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Prevalence of SARS-CoV-2 with receptor-binding protein N501Y mutation in Thi-Qar governorate, Iraq

Nuha Jabori Hadi
Department of Biology, College of Sciences, University of Thi-Qar, Nasiriya / Iraq
nuhahadi@sci.utq.edu.iq
Ahmed Salman Abdulhasan
Department of Biology, College of Sciences, University of Thi-Qar, Nasiriya / Iraq
Ahmad.sal_bio@sci.utq.edu.iq
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Abstract

Since the outbreak of SARS-CoV-2, which started in china, Wuhan city, in late December 2019, the pandemic has involved more than 200 countries worldwide. Many countries started to do research and profound studies to evaluate and discover this virus's weak point, hoping to produce a vaccine that might stop or slow down the spreading of the virus. The first wave that hit our country at the beginning of February 2020 was brutal for our health system since we were unprepared to fight back. Beginning of 2021, new variants showed up around the world the alpha variant (B.1.1.7, 501Y.V1), the Beta variant (B.1.351, 501Y.V2), and the Gamma variant (P.1, 501Y.V3) variant. According to the new studies, the new variant is more transmissible than the classic one. This new

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variant spread from the UK to other countries like Brazil, South Africa, and the Middle East, including Iraq. The variant with the N501Y mutation is more transmissible, causing the spreading of the virus. Our study aims to screen the prevalence of N501Y mutation in protein- binding domain of spike protein in Thi-Qar governorate community, in Iraq. The study included suspected individuals who visited the main isolation centre in Nasiriya city (Al Hussein teaching hospital and Al-Shifa quarantine centre) and from an active survey that involved students and public screening through mobile medical staff visiting from the end of February to the mid of March 2021. Our data included 10628 samples and showed that the prevalence of N501Y mutation in Thi-Qar governorate community was (22.80%) showing a genuine concern regarding the new virus variants. Our current result showed that asymptomatic individuals could be a source of transmissible SARS-CoV-2 with a rate (9.35%) positive for N501Y mutation since they feel they are not sick and do not have any reason to get a test for SARS-CoV-2.

Keywords: RBD N501Y mutation, Spike N501Y mutation, SARS-CoV-2 N501Y mutation.

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1- Introduction

Wuhan city in China was the first place when the novel coronavirus hit in late December 2019. Then the virus moved around the world and was announced as a pandemic coronavirus disease (COVID-19) in March 2020 by WHO [1]. The new virus was named severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) by the international committee of Taxonomy of Viruses (ICTV) [2]. Coronavirus belongs to a family of *coronaviridae* genera of Beta coronaviruses which contain a positive sense single strand RNA with approximately (2.9 Kilobase pair) genome. The virus's genome encodes four structural proteins involving the S protein, which has a crucial role in viral fusion and entry to the human cell via the angiotensin-converting enzyme 2 receptor (ACE2). Spike protein has two subunits, S1 and S2; S1 has the role of anchoring viral particles to the human cell receptor. In addition to the S protein, the virus genome encodes nucleoprotein (NP), envelope (E), and membrane protein (M) figure 1 [3, 4]. Virus S protein is processed into two fragments: the N terminal S1, responsible for receptor binding, and the C terminal S2, responsible for membrane fusion [5]. N501Y mutation replaces asparagine with tyrosine in position 501 at the receptor-binding domain (RBD). It has been shared with the three virus variants, the alpha variant (B.1.1.7, 501Y.V1), the Beta variant (B.1.351, 501Y.V2), and the Gamma

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variant (P.1, 501Y.V3), which makes the virus more infectious to the human enhancing binding affinity of RBD to ACE2 receptor figure 2 [6-8]

Studies data revealed many mutations in spike protein which spread worldwide, starting in the UK, Brazil, and South Africa [6]. The receptor binding domain (RBD) of spike mutation in position 501 showed a change from asparagine (N) to tyrosine (Y) and was noted as an (N501Y) mutation. Furthermore, the high human-to-human transmission new variant (20B/501Y.V1, B1.1.7) showed in the UK also showed the same mutation (N501Y) in the spike protein[7]. Sequencing analysis data showed that the N501Y mutation is shared by South African and UK variants [9]. Moreover, UK variant sequencing data revealed that this variant has a D614G mutation by substitution of Asparagine (D) for Glycine (G) in the S1 subunit of spark protein [10]. These mutations are of potential biological importance that increases the binding efficiency of the receptor binding domain (RBD) to the human angiotensin-converting enzyme 2 receptor (ACE2). This feature showed that virus spike protein with N501Y mutation improved the virus entry and infection, increasing virus transmissibility [11].

N501Y mutation is more concerned, which involves serval mutations like deletion of the amino acid at the 69^{th} and 70^{th} residues of the N terminal domain of the S1 subunit that is noted as (△69/△70) in addition to P681H mutation. [11]. Data

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showed the co-circulating of 501Y (variant 1) with the 501N in Wales in early September and mid-November after variant 2 of 501Y lineage, which was named B.1.1.7, showed in the UK, and some called it the UK variant [12]. Twenty-four genetic change mutations in 501Y variant 2 have been noticed in this lineage. There are six silent mutations in ORF8, ORF1aB, spike proteins, and nucleocapsid, with 14 non-synonymous mutations and four deletions [2]. Furthermore, another mutation in the RBD of the virus showed up by substituting amino acids. Data revealed that this mutation is resistant to several monoclonal antibodies, bringing global concern regarding virus development [13, 14]. Most invented vaccines against SARS-CoV-2 rely on spike protein antigen to stimulate the immune system. With frequent mutations in spike glycoproteins, and many variants co-circulating around the world, South Africa has paused using the Oxford-AstraZeneca vaccine relying on a study of 2000 healthy volunteers that showed the vaccine is not protected against mild and moderate cases with variant-2 (501Y) mutation [15].

Globally, from the beginning of the pandemic till September 2, 2022, the world health organization (WHO) recorded (601,189,435) confirmed cases of SARS-CoV-2, involving (6,475,346) deaths and (12,449,443,718) vaccine doses have been administrated. On the other hand, Iraq registered (2,457,871) confirmed

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cases including (25,346) deaths [16]. Iraq started vaccinating the population on two march 2021, and till September 2, 2022, the total doses were (19,097,435)[17]. Currently, there is no study showing the circulation of SARS-CoV-2 variants with N501Y mutation in our community in Iraq. Our study assessed the epidemiological outbreak of SARS-CoV-2 (N501Y) spike mutation in Thi-Qar governorate, Iraq, from the end of February to the mid of March 2021. This study has a crucial role in viral variant diagnosis tools. It might be involved in vaccine efficiency since we started vaccinating the first line of the medical staff with the Sinopharm-inactivated vaccine at the beginning of March 2021. Other vaccines, like Pfizer and AstraZeneca, have been used to stimulate the immune system against viral spike protein.

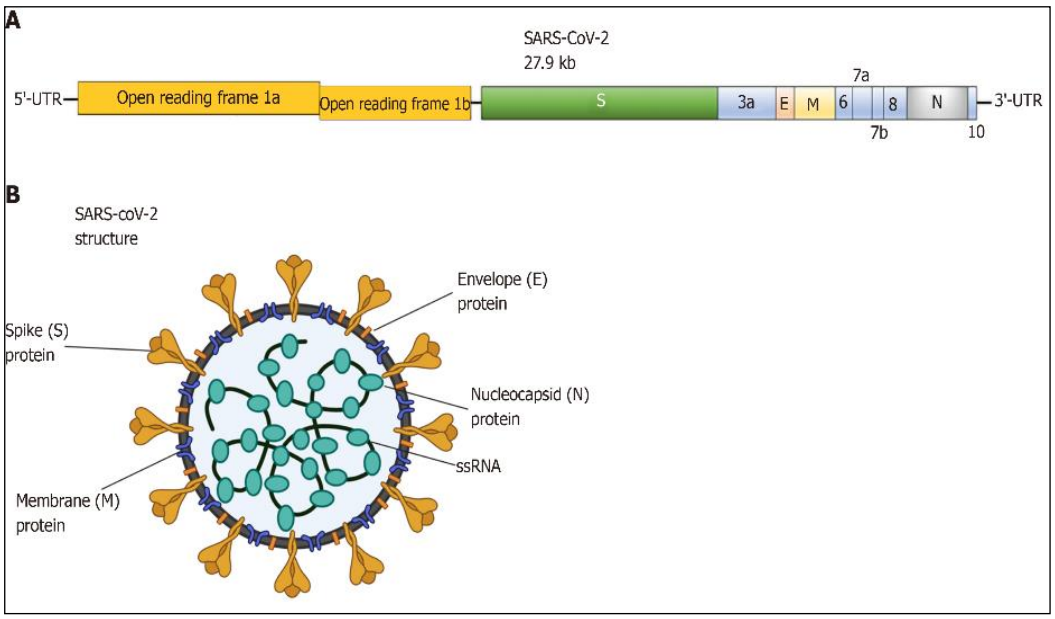

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Figure 1: Schematic structure of genomic organization of SARS-CoV-2 **(A)**. Schematic diagram of primary structural protein **(B)**. This image was adapted from (4). (**ORF**: Open reading frame; **S**: Spike protein; **N**: Nucleocapsid protein; **M**: Membrane protein; **RBD**: Receptor -binding domain; **E**

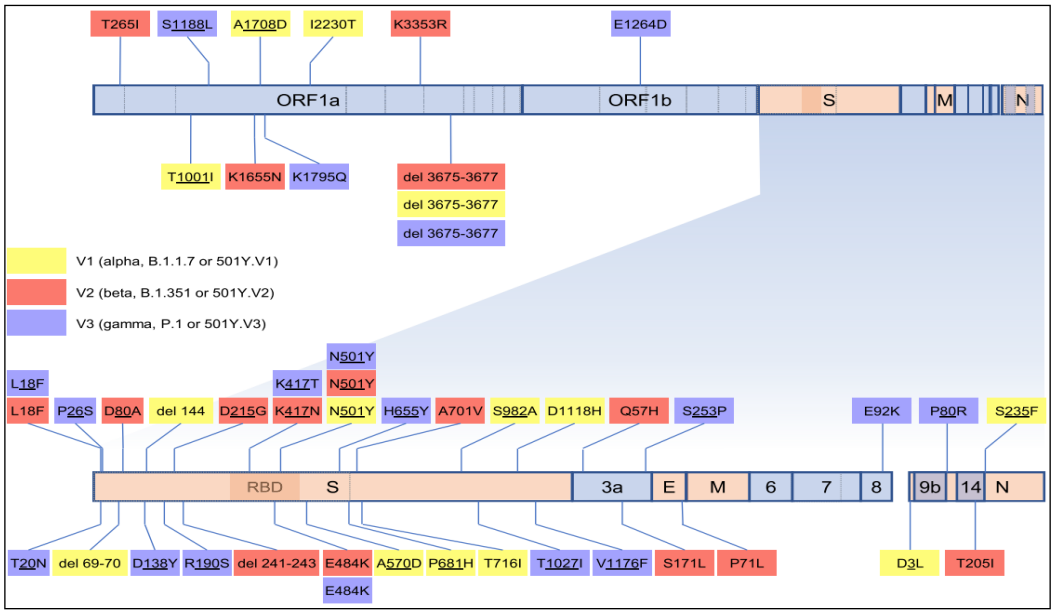

Figure 2: Elucidates mutations types and locations of ORF1a, ORF1b, S, M, and N genes of SARS-CoV-2. Shared mutation among three variants included N501Y mutation in RBD and (Del 3675-3677) mutation in Orf1a, while (E484K, K417T) mutations in RBD and (L18F) mutation in spike protein are shared between V2 and V3 variants. Image was adapted from (6, 7).

2- Materials and Methods

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I-Samples collection:

In the current study, samples were collected from the end of February to the mid of March 2021, 10628 samples were collected from all regions of Thi-Qar governorate were collected from male and female individuals, including suspected symptoms and individuals from the public health department team, called the active survey of SARS-COV-2 that included markets, universities, and students. SARS-COV-2 sample handling and collection process are subjected to the WHO precaution guide protocol. This study was conducted at Al-Hussein Teaching Hospital involving the Al-Shifaa quarantine facility and SARS-CoV-2 laboratory. Samples were collected according to the WHO protocol for SARS-CoV-2 collection and transportation guidelines. Upper respiratory samples were collected from individuals who visited the hospital with one or more symptoms, including fever, sore throat, headache, tiredness, dry cough, abdominal pain, diarrhea, runny nose, and loss of smell, and taste sensations, in addition, an active survey conducted by the staff of mobile medical public health department to assess the prevalence of the virus in schools, colleges, and markets. Two swabs were collected from each individual, one from the nasopharyngeal and the other from the oropharyngeal. All swabs were placed in the viral transport media (VTM) (Biobase, China) and stored at 2-8^{o}C. Samples were transported no more than 24

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hours to the COVID-19 testing center at Al-Hussein Teaching Hospital for detecting viral RNA in samples.

II-RNA isolation

All samples have been processed in the COVID-19 testing center at Al-Hussein Teaching Hospital. MagPure viral nucleic acid isolation kit (Wondfo, China WF5412) was used to extract viral RNA from samples. According to the manufacturer's instructions, 200 µl of VTM has been used to extract the virus RNA from the sample .Protease K enzyme and magnetic bead were added to the sample with PCR internal control for quality assurance to monitor extraction processes. All extraction processes were carried out by the automated extraction system (Smart32, China). Extracted RNA has been processed directly for RT-PCR for SARS-CoV-2 RNA detection. All precautions and instructions for safety and quality were followed during the extraction process.

III- Reverse transcriptase PCR

Extracted RNAs were processed to RT-PCR using (Bio-Rad CFX96) instruments. A one-step RT-PCR detection kit (Wondfo, China) was used in our study. ORF1ab and S genes were used to detect the presence of SARS-CoV-2 RNA. Spike mutation (N501Y) was detected by the green channel (FAM

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fluorophore). In contrast, the ORF1ab gene was detected by the yellow channel (VIC fluorophore) and internal control by the red channel (Cy5 fluorophores). All RT-PCR materials were lyophilized, and 25 µl from each sample was added; positive control (PC) , negative control (NC), and non-template negative control (NTC) were included in each run for quality assurance. The cycling program was adjusted according to the manufacturer's instruction, stared with the reverse transcriptase step to convert RNA to cDNA at 50^{o}C for 10 minutes (1 cycle); the enzyme activation step at 95^{o} C for 2 minutes (1 cycle); the denaturation step at 95^{o} C for 5 seconds (40 cycles) and annealing and extension steps at 60^{o} C for 32 seconds (40 cycles) with data collection. All samples passed the quality control with PC (Ct <= 33) on all three channels. Negative control (NC) and non-template control (NTC) Ct > 38 on both green and yellow while internal control red channel Ct<=33. A special primer was used and detected with the FAM channel for (N501Y) spike mutation.

3- Results

I-N501Y mutation confirmed positive cases among suspected individuals:

This study included 10628 samples, 2423 (22.80%) were positive for N501Y mutation while 8205 (77.20%) were negative. Positive RT-PCR for suspected

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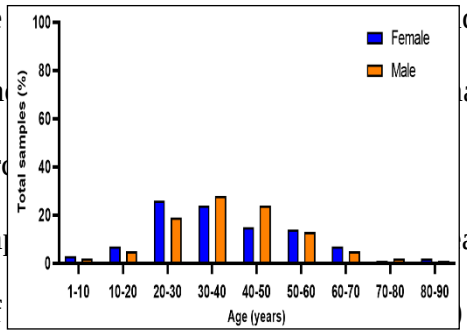
individuals was 1410 (13.26%), and while positive for active survey individuals was 1013 (9.53%), the total positive rate was (22.80%). Our data showed the prevalence

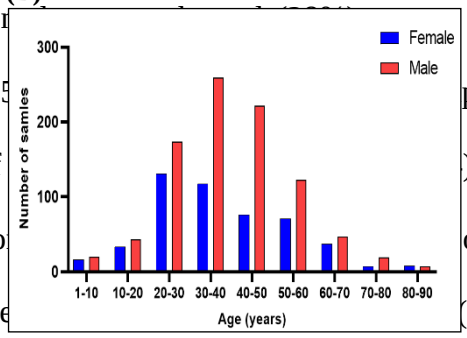
(A)



Age (years)	Female	Male	Grand total
1-10	3%	2%	3%
10-20	7%	5%	5%
20-30	26%	19%	22%
30-40	24%	28%	27%
40-50	15%	24%	21%
50-60	14%	13%	14%
60-70	7%	5%	6%
70-80	1%	2%	2%
80-90	2%	1%	1%
Grand total	100%	100%	100%

when atten higher per (131) com positive of

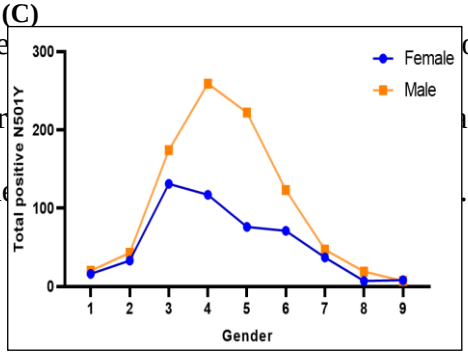
(B)



Age (years)	Female	Male	Grand total
1-10	16	20	36
10-20	33	43	76
20-30	131	174	305
30-40	117	259	376
40-50	76	222	298
50-60	71	123	194
60-70	37	47	84
70-80	7	19	26
80-90	8	7	15
Grand total	496	914	1410

hand, the positive N5 positive of positive fo while male

(C)



highest age group in both ge oup (30-40) years and 22% (305) in the age gr nt difference was found *(P=0.209)* between th .

Figure 3: Positive N501Y mutation among suspected individuals with symptoms showing the percentage of samples per age group (**A**) and the total samples per age groups (**B**). No significant difference between female and male in total positive cases (**C**). *P=0.209*

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II- N501Y confirmed positive cases among active survey individuals:

Our data showed that among active survey individuals, 24% (89) N501Y positive female was in the age group (30-40) years, while in the age group (20-30) years, the percentage of positive was 22%(82) cases. On the other hand, male groups showed a high positive rate of 28% (177) in the age group (30-40) years and 24% (152) in the age group (40-50) years. Total positive N501Y in females was 37.11% (376) out of 1013 and in males was 62.88% (637) out of 1013. The highest positive age group in both genders was 26% (266) in the age group (30-40). No significant difference *(P=0.25)* was found in total positive between females and males confirmed positive cases (figure 4).

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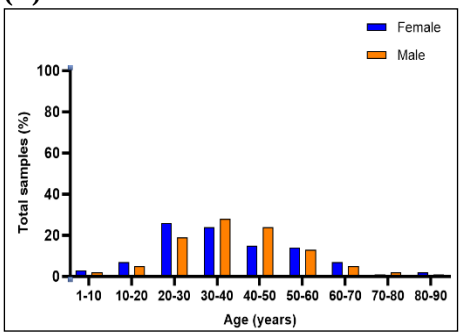
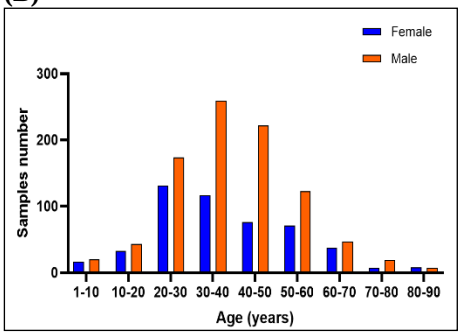
(A)



Age (years)	Female	Male	Grand total
1-10	2%	2%	2%
10-20	9%	5%	6%
20-30	22%	16%	18%
30-40	24%	28%	26%
40-50	19%	24%	22%
50-60	14%	17%	16%
60-70	7%	6%	6%
70-80	4%	2%	3%
80-90	0%	1%	0%
Grand total	100%	100%	100%

(B)



Age (years)	Female	Male	Grand total
1-10	6	15	21
10-20	32	29	61
20-30	82	103	185
30-40	89	177	266
40-50	72	152	224
50-60	53	108	161
60-70	26	39	65
70-80	16	10	26
80-90	0%	4	4
Grand total	376	637	1013

(C)

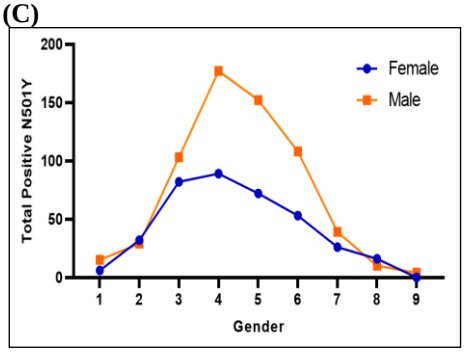


Figure 4: Positive N501Y mutation among active survey individuals without symptoms showing the percentage of samples per age group (**A**) and the total samples per age groups (**B**). No significant difference between female and male in total positive cases (**C**). *P=0.25*

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4- Discussion

The main concern regarding the new variant and new mutation is the transmissibility rate in the populations and the effectiveness of immune response and vaccines against the virus. Many studies have been conducted since starting the pandemic of SARS-CoV-2 on December 2019 in Wuhan, China. New variants of the virus appeared during the first year after the pandemic. N501Y mutation in RDB is one of the variants co-circulated worldwide. It is shared with three variants, including the alpha variant (B.1.1.7, 501Y.V1), the Beta variant (B.1.351, 501Y.V2), and the Gamma variant (P.1, 501Y.V3), which makes the virus more infectious to human [18-20]. Our data revealed that epidemiologically prevalence of N501Y mutation is co-circulating in our community, with total positive cases being 2423 (22.80%) out of 10628. Suspected individuals numbered 1410 (13.26 %), and the active survey numbered 1013 (9.53%). Interestingly, we conducted an active survey to assess the prevalence of SARS-CoV-2 among asymptomatic individuals who had no or negligible or not noticed symptoms and were doing their daily routine in markets, schools, and universities. The results were positive for 1013 (9.53 %).

This result reveals the virus's transmissibility among individuals who have no symptoms or do not feel that they are ill. Hence, spreading the virus around the community will be high because those do not think they need to wear a face mask or isolate their selves because they do not feel they are unwell and doing their routine work. A study conducted in northern Virginia, U.S.A., among asymptomatic health workers, showed the incidence rate of SARS-CoV-2 was (4.8 %) and was higher (7.9 %) in the age group (20-29 years) [21]. Furthermore, in another study of 1423 asymptomatic health workers, 780 (55%) were positive

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for SARS-CoV-2 [22]. In another study conducted in Spain on 16308 asymptomatic pregnant women, results came positive for 338 (2.07 %)[23]. These results are exciting findings showing that individuals with no symptoms can be holding the virus, and it can be transmitted to their contact leading to the spreading of the virus, making it challenging to contain the virus.

Studies showed that spike mutation N501Y enhances SARS-CoV-2 transmissibility efficiency leading to an increase in infectious rate among populations [24, 25]. Furthermore, the N501Y mutation enhanced virus resistance to antibodies, making it more virulent and weakening the immune response [26]. Another study showed using the computational biology approaches using the docking technique that N501Y spike mutation increases the stability and affinity of spike receptor with reduced immunogenicity to the virus leading to reducing the activity of vaccines that stimulates the host immune system against the viral spike protein [27]. Also, another study data showed that the N501Y mutation in spike protein increases the replication of the virus in the upper airway with increasing virus shedding in the nasal secretion in both the animal module experiments and human cells [28]. The N501Y mutation prevalence has been estimated from November 2020 to May 2021 in Cyprus, and the data showed that out of the total (658) cases, 433 (65.8%) were positive for the N501Y mutation and 225 (34.2%) were negative [29].

These results indicate that the prevalence rate is much higher than our study rate (22.80%) since the mutation variant started in Europe and moved worldwide to the Middle East, including Iraq. A study used a novel single nucleotide polymorphism assay to detect the N501Y mutation in the last week of January 2021; data showed that 206 (27.4%) out of 757 clinical nasopharyngeal

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swabs samples were positive for N501Y mutation, 94 (28.2%) male and 112 (26.85%) female with no significant difference between both gender [30].

Another study assessed the neutralizing and binding affinity of 12 monoclonal antibodies against spike protein. Data revealed that the N501Y mutation decreased the neutralizing affinity of monoclonal antibodies; ten were unaffected, while two were affected. These results indicate that the antibodies might have lost their affinity binding function to spike protein leading to decrease vaccination efficiency [31]. In Switzerland, a study screened the prevalence of the variant of concern from October 2020 to February 2021. The N501Y mutation in the community spreading was 739 (17.62%) out of 4194 [32]. These results indicated a lower percentage of N501Y mutation compared to our results. Many factors affect the spreading of the virus in the community. They might rely on the health system instructions to control the spreading of the virus and the people's actions regarding following the safety instruction, which included wearing masks, washing hands, and preventing the gathering from reducing the virus during the pandemic.

Furthermore, data showed that the combination of the N501Y mutation with other mutations like (K417N-E484K-N501Y) in the South African variant and the Brazilian variant (K417T-E484K-N501Y) is more lethal than the single mutation (N501Y) like in the UK variant. These results also uncovered the effects of triple mutation on vaccine efficiency since those mutations alter the Receptor-binding domain (RBD) [33]. In the UK, the study conducted from early September to mid-November 2020 revealed that the prevalence of SARS-CoV-2

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with N501Y mutation was 10%, and it was (6-13%) more transmissible than 501Y mutation lineage [2].

5- Conclusions

In general, the world's concern about the virus is the mutagenic ability during virus replication leading to new variants that, according to studies, have a weak affinity of the antibodies and can affect vaccine efficiency. Mutations, especially in viral spike protein, have been under focus since then; many mutations have been registered like (K417N-E484K-N501Y) and (K417T-E484K-N501Y). Viral spike protein via receptor-binding domain plays a crucial role during infectivity through binding to the ACE2 receptor on the human cells. Mutation in spike protein sequence might lead to an increase in virus transmissibility. The studies showed that lineages with N501Y mutation have (6-13%) more transmissibility than other variants [2]. Our data showed the prevalence of the mutation in the variant of SARS-Cov-2 in our governorate which was (22.80%) and that can effect the vaccine efficacy.

New invented vaccines like AstraZeneca and Pfizer stimulate the immune system against viral spike protein. Spike mutation like the N501Y can negatively reduce the vaccine's efficiency because both vaccines depend on the structural stability of the spike protein. When it changes by mutations, that can decrease the efficiency of vaccines and immune response via neutralizing antibodies that help to prevent or reduce symptoms when the second infection occurs. Finally, controlling virus spreading is a challenge, and studies need to be done regarding the screening process to evaluate the virus mutagenicity and detect new mutations

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that can accelerate the virus transmissibility, leading to elevated infectious rates and death.

Viral mutation during the pandemic can negatively affect the vaccine's efficiency and antibody affinity against spike protein. The quarantine instructions during the pandemic must be followed, which include preventing gathering, wearing face masks, washing hands, and isolation to prevent or reduce the probability of virus mutation during the wave.

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