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Review Article

Implications of SARS-CoV-2 genetic diversity and mutations on pathogenicity of the COVID-19 and biomedical interventions

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الملخص

أهداف البحث: تسبب مرض الحمة التاجية لعام ٢٠١٩ في حالة طوارئ صحية عالمية غير مسبوقة. فلقد أودى هذا الوباء بالفعل بحياة أكثر من ٣٥٠٠٠٠ شخصا في غضون خمسة أشهر من ظهوره، خاصة في الولايات المتحدة الأمريكية والقارة الأوروبية. حللت هذه الدراسة الآثار المترتبة على السارس-٢ الجينية، والطفرات على تنوع ضراوة الحمة التاجية لعام ٢٠١٩، وكيف يمكن لهذه العوامل أن تؤثر على التطوير والتطبيق الناجحين للعلاج الكيميائي المضاد للفيروسات، والعلاج المناعي والتشخيص المصلي والتطعيم.

طرق البحث: تمت تصفية واستعراض نقدي لمقالات النص الكامل المناسبة والمؤهلة، التي تم نشرها خلال الفترة من ٣١ ديسمبر ٢٠١٩ إلى ٣١ مايو ٢٠٢٠، واستخراجها من "PubMed" و "Scopus" و "Web of Science" و. "Hinari" استخدمنا مصطلحات رؤوس الموضوعات الطبية "الحمة التاجية لعام ٢٠١٩" و"الطفرة" و"التنوع الجيني" و" سارس -٢" و"الضراوة" و"الإمراضية" و"التطور" و"انتقال" لهذا البحث.

النتائج: أظهر بحثنا أن سارس-٢ تعرض لطفرات كبيرة باستمرار في أجزاء مختلفة من البروتينات غير الهيكلية، كان بروتين S هو المحدد الرئيس لتطور السارس-٢، وانتقاله، وضراوته وهدفه لتطوير اللقاح. بالإضافة إلى ذلك، يمثل البروتين غير الهيكلي هدفا مضادا للفيروسات في علاج الحمة التاجية لعام ٢٠١٩.

الاستنتاجات: نظرا للأهمية الحاسمة لطفرات سارس-٢على مسببات أمراض الحمة التاجية لعام ٢٠١٩، والتشخيص المستمر للمصل، والأدوية المضادة للفيروسات، وتطوير اللقاحات، توصي هذه الدراسة باستمرار جهود المراقبة الجزيئية لـ سارس-٢ حيث من المحتمل أن يؤدي هذا النهج إلى تحديد المسوخات الجديدة وتأثيرها على التدخلات الطبية الحيوية الجارية وتدابير مراقبة الحمة التاجية لعام ٢٠١٩.

الكلمات المفتاحية: الحمة التاجية لعام ٢٠١٩؛ السارس-٢؛ التشخيص المصلي. تلقيح

Abstract

Objective: Coronavirus disease 2019 (COVID-19) has caused an unprecedented global health emergency. The COVID-19 pandemic has claimed over 350,000 human lives within five months of its emergence, especially in the USA and the European continent. This study analysed the implications of the genetic diversity and mutations in SARS-CoV-2 on its virulence diversity and investigated how these factors could affect the successful development and application of antiviral chemotherapy, immunotherapy, serodiagnosis, and vaccination.

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Methods: All the suitable and eligible full text articles published between 31st December 2019 and 31st May 2020 were filtered and extracted from "PubMed", "Scopus", "Web of Science", and "Hinari" and were critically reviewed. We used the Medical Subject Headings (MeSH) terms "COVID-19, "Mutation", "Genetic diversity", "SARS-CoV-2", "Virulence", "Pathogenicity", "Evolution" and "SARS-CoV-2 transmission" for this search.

Results: Our search showed that SARS-CoV-2 has persistently undergone significant mutations in various parts of its non-structural proteins (NSPs), including NSP2 and NSP3, S protein, and RNA-dependent RNA polymerase (RdRp). In particular, the S protein was found to be the key determinant of evolution, transmission, and virulence of SARS-CoV-2, and could be a potential target for vaccine development. Additionally, RdRp could be a major target in the development of antivirals for the treatment of COVID-19.

Conclusion: Given the critical importance of mutations in the pathogenicity of SARS-CoV-2 and in the development of sero-diagnostics, antivirals, and vaccines, this study recommends continuous molecular surveillance of SARS-CoV-2. This approach would potentially prompt identification of new mutants and their impact on ongoing biomedical interventions and COVID-19 control measures.

Keywords: COVID-19; RNA-dependent RNA polymerase; SARS-CoV-2; Serodiagnosis; Vaccination

Introduction

The incidence of coronavirus disease 19 (COVID-19) continues to rise globally. In addition, the case fatality rate (CFR) of COVID-19 has appeared to be disproportionate among countries across the world. As on 29th May 2020, 9:00 AM GMT+1, there were 5,920,086 confirmed cases of COVID-19 globally with CFR of 6.1%.[1]

Majority of people infected with SARS-CoV-2 remain asymptomatic and infection being self-limiting. However, approximately 2% of infected persons suffer from severe form of COVID-19.[1] The major factors that seem to determine the severity and fatality of COVID-19 include old age (>65 years) and underlying cardiovascular, immunological, metabolic, and respiratory comorbidities. Based on the data of available scientific reports, the transmission of SARS-CoV-2 revolves around human, animals, and the environment.

Genomic sequences of the early isolates of SARS-CoV-2 from infected patients in Wuhan showed over 88% nucleotide homology with two bat-like SARS coronaviruses, indicating the zoonotic source of the virus. In fact, bats have been identified as reservoir hosts of SARS-CoV-2.[2] Epidemiologically, sub-Saharan Africa has the least reported incidence of SARS-CoV-2 infection. Several observers have attributed this to underdiagnosis probably due to inadequate molecular diagnostic capacity and skilled work force. Conversely, the United States of America and many European countries appear to have the worst mortality and CFRs associated with COVID-19 (Table 1). Although, there Q10 is no categorical explanation for this variation, the genetic makeup and stability of SARS-CoV-2 are key determinants that contribute to its virulence and pathogenesis. Therefore, understanding these features is crucial for predicting the future transmission dynamics of SARS-CoV-2 infection, immune protection against reinfection, and antiviral and vaccine development.[3] Hence, in this perspective review, we aimed to analyse and discuss the implications of genetic variation and mutations in SARS-CoV-2 on the virulence diversity of the virus and to discuss how these features could impact the successful development and application of antiviral chemotherapy, immunotherapy, serodiagnosis, and vaccination (see Table 2). Q11

Materials and Methods

All the suitable and eligible articles published between 31st December 2019 and 31st May 2020 were filtered and extracted from "PubMed", "Scopus", "Web of Science" and

Table 1: Top 10 countries affected by COVID-19 (As on 29th May, 2020).[1]

Countries	Total cases	Mortality	Severe cases	Active cases
USA	1,768,461	103,330	17,202	1,166,406
Brazil	438,512	26,764	8318	218,807
Russia	387,623	4374	2300	223,992
Spain	284,986	27,119	854	60,909
UK	269,127	37,837	1559	NA
Italy	231,732	33,142	439	47,986
France	186,238	28,662	1429	90,385
Germany	182,452	8570	744	9782
India	165,829	4713	8944	90,010
Turkey	160,979	4461	883	32,149

Note: These are live and ongoing COVID-19 data.
Key: NA = Not available.

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Table 2: Studies that reported cases of genetic diversities and mutations in SARS-CoV-2.

Citation	Country	Experimental design	Mutations	Key Findings
Tang et al.[13]	China	Population genetic analyses of 103 SARS-CoV-2 genomes	Receptor-binding domain of the S protein	L and S lineages discovered. L lineage was more prevalent than the S lineage. L lineage was evolutionarily aggressive and contagious compared to S lineage
Angelettie et al.[12]	Italy	Fast-unconstrained Bayesian approximation and Homology modelling	NSP2 and NSP3	a. NSP2 mutation could explain why SARS-CoV-2 is more contagious than SARS-CoV-1 b. NSP3 mutation could explain the difference in pathogenicity between SARS-CoV-2 and SARS-CoV-1
Yao et al.[18]	China	Functional characterisation of 11 patient-derived viral isolates	Intrapersonal variation and 6 different mutations in S protein	S protein mutation capable of substantially changing its pathogenicity
Xi et al.[19]	China	Phylogenetic analysis and heat mapping of 788 confirmed patients with COVID-19	Furin cleavage site mutation on S protein	FCS mutation may represent an important SARS-CoV-2 evolution site
Holland et al.[26]	USA	Genomic characterisation of a 27 amino acid in frame deletion in accessory protein ORF7a	An 81-nucleotide deletion in SARS-CoV-2 ORF7a	Phylogenetically distinct mutants that indicate independent transmissions pattern
Korber et al.[26]	USA	Phylogenetic analysis of S protein	D614G mutation in S protein	Significant implications for SARS-CoV-2 transmission, pathogenesis, and immune interventions
van Dorp et al.[27]	UK	Curation of dataset of 7666 public genome and genomic diversity analysis	Nsp6, Nsp11, Nsp13, Spike protein	Possible ongoing adaptation events of SARS-CoV-2
Pachetti et al.[39]	Italy	220 genomic sequences analysis from database derived from patients with COVID-19	8 novel recurrent mutations of SARS-CoV-2 RdRp	a. Findings suggest SARS-CoV-2 evaluation and co-existence in European, North American, and Asian strains b. RdRp mutation could be involved in antiviral drug-resistance
Happi et al.[40]	Nigeria	Genome annotation and Mutation Analysis	D614G in S protein	D614G mutation in S protein could be associated with higher transmission and pathogenicity and evasion of immune interventions

"Hinari" and were critically reviewed. The articles were searched using the Medical Subject Headings (MeSH) terms "COVID-19, "Mutation", "Genetic diversity", "SARS-CoV-2", "Virulence", "Pathogenicity", "Evolution", and "SARS-CoV-2 transmission". Articles that described mutations, genetic diversity, and amino acid and strain variations of SARS-CoV-2 were included in this study. Additionally, only full-text articles published in English language were included in the study and the consistency in the main findings of these selected studies was substantially evaluated.

Discussion

SARS-CoV-2 is single-stranded RNA virus with positive polarity and variable open reading frames (ORFs).[4] It has been shown that two-third of the SARS-CoV-2 genome is located within the 1st ORF, which translates the pp1a and pp1ab polyproteins. These polyproteins encode 16 non-structural proteins (NSPs).[4] Conversely, the remaining ORFs code for the structural and accessory proteins of SARS-CoV-2. The remaining one-third of the genome codes for the nucleocapsid (N) protein, spike (S) glycoprotein, matrix (M) protein, and small envelope (E) protein.[4] Out of the four structural proteins, the S protein plays the most important role in host cell attachment and entry. It is also the target for development of antibodies, antivirals, and vaccines. The S protein primarily mediates invasion of the host cell by binding to a receptor called angiotensin-converting enzyme 2 (ACE2).[5] The S protein is cleaved

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into an N-terminal S1 subunit and a membrane bound C-terminal S2 region by the host proteases.[6]

Destabilisation of the pre-fusion trimer could occur during the binding of the S1 subunit to the host receptor, which could lead to shedding of the S1 subunit and formation of a highly stable post-fusion conformation by the transitioned S2 subunit.[7] Essentially, the receptor binding domain (RBD) of the S1 unit could undergo a hinge-like conformational movement, which ephemerally reveals or hide the determinants of the receptor binding during an interaction with the host receptor.[8] These two states of the S1 subunit can be referred to as down conformation, which represents the inaccessible state of the receptor, and up conformation, which represents the accessible state of the receptor.[7,8]

Genetic diversity, SARS-CoV-2 transmission, and pathogenicity

Indeed, RNA viruses including SAR-CoV-2 have high mutation rates, which are significantly correlated with enhanced virulence and evolvability of the viruses.[9] Mutation in the S protein is of major clinical and public health concern since it could change the tropism of a virus, including adaptation of the virus to new hosts, or increase the pathogenesis of the virus.[10] Thus, detecting and understanding mutations in the S protein from different countries could provide an idea about the constant shift in its structure and could probably provide an insight into how these mutations enable variable transmission of SARS-CoV-2 in different parts of the world. However, to date, little is known whether S protein mutation-mediated transmission of SARS-CoV-2 depends on the race, ethnicity, or geographical location of people.

At proteomic level, amino acid substitutions have been reported in NSP2, NSP3 and S protein.[11] Interestingly, another study suggested that NSP2 and NSP3 mutations play a significant role in virulence and differentiation mechanism of SARS-CoV-2.[12] Of particular interest is the mutation in S protein. This has made scientists explore the possible differences in host tropism and transmission rate of SARS-CoV-2. The NSP2 and NSP3 mutations in SARS-CoV-2 isolated from several patients with COVID-19 in China are worth noting.[12] In addition, genetic analysis of over 100 SARS-CoV-2 isolates revealed that approximately 70% of the isolates were L-type rather than S-type strains. It has been shown that the former strain tends to be evolutionarily aggressive and contagious compared to the later.[13] This has caused scientists to embark on genomic surveillance of SARS-CoV-2 to determine the correlation of these mutations with virulence diversity and to detect their implications on reinfection, immunity, and vaccine development.

Physiologically, the ACE2 receptors are expressed in the nasal epithelial, lung, spermatogonial, leydig, sertoli, gastric, duodenal, and rectal epithelial cells.[14–16] It has been reported that the RBD on the S protein is the most variable genomic component of SARS-CoVs and some sites of this protein might be subjected to positive selection.[17] Despite the significantly high variability of SARS-CoV-2, one key phenomenon that needs thorough investigation is how S protein mutations affect the functional pathogenicity of SARS-CoV-2.[18]

An important and common feature of viruses is their increased transmissibility usually accompanied by decreased virulence, which can also be observed for SARS-CoV-2. Indeed, this has reflected in the COVID-19 trajectory.[19] For instance, COVID-19 was more severe in Wuhan in the early stage of the pandemic with 32% severe cases and 11% case fatality.[20,21] However, later data from Wuhan showed more mild form of SARS-CoV-2 infection compared to Zhejiang[22] and the entire China.[23] The transmissibility of SARS-CoV-2 increased from varied reproductive number (R_0) of 2.212−2.686 in Wuhan to R_0 of 3.7713 in the entire China.[19] In addition, this observation was similar to SARS-CoV-2 viral load of symptomatic and asymptomatic COVID-19 patient which revealed the capacity of occult SARS-CoV-2 transmission.[24] Indeed, these observations in the clinic-epidemiological features of COVID-19 were related to mutations in S protein of SARS-CoV-2.[24]

Available genomic surveillance data of SARS-CoV-2 suggest presence of abundant single nucleotide variants. For instance, in a recent study, Yao et al.[18] reported a direct link between genomic mutations and variation in the pathogenicity of SARS-CoV-2. The study characterised SARS-CoV-2 isolates from 11 patients. From these, six different mutations in the S protein were detected. Out of the six mutations, two were different SNVs that led to similar missense mutation.[18] Importantly, the SARS-CoV-2 isolates showed significantly varied cytopathic effects (CPEs) and viral loads in Vero-E6 cells, indicating that SARS-CoV-2 mutations are capable of causing substantial changes in the pathogenicity of the virus.[18]

In early May 2020, two new studies on deep RNA sequencing of SARS-CoV-2 conducted in search for mutations were made available online. One of the studies conducted at Arizona State University discovered a huge base pair deletion in SARS-CoV-2 isolated from the sample of a patient in Tempe.[25] The other article, which was a preprint publication from the Los Alamos National Laboratory, tracked mutations throughout the outbreak and hypothesised that one of the strains of SARS-CoV-2 is more infectious than the first Wuhan strain.[26] The study by Holland et al.[25] revealed three full-length SARS-CoV-2 genomes from series of samples collected. The investigators found that one of the three genomes that they named AZ-ASU2923 had an 81 base pair deletion in a gene called ORF7a.[26] The major function of this ORF7a gene is to synthesise an accessory protein, which helps SARS-CoV-2 in infecting, replicating, and spreading inside the human host.[26] The accessory protein is believed to assist SARS-CoV-2 in evading the host immune system and kill the infected cell once viral replication is complete.[26]

In another study by van Dorp et al.,[27] genome sequencing of SARS-CoV-2 isolated from more than 7500 patients of COVID-19 was undertaken. The study identified about 200 recurrent genetic mutations in SARS-CoV-2. This highlights how SARS-CoV-2 might have been adapting and evolving in humans.[27] Scientists have identified that a large proportion of the global genetic diversity of SARS-CoV-2 can be found in the countries hardest-hit by COVID-19, suggesting extensive global transmission of SARS-CoV-2 early during the epidemic and the absence of single first patient in most countries and territories.

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For instance, the genomic sequences of the original isolates from China are significantly related to those circulating in the U.S. and Europe. However, SARS-CoV-2 has been undergoing several mutations, which has made the world wonder whether these mutations could lead to a more severe and deadlier COVID-19.[28] Perhaps, the SARS-CoV-2 strains circulating in sub-Saharan Africa might be those that initially circulated during the early phase of the COVID-19 pandemic, which have probably undergone little or no mutation. For instance, the first SARS-CoV-2 sequenced from Africa revealed a phylogenetic relation to early isolates from Wuhan.[29] The S-type strains of SARS-CoV-2 were the first circulating strains and were reported to be less virulent.[30] Hence, there is a need for more stringent quarantine measures for people with recent international travel history in the last 14 days to areas of low incidence and case fatality rates.

Implications of SARS-CoV-2 genetic mutations on COVID-19 biomedical interventions

Monitoring the genetic diversity, dynamics, and mutations of SARS-CoV-2 are very important in the development of effective antivirals and vaccines that could halt the replication and spread of the virus. Based on the available genome sequence data, it appears that the rate of mutation in SARS-CoV-2 is significantly lower than that reported during the SARS outbreak.[31]

One of the easiest ways of treating SARS-CoV-2 infections during the pandemic could be through the use of plasma derived from convalescent patients with COVID-19.[32] Polyclonal neutralization antibodies (Nabs) could be harvested from convalescent patients and effectively used in the treatment of newly infected patients.[33] The RBD of SARS-CoV-2 S protein has been considered the most important target for the development of Nabs. This immunotherapeutic agent blocks the binding and fusion of SARS-CoV-2 to cells/tissues expressing ACE2.[33] A major concern in the use of Nabs in the immunotherapy of patients with COVID-19 is the emergence and expansion of multiple mutations in the RBD of SARS-CoV-2 S protein. There are fears that patients carrying a mutant S protein might not respond to Nabs from a donor with a different S protein phenotype. Although SARS-CoV Nabs are likely to be beneficial for an infected individual, these antibodies could potentially trigger immunopathogenic processes in patients with COVID-19 with dissimilar viral genome content or enhanced infection.[34] Antibodies to SARS-CoV-2 with different epitopes expressed by mutants of RBD generally fail to cross-neutralise all strains of SARS-CoV-2 and thus becomes suboptimal in treatment.[34]

Due to the impact of COVID-19 on the global economy and the need to scale up public health laboratory tests for COVID-19, there is an urgency to consider the evaluation and validation of SARS-CoV-2 infection using enzyme linked immunosorbent assay (ELISA) and lateral flow immunochromatography rapid diagnostic test (RDT). Even though not all the available antigen- and antibody (IgA, IgM, and IgG)-based serological tests have been validated by the World Health Organization (WHO), it has been suggested that serological assays could assist in the analysis of an ongoing SARS-CoV-2 outbreak and retrospective evaluation of the incidence rate of an outbreak, and could support diagnosis of COVID-19 when RT-PCR results are negative.[35]

In addition, RDTs for both IgM and IgG antibodies will undoubtably play an important role in the detection of asymptomatic cases and in determining the immunity of health care workers as the outbreak progresses.[36] However, one of the major concerns with serological tests is the possibility of cross-reaction with other SARS-CoVs, which share ~76% nucleotide homology with SARS-CoV-2.[37] Indeed, cross-reactive antibodies are frequently detected in S protein ELISA.[38] Antibodies to SARS-CoV-2 with different epitopes expressed by mutant proteins (either S or N) may reduce the positive predictive value of antibody-based anti-SARS-CoV-2 assays.

In a study that characterised eight mutation loci on the SARS-CoV-2 genome, researchers found that five loci with mutations had predominantly occurred in Europe, whereas the remaining three were exclusively present in North America.[39] They also reported a silent mutation in the RdRp gene circulating in England in early February 2020 and different mutations in RdRp gene that gave rise to variations in RdRp enzyme in Lombardy.[39]

The findings of Pachetti et al.[39] suggest that the SARS-CoV-2 that evolved in European, North American, and Asian strains have coexisted, with each having characteristic mutation pattern. Indeed, the impact of RdRp mutation to the evolution of SARS-CoV-2 needs to be investigated. There are several antivirals that target SARS-CoV-2 RdRp. Consequently, it is important to investigate and characterise SARS-CoV-2 RdRp mutations in order to detect possible drug-resistant SARS-CoV-2 traits. In addition, evaluation of the correlation of the presence of some mutations of RdRp with COVID-19 mortality rates will be clinically useful.[39] In the study, the investigators found RdRp mutation at position 14,408 of SARS-CoV-2 genome circulating in Europe and associated with a higher number of point mutations compared to viral genomes from Asia.[39] Hence, clinicians need to be very careful in the use of antiviral that target SARS-CoV-2 RdRp enzyme.

Conclusion

Investigations and surveillance of genetic diversity and mutation in SARS-CoV-2 may be valuable for scientists and clinicians. These may also help in better understanding the ways in which the genetic diversity and mutation affect the transmission and pathogenesis of SARS-CoV-2. Given the critical importance of SARS-CoV-2 mutations in COVID-19 pathogenicity, and in development of sero-diagnostics, antivirals, and vaccines, it is recommended that SARS-CoV-2 molecular surveillance efforts be sustained in order to facilitate the prompt identification of new mutants and their impact on ongoing biomedical interventions and COVID-19 control measures.

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Conflict of interest

The authors have no conflict of interest to declare

Ethical approval

Not applicable.

Authors contributions

INA and OAA conceived and designed the study, and conducted the preliminary review of articles. INA, AUE, and AIO provided research scope, and collected and organised the extracted data. INA, AUE, DOA, and BSO analysed and interpreted the data. INA, OAA, AUE, DAO, and AIO wrote the initial and final drafts of the article, and provided logistic support. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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