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Mortality Due to COVID-19 in Renal Transplant Recipients, Related to Variants of SARS-CoV-2 and Vaccination in Mexico

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ABSTRACT

Background. SARS-CoV-2 infection in transplant patients has shown greater lethality and vaccination in this group of patients has shown less information. The objective of this study is to show the statistics in Mexico of lethality in kidney recipients infected with COVID-19 in relation to vaccination and variants of the coronavirus.

Methods. This is a bibliographic search of kidney transplant recipient patients since the start of the pandemic in Mexico to determine lethality after SARS-CoV-2 compared to the general population and in relation to patients, the 4 most important infectious peaks in the country due to identified variants, and also before and after vaccination.

Results. The global lethality is 26.91% from the beginning of the pandemic to April 9, 2022 in kidney recipients in Mexico (130 deaths of 483 infected kidney transplant recipients) compared to the national lethality of 5.60%. Variant B. 1.1.220 represented the highest lethality with 30.43% and the lowest lethality was Omicron with 16.41%. The lethality prior to vaccination was 30.94% and 23.46% after it.

Conclusion. Both some variants and vaccination have influenced a lower lethality due to COVID-19 in Mexico in kidney transplant patients; It is important to consider global recommendations, such as a third or fourth dose, a combination of mRNA vaccines and vectors in order to reduce lethality in this group of patients.

DUE to the COVID-19 pandemic, it was expected that immunocompromised patients would have a higher number of complications and higher associated lethality [1−2]. Within the first days of the pandemic, few data were available regarding renal recipients infected with SARS-CoV-2, where the most vigilant surveillance was based. narrow in the context of immunosuppression, although the symptoms were very similar to the non-transplanted population [3−4]. Despite numerous studies, mortality can still be highly variable, some studies mention probabilities of death of 21.3%, assuming that the 28-day case - fatality rate is high in transplant patients, even newly transplanted patients may have a higher risk of death by COVID-19 compared to dialysis patients on the transplant waiting list [5]. Another study determines a mortality of 28% in renal transplant recipients, compared to 1% to 5% of the general population or even 8% to 15% of those >70 years of age in the

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United States [6]. And yet another study on mortality of 17.9% highlighted that age >60 years, cardiovascular disease, dyspnea, and fever maintained a risk association for death in a multivariate analysis [7]. It has also been determined that in addition to the higher mortality associated with SARS-CoV-2, kidney transplant recipients have a higher percentage of acute kidney injury [8].

With the knowledge of the high lethality and with the advent of vaccination, the first studies appear after the application of the first dose of the vaccine, regardless of which, documenting the low response of detectable antibodies, with only 17% of transplant recipients vaccinated [9] and considered a higher seroconversion after the second dose of the vaccine [10−11]. Subsequently, studies with second doses of vaccination appear where the detection of antibodies increases considerably to 54% of transplanted people; however, these data demonstrate that a significant population of transplant recipients remain at risk of COVID-19 after the second dose of the vaccine, and interventions are proposed to improve this response to the vaccine such as additional doses (third dose) or modulation of immunosuppression [12].

Some explanations have been sought for this deficiency of antibody formation and a suboptimal effect of vaccination against SARS-CoV-2; a meta-analysis including data from 947 recovered transplant recipients from 15 clinical trials showed significantly lower rates of seroconversion among those who received mycophenolate mofetil, unlike other immunosuppressive agents [13], even with the measurement of antibodies of 37% against 63% of those who did not have antimetabolite against those who did, respectively [14]. With current knowledge, possible solutions lie in: 1. additional vaccination, 2. combination of mRNA and vector vaccines, 3. temporary interruption or reduction of the dose of mycophenolate, and 4. possibly increasing the dose of steroid; however, all of these should require additional focus [13]. Encouraging data suggest that age >68 years and longer time since transplantation were factors associated with antibody response [15]. In transplanted people, a deficient initial formation of antibodies has been observed, as well as low antibody production when the infection is acquired, the follow-up has resulted in a considerable decrease in a short time, 3 months, with a drop of up to 87% of the levels of anti-SARS-CoV-2 antibodies [16]. In addition, it was also documented that patients who received mRNA vaccines had significantly higher rates of seroconversion compared to vector-based vaccines [17].

Recent studies with a third dose of the vaccine showed that COVID-19 infection was observed in low responders and nonresponders, representing the 29% who did not show a humoral response after the third dose, and the humoral response to the vaccine was affected in patients receiving mycophenolate acid or belatacep; in addition, reduced kidney function and CD4 lymphopenia were also associated with a poor response to the vaccine [18,19]. Therefore, the objective of this study is to show the epidemiologic data of Mexico in relation to vaccination in our country and the influence on the lethality of kidney transplant patients due to SARS-CoV-2 in relation to the general population, as well as with variants of the same coronavirus.

MATERIAL AND METHODS

Design

This is a bibliographic search of patients infected with SARS-CoV-2 in Mexico that included the general population and kidney transplant patients.

Patients

All patients infected with SARS-CoV-2, both the general population and kidney transplant recipients, were considered eligible from February 28, 2020 in Mexico to April 9, 2022 of the official records in the country. The patients were classified in two ways: (1) by the peaks (waves) of greater infection identified in Mexico and (2) based on data from the National Institute of Genomic Medicine (INMEGEN) where SARS-CoV-2 variants were identified where they were established four groups: (1) the first wave of infection, when the variant of the coronavirus B 1.1.220 predominated; (2) the second wave of infection, when the variant B 1.1.519 predominated; (3) the third wave of infection, when the Alpha and Gamma variants predominated at the beginning and later multiple Delta variants dominated; and (4) from the end of December 2021 to April 2022, when the Omicron variant predominated. A classification was also made in relation to vaccination: (1) patients infected before vaccination in Mexico, before January 7, 2021 (although vaccination was officially on December 25, 2020, protection by vaccination usually starts 15 days after application, which is why the date was considered in January); and (2) after vaccination. From these statistics, the number of infected people and those with a death outcome were sought in order to determine their lethality at the moments mentioned historically.

Data Collection

The data of the registered patients were obtained from the national statistics of the Secretary of Health of Mexico, as well as the official data of the National Transplant Center, from which the number of infected people per period and the corresponding lethality.

Statistics

The lethality data are presented in frequencies and percentages globally in the general population and transplant recipients, as well as the subdivision of lethality by variants in each wave of infection in Mexico and by the effect of vaccination.

RESULTS

The bibliographic search is carried out starting with the National Institute of Genomic Medicine data, where it establishes the main variants during the time of the pandemic in Mexico; the typing of all the cases of the variants was not carried out, with initial percentages close to 10%, a gradual increase until the number of genomes was around 70% to 90% of the cases, and remaining consistent since then. The most predominant variants were identified in each of the peaks, with the highest incidence in Mexico, there have been 4 peaks of infection in the country: the first peak with its nadir on July 20, 2020; second peak with its nadir on January 21, 2021; third

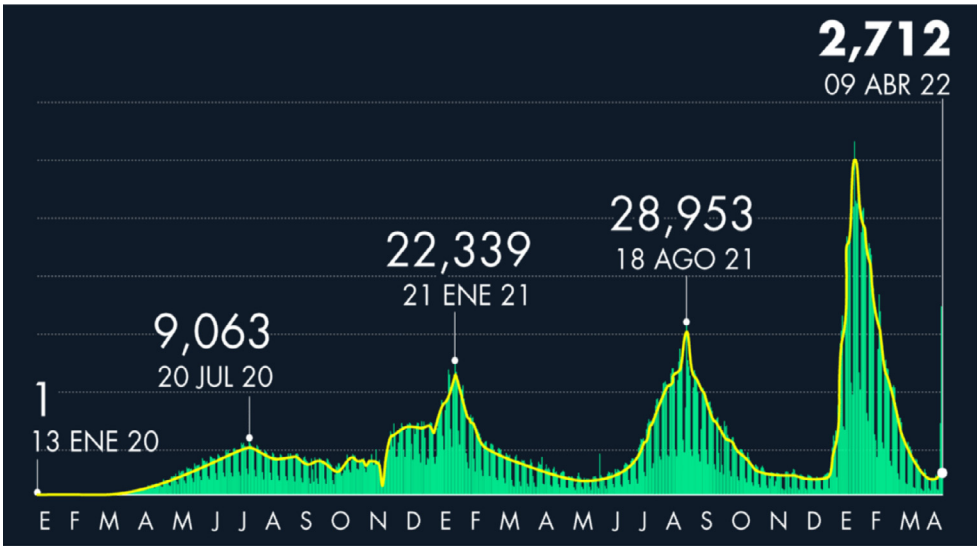

Fig 1. Number of cases per day of COVID-19 in Mexico. Cumulative cases as of April 9, 2022 of 5,722,541 deaths up to this same period of 323,729. Source: The Secretary of Health of Mexico, image taken from the newspaper El Economista [20].

peak with its nadir on August 18, 2021; and fourth peak with its nadir on January 19, 2022. Currently in Mexico with a fourth peak due to the Omicron variant, of which the final lethality will not be reported, because it is active at this time with its highest moment of contagion in a single day for January 19, 2022 (60,552 people infected), from there with a continuous decrease until the end of the data analysis on April 9, 2022, where there are 5,722,541 accumulated cases of infected people with 323,729 deaths officially registered by the Mexican Secretary of Health (Fig 1).

The lethality in the general population is 5.60% compared to 26.91% for the transplanted population. Regarding the cases, an analysis is made first in relation to the moments of greatest infection by wave of infection in Mexico and later in relation to vaccination.

In Relation to the Variants

The first wave was dominated by the B 1.1.220 variant, with a lethality in the general population of 9.37% (109,456 deaths per 1,168,395 infected people) and 30.43% (63 deaths per 207 infected people) in the transplanted population in this same period. In the case of the second wave, with a predominance of variant B 1.1.519, the lethality in the general population was 9.15% (110,924 deaths out of 1,212,295 of the total number of people infected in the period), compared to the lethality of transplanted people of 23.02% (29 of 126 people). In the third wave there was no variant predominance and it was mainly distributed among the Alpha, Gamma, Delta, and other variants with a lethality of 4.99% in the general population (78,439 of 1,571,256 people for the period) against 29.67% in transplant recipients (27 of 91 people for the same period). Finally, the fourth wave, current in Mexico, with a predominance of the Omicron variant as of April 9, has a lethality of 1.40% (24,910 of 1,770,595 people) compared to 16.41% in renal recipients for this same period 11 of 67) (Table 1).

Regarding Vaccination

Before vaccination in Mexico, the lethality was 8.77% (131,031 of 1,493,569 of the total infected people) compared to 30.94% for the transplant population (69 of 223 for the period before vaccination). The figures after vaccination started was 4.55% lethality in the general population (192,698 of 4,228,972 of the population that contracted COVID-19) against 23.46% of renal recipients (61 of 260) (Table 1).

DISCUSSION

The lethality in transplant patients in Mexico by SARS-CoV-2, according to official figures, is 4 times more than in the general population, 26.91% against 5.60%. In our country there were 4 "peaks" (also called "waves") of contagion where a particular variant predominated, compared to others in smaller numbers, according to studies by the National Institute of Genomic Medicine. In the general population, these variants also had a specific lethality that decreased as each wave of contagion appeared; from the first to the second wave it was almost constant 9.37% against 9.15%, then in the third to 4.99% (almost half of lethality) and in the fourth wave 1.40% (7 times the lethality of the first wave). On the other hand, in people with kidney transplants, this lethality was initially 30.47% in the first wave and decreased to 16.41% for the current wave of contagion (half of the initial lethality), with the number of deaths still being extremely high among people who become infected.

An important point to clarify is that immunity conditions are decreased in patients with kidney disease mainly owing to uremia. In addition, community immunity is also interrupted in

Table 1. General and transplant population with COVID-19; as well as deaths associated with variants and vaccination

	Infected		Deaths		Lethality
	Totals at the end of the period	During the period	Totals at the end of the period	During the period	%
IN RELATION TO THE VARIANTS					
Total population in Mexico	5,722,541		323,729		5.60
B 1.1.220/Others (28-02-2020 to 05-12-2020)	1,168,395	1,168,395	109,456	109,456	9.37
B 1.1.519/Others (06-12-2020 to 15-05-2021)	2,380,690	1,212,295	220,380	110,924	9.15
Alpha/Gamma/Delta/Others (16-05-2021 to 27-12-2021)	3,951,946	1,571,256	298,819	78,439	4.99
Omicron/Others (28-12-2022 to 09-04-2022)	5,722,541	1,770,595	323,729	24,910	1.40
Population with kidney transplant in Mexico	483		130		26.91
B 1.1.220/Others (28-02-2020 to 05-12-2020)	207	207	63	63	30.43
B 1.1.519/Others (06-12-2020 to 15-05-2021)	333	126	92	29	23.02
Alpha/Gamma/Delta/Others (16-05-2021 to 27-12-2021)	424	91	119	27	29.67
Omicron/Others (28-12-2022 to 09-04-2022)	483	67	130	11	16.41
IN RELATION TO VACCINATION					
Total population in Mexico	5,722,541		323,729		5.60
Pre-vaccination (28-02-2020 to 07-01-2021)	1,493,569	1,493,569	131,031	131,031	8.77
Post-vaccination (08-01-2021 to 09-04-2022)	5,722,541	4,228,972	323,729	192,698	4.55
Population with kidney transplant in Mexico	483		130		26.91
Pre-vaccination (28-02-2020 to 07-01-2021)	223	223	69	69	30.94
Post-vaccination (08-01-2021 to 09-04-2022)	483	260	130	61	23.46

elderly people, people with chronic degenerative diseases, and in patients with chronic kidney disease or transplants, because the differentiation of B cells, as their activating factor, compromises the formation of antibodies and thus the effectiveness of vaccination [21−22]. In renal transplant patients, both innate and adaptive immunity are impaired. Innate immunity with impairment of costimulatory molecules such as CD80 and CD86 for antigen-presenting cells and dendritic cells are common in patients with elevated uremic toxins, and Toll-like receptor expression is also modified, all of which decreases antibody production. In the case of adaptive immunity it is diminished, with deterioration in the ability to present antigens incapable of recognizing the pathogen and B-cell lymphopenia; They also mention that the neutralizing antibody titers for SARS-CoV-2 protein S are adequate after the third dose of the vaccine, especially in mRNA vaccines in solid organ transplant recipients in general [23]. In some way, this may explain why after vaccination in the general population, lethality is reduced by half (8.77%-4.55%), and in the case of people with kidney transplants, said lethality did not drop even a third of the stage before vaccination (30.94%-23.46%) in our country [24].

A study in Scotland [25] shows that 93% of its transplant population (5281 transplant recipients) had a schedule of 2 vaccines. Where the rate of infection and hospitalization was evaluated and where its efficacy was 33% and 38%, respectively, for each event, the outcome of death was 10% in kidney recipients and <0.1% in the vaccinated population. These figures contrast with those found in our population, with a lethality rate of 23.46% when vaccination has already started. Unfortunately, we also do not have the figures of the transplanted population that has already complied with the 2-dose scheme, much less a booster with a third, which is recommended in this vulnerable group in addition to other complementary strategies to reduce the risk of COVID-19 infection and its complications. Figures closer to our lethality are described in some meta-analyses [26−27] where it ranged from 18.6% to 23%, respectively, and in studies in Europe and America, mortality ranges from 20% to 32% in kidney transplant recipient patients compared to the general population (between 1% to 14% after adjusting for age and comorbidities) [28]. However, within the guidelines to be followed is that transplant patients should receive vaccination schedules of 3 and ≤4 doses; reduction of immunosuppression is a consideration in the early stages of the infection, as well as considering the comorbidities that each patient presents in a particular way with the intention of making preventive maneuvers.

Finally, regarding the variants of SARS-CoV-2 that are appearing, they are known to have compromised the effect of the vaccines used, but despite this, there is considerable efficacy in reducing infection, serious events that require hospitalization and, above all, mortality [29].

The main limitation of the study is to base it solely on national statistics without being able to establish a cohort of patients infected by SARS-CoV-2 in renal recipients in order to determine all the variables to establish risk factors, knowledge of evolution, type of vaccine, measurement of antibodies, and so on.

CONCLUSIONS

There is a very high lethality in kidney transplant patients with SARS-CoV-2 infection owing to the their poor immune response. In Mexico, the lethality is 1 death for every 4 transplanted people, unlike the general population (1 death for every 20 people infected). We must reinforce the idea of 3 to 4 doses of the vaccine in this group of patients, the reduction of immunosuppression in the first phase of the infection, attention to the comorbidities present in each renal transplant recipient, and a combination of mRNA and vector vaccines in order to reduce lethality in this group of patients.

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