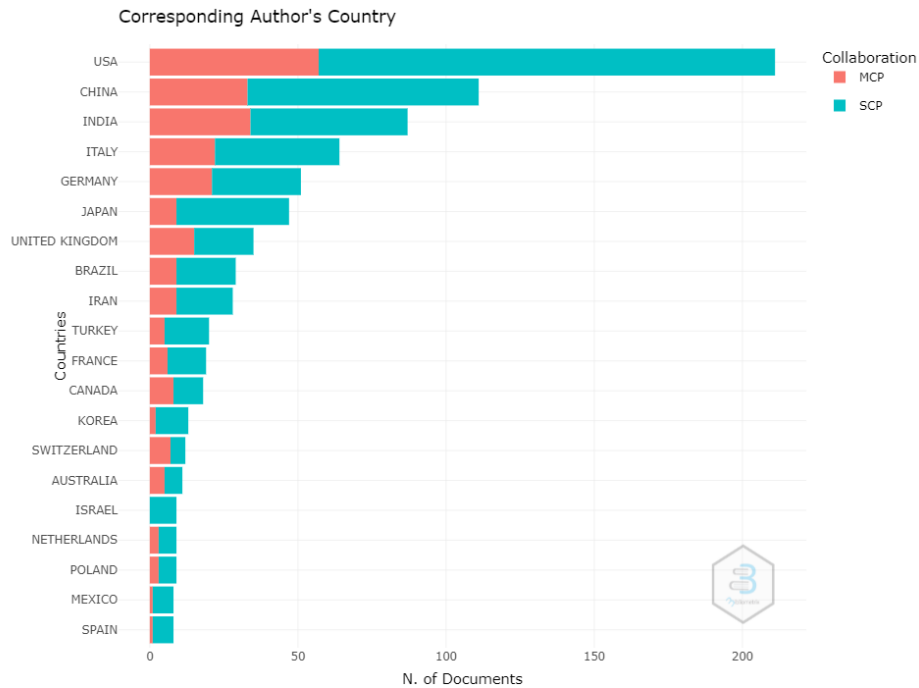


Figure 6. Research collaboration among countries with minimum research output of 32 documents for TMPRSS2 publication

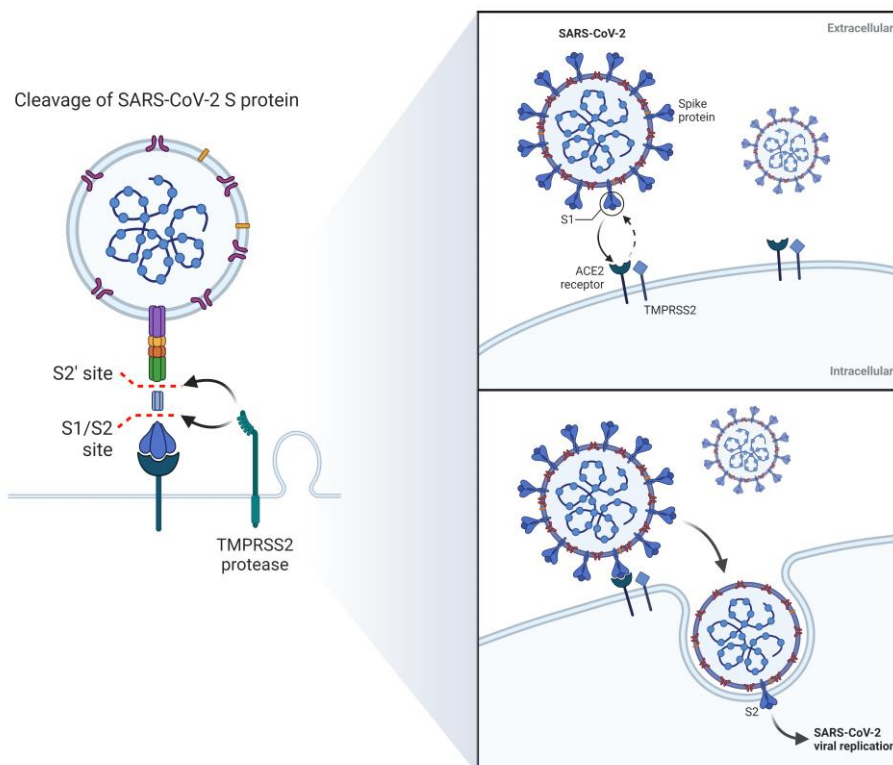


Figure 7. SARS-CoV-2 Entry through Host TMPRSS2 and ACE2 (by Biorender.com under license number GS24Y4YZSS)

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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