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REVIEW ARTICLE

Vaccines Against SARS-CoV-2 and their Effects on Mortality in Transplant Patients: A Systematic Review with Meta-analysis

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ABSTRACT

Objectives: With the advancement of the pandemic and better knowledge of coronavirus disease 2019 (COVID-19), new ways of tackling this disease have come to light. Therefore, we propose this systematic review to better understand the action of vaccines in combating mortality caused by this virus, especially in transplant patients. **Methods:** In this systematic review with meta-analysis, the reviewers analyzed 389 eligible articles according to the criteria used and blindly selected the studies that provided data on transplant patients and mortality, resulting in 15 works included in the study. The screening results were added to a spreadsheet, and data was compiled. **Results:** Of the 15 articles included, it was possible to observe a significant drop in the overall mortality rates of vaccinated patients, except in studies that used the inactivated virus immunizer. Furthermore, the mortality of infected patients, even after vaccination, remained close to that of the unvaccinated group, as did the need for mechanical ventilation. **Conclusion:** Immunization of transplant patients can significantly reduce mortality rates for this portion of the population. However, as they have a reduced seroconversion rate, different ways of achieving an adequate immune response must be considered.

Descriptors: SARS-CoV-2; COVID-19; Vaccines; Transplanted; Efficiency; Mortality.

Vacinas contra SARS-CoV-2 *e seus Efeitos Frente à Mortalidade em Pacientes Transplantados: Uma Revisão Sistemática com Meta-Análise*

RESUMO

Objetivos: Com o avançar da pandemia e o melhor conhecimento da doença do coronavírus 2019 (COVID-19), novas maneiras de enfrentar essa enfermidade vieram à tona. Assim, propomos esta revisão sistemática para entender melhor a ação das vacinas no combate à mortalidade causada por esse vírus, em especial nos pacientes transplantados. **Métodos:** Nesta revisão sistemática com metanálise, os revisores analisaram 389 artigos elegíveis de acordo com os critérios utilizados e selecionaram cegamente os estudos que traziam dados sobre pacientes transplantados e mortalidade, resultando no total de 15 trabalhos inseridos no estudo. Os resultados da triagem foram adicionados a uma planilha e seus dados compilados. **Resultados:** Dos 15 artigos incluídos, foi possível observar uma queda significativa nos índices de mortalidade geral dos pacientes vacinados, exceto nos estudos que utilizaram o imunizante de vírus inativado. Além disso, a mortalidade dos pacientes infectados mesmo após a vacinação manteve-se próxima à do grupo dos não vacinados, assim como a necessidade de ventilação mecânica. **Conclusão:** A imunização dos pacientes transplantados é capaz de reduzir significativamente os índices de mortalidade dessa parcela da população. No entanto, por terem uma taxa de soroconversão reduzida, diferentes maneiras de atingir uma resposta imune adequada devem ser consideradas.

Descritores: SARS-CoV-2; COVID-19; Vacinas; Transplantados; Eficácia; Mortalidade.

INTRODUCTION

The current coronavirus disease 2019 (COVID-19) pandemic has brought severe harm to patients with different comorbidities. Diabetes, hypertension, obesity and chronic obstructive pulmonary disease (COPD) are some conditions that cause a significant increase in the death rate from COVID-19 pneumonia[1]. Among these patients, solid organ transplant recipients are particularly affected. Up to 78% of infected transplant patients require hospitalization, and of these, more than 20% die[2].

This high mortality can be explained by the patient's degree of immunosuppression, which prevents them from establishing an effective immune response against the infection. Another critical factor is the baseline characteristics of these patients, as this subgroup tends to have other associated comorbidities and an older age[3].

In this context, vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are an essential tool for preventing the occurrence of the disease in its severe form. In addition to their effectiveness, these immunizers have been proven in several Phase III studies and are widely available to the population in several countries. Such results, however, still need to be validated for transplant patients, as this subgroup has been excluded from most clinical trials[4,5].

It has already been demonstrated that solid organ transplant recipients cannot establish a satisfactory immune response to the vaccine, as they have lower antibody and seroconversion levels than those presented by control groups[6,7]. Due to these results, it is questioned whether the level of protection offered by the vaccine is satisfactory in this group concerning that seen in the general population.

Given the above, it is possible to discuss the effectiveness of vaccination in transplant patients and whether such a strategy effectively reduces the number of deaths in this population. Therefore, this review seeks to compare the levels of mortality and hospitalization of solid organ transplant patients who have or have not had their vaccination schedule established.

METHODS

Protocol and registration

The PROSPERO platform analyzed and approved this systematic review, with registration CRD42022315426.

Literature search strategy

The article's structure, methodological strategies, and design were considered during the selection to answer the following question: "Do vaccines against SARS-CoV-2 influence the mortality of transplant recipients?" The following inclusion criteria were considered: consistent data on transplant patients, the study group having received at least one dose of vaccine against SARS-CoV-2 and the mortality of this group, regardless of the written language, year of publication or methodological design of the study. As exclusion criteria, documents such as letters to the editor or incomplete documents were disregarded.

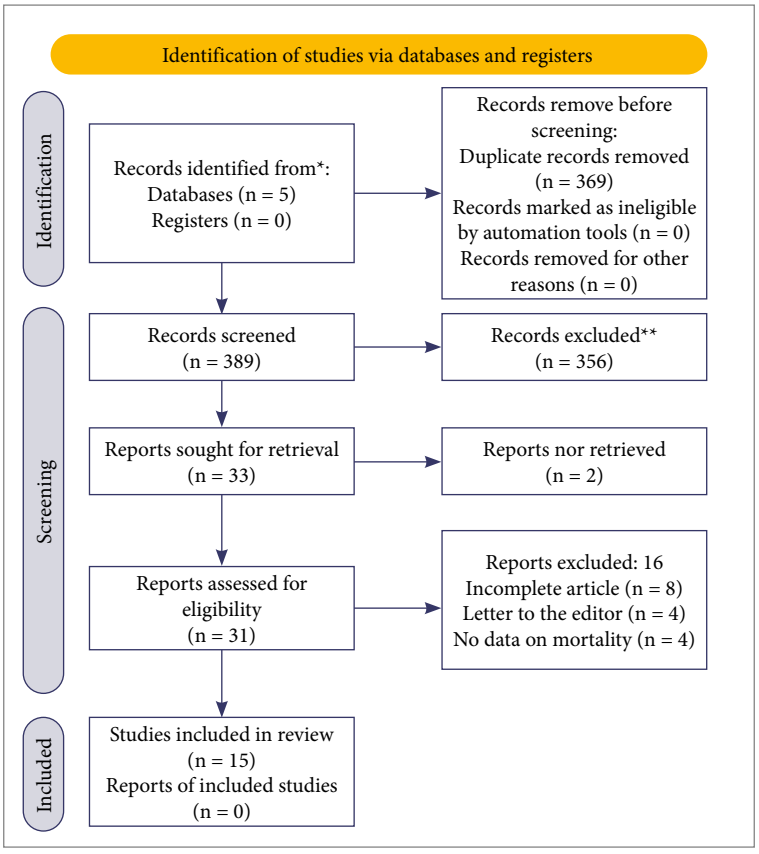
The search was carried out using the electronic databases Embase, PubMed, Cochrane Library, Web of Science, and Scopus. These databases were searched on May 24, 2022, and no search filters such as date, structure or nationality were applied. Communication with one of the authors of an article was carried out successfully when it was difficult to access the article in its entirety, and it was recovered. However, the article was not included because it needed to meet the proposed inclusion criteria.

During the search, the following Medical Subject Headings (MeSH) terms were used: ("COVID-19" OR "SARS-CoV-2") AND ("COVID-19 Vaccines" OR "2019-nCoV Vaccine mRNA-1273" OR "ChAdOx1 nCoV-19" OR "BNT162 Vaccine" OR "Ad26COVS1" OR "Vaccines") AND ("Transplantation" OR "Transplant Recipients") AND ("Mortality" OR "Hospital Mortality"). These terms were used in all search bases, with their respective entry terms, to keep the review as comprehensive as possible. For the Embase platform, MeSH terms were replaced by their Emtree counterparts.

The inclusion and exclusion criteria were established and explained at a research group conference. Two reviewers independently and blindly conducted the initial selection of studies, using the title and abstract as screening tools. All studies found were added to the Mendeley® software (1.19.8) to eliminate duplicates from the analysis. The reviewers analyzed 389 eligible articles according to the criteria used. The screening results were added to a Google Sheets® spreadsheet, reaching a kappa agreement of 0.855, which is considered significant and sufficient to continue the verification steps.

RESULTS

Of the 389 articles screened, 33 were selected for full reading based on the title and summary; however, two could not be retrieved, resulting in 31 articles read in full. Of these, eight documents were conference summaries and were not included, considered incomplete articles; four letters to the editor and four articles did not contain data on mortality or had incomplete data, leaving 15 articles that met the inclusion criteria. These data processing steps were illustrated in the flowchart based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria, represented in Fig. 1.



Source: Elaborated by the authors according to the diagram available at https://www.prisma-statement.org/prisma-2020-flow-diagram.

Figure 1. PRISMA flowchart.

The data were displayed in Table 1 to characterize the sample used in each study, including the identification of the study, type of population transplant, the country where the study was conducted, groups studied, and the age of participants defined by the interquartile range and its minimum and maximum values presented, in addition to the sex of the participants. Male patients were predominantly over 45 years of age, and the country that offered the most significant number of studies on the subject was the United States of America.

Among these 15 articles[8-22], two methodologies for presenting results were highlighted. The first, defined as overall mortality, compares the death rate between vaccinated and unvaccinated patients, regardless of SARS-CoV-2 infection. Relative mortality refers to the death rate exclusively of transplant patients (vaccinated or not) and infected by the virus. In articles that provided general mortality data, it was possible to calculate relative mortality based on the infection rate presented.

Table 2 presents data from the risk of bias analysis using the Newcastle-Ottawa scale. All studies, except for Medina-Pestana et al.[17], presented an observational design and followed an appropriate methodology regarding the biases analyzed. The Medina-Pestana et al. study[17] presents a clear bias in its comparability, using control and intervention samples at different times of the pandemic, demonstrating uncertainty in the level of evidence provided by its methodology.

Table 1. Epidemiological data from selected studies.

Author	Transplant	Center Country	Group	Average age in years (IQR)	Sex (n)
Demir et al.[8]	Kidney	Turkey	Vaccinated	45 (38-63)	M = 41 F = 41
			Non-Vaccinated	47 (39-60)	M = 41 F = 41
Chavarot et al.[9]	Kidney	France	Vaccinated	NR	NR
Bell et al.[10]	Kidney	Scotland	Vaccinated	60 (49-69)	NR
Hippisley-Cox et al.[11]	Kidney	UK	Vaccinated	NR	NR
Callaghan et al.[12]	Solid organ	England	Non-Vaccinated	NR	M = 1,913 F = 1,167
			Vaccinated with one dose	NR	M = 697 F = 444
			Vaccinated with two doses	NR	M = 23,848 F = 15,412
Kuczaj and Przbyłowski[13]	Heart	Poland	Vaccinated	54 (39-69)	M = 425 F = 127
			Non-Vaccinated	NR	NR
Hall et al.[14]	Solid organ	Canada	Vaccinated	58	M = 52 F = 25
			Non-Vaccinated	55	M = 147 F = 73
Peters et al.[15]	Heart	USA	Vaccinated	56	M = 255 F = 111
			Non-Vaccinated	45	M = 48 F = 22
Reischig et al.[16]	Kidney	Czech republic	Vaccinated	58 (47-69)	M = 143 F = 83
			Non-Vaccinated	58 (45-71)	M = 130 F = 64
Medina-Pestana et al.[17]	Kidney	Brazil	Vaccinated	53 (45-60)	M = 140 F = 92
			Vaccinated with two doses	52-56	M = 94 F = 70
			Vaccinated with one dose	52	M = 46 F = 22
			Non-Vaccinated	45	M = 214 F = 127
Sutharattanapong et al.[18]	Kidney	Thailand	Vaccinated	55	M = 18 F = 5
			Non-Vaccinated	48	M = 12 F = 10
Mazuecos et al.[19]	Kidney	Spain	Vaccinated	58 (48-68)	M = 220 F = 131
			Non-Vaccinated	58 (47-67)	M = 78 F = 52
Bollineni et al.[20]	Lung	USA	Vaccinated	60 (20-73)	M = 9 F = 5
			Non-Vaccinated	54 (30-62)	M = 39 F = 17
Aslam et al.[21]	Solid organ	USA	Vaccinated	58	M = 879 F = 487
			Non-Vaccinated	53	M = 349 F = 193
Saharia et al.[22]	Solid organ	USA	Vaccinated	NR	M = 37 F = 28

Source: Elaborated by the authors. IQR = interquartile range; NR = not reported.

Table 2. Bias risk analysis.

Author	New Castle-Ottawa
Demir et al. [8]	6
Chavarot et al.[9]	8
Bell et al.[10]	8
Hippisley-Cox et al.[11]	8
Callaghan et al.[12]	9
Kuczaj and Przbyłowski[13]	8
Hall et al.[14]	8
Peters et al.[15]	6
Reischig et al.[16]	7
Medina-Pestana et al.[17]	Clinical trial
Sutharattanapong et al.[18]	8
Mazuecos et al.[19]	8
Bollineni et al.[20]	8
Aslam et al.[21]	8
Saharia et al.[22]	8

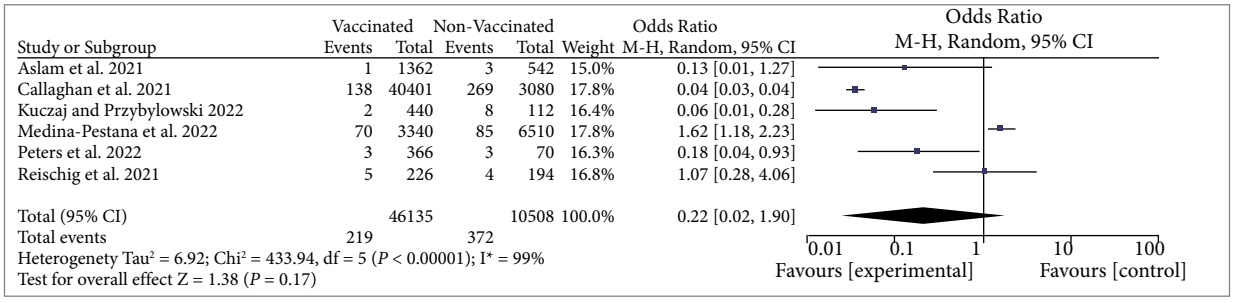
Source: Elaborated by the authors.

Regarding the demonstration of general mortality, the primary outcome analyzed in this review, Table 3 describes the results presented in each study, differentiating the population between the types of transplant previously received, the situation concerning the vaccination schedule, the sample number of each group and overall mortality rates and percentages of infection. These results will be compared statistically in Figs. 2 and 3. It is essential to highlight that seven articles were excluded from this presentation of results because they needed to describe this data clearly.

Table 3. Description of general mortality data for transplant patients infected with SARS-CoV-2.

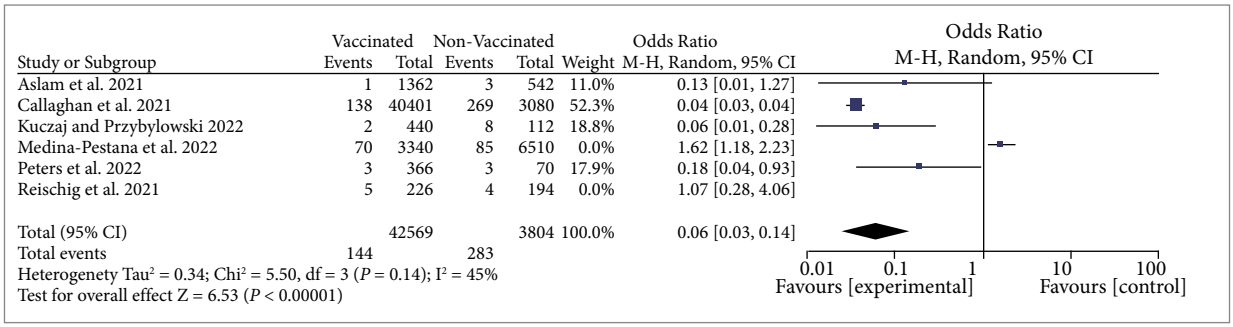
Authors	Type of transplant	Sample size	Groups	n sample	General mortality % (n)	Infection % (n)
Chavarot et al.[9]	Kidney	181	Vaccinated	181	3.31 (6)	6.62 (12)
Bell et al.[10]	Kidney	3,315	Vaccinated	3,119	0.83 (26)	8.30 (259)
Hippisley-Cox et al.[11]	Kidney	4,565	Vaccinated	4,565	0.11 (5)	NR
Callaghan et al.[12]	Kidney	43,481	Non-Vaccinated	2,146	9.73 (209)	92.49 (1,985)
			Vaccinated with one dose	770	2.85 (22)	27.28 (191)
			Vaccinated with two doses	28,016	0.28 (78)	0.34 (96)
	Pancreas + kidney		Non-Vaccinated	110	6.36 (7)	76.36 (84)
			Vaccinated with one dose	40	0.00 (0)	25.00 (10)
			Vaccinated with two doses	1,518	0.13 (2)	4.01 (61)
	Liver		Non-Vaccinated	588	4.93 (29)	62.92 (370)
			Vaccinated with one dose	218	1.83 (4)	15.13 (33)
			Vaccinated with two doses	6,747	0.18 (12)	2.58 (174)
	Heart		Non-Vaccinated	127	7.00 (9)	56.69 (72)
			Vaccinated with one dose	58	3.44 (2)	20.69 (12)
			Vaccinated with two doses	1,690	0.29 (5)	4.38 (74)
	Lung		Non-Vaccinated	83	18.07 (15)	69.88 (58)
			Vaccinated with one dose	44	2.27 (1)	18.18 (8)
			Vaccinated with two doses	1,062	1.03 (11)	3.86 (41)
	Intestine and multiorgan		Non-Vaccinated	26	0.00 (0)	23.07 (6)
			Vaccinated with one dose	11	9.09 (1)	36.36 (4)
			Vaccinated with two doses	227	0.00 (0)	1.76 (4)
	Solid organ		Non-Vaccinated	3,080	8.73 (269)	83.60 (2,575)
			Vaccinated with one dose	1,141	2.62 (30)	22.61 (258)
			Vaccinated with two doses	39,260	0.27 (108)	3.34 (1,314)
Kuczaj and Przybylowski[13]	Heart	552	Vaccinated	440	0.45 (2)	2.04 (9)
			Non-Vaccinated	112	7.14 (8)	83.92 (94)
Peters et al.[15]	Heart	436	Vaccinated	366	0.81 (3)	19.67 (72)
			Non-Vaccinated	70	4.28 (3)	48.57 (34)
Reischig et al.[16]	Kidney	420	Vaccinated	226	2.21 (5)	16.37 (37)
			Non-Vaccinated	194	2.06 (4)	22.16 (43)
Aslam et al.[21]	Solid organ	1,904	Vaccinated	1,362	0.07 (1)	0.88 (12)
			Non-Vaccinated	542	0.55 (3)	19.00 (103)

Source: Elaborated by the authors.



Source: Elaborated by the authors.

Figure 2. Forest Plot of the overall mortality analysis between vaccinated and unvaccinated patients.



Source: Elaborated by the authors.

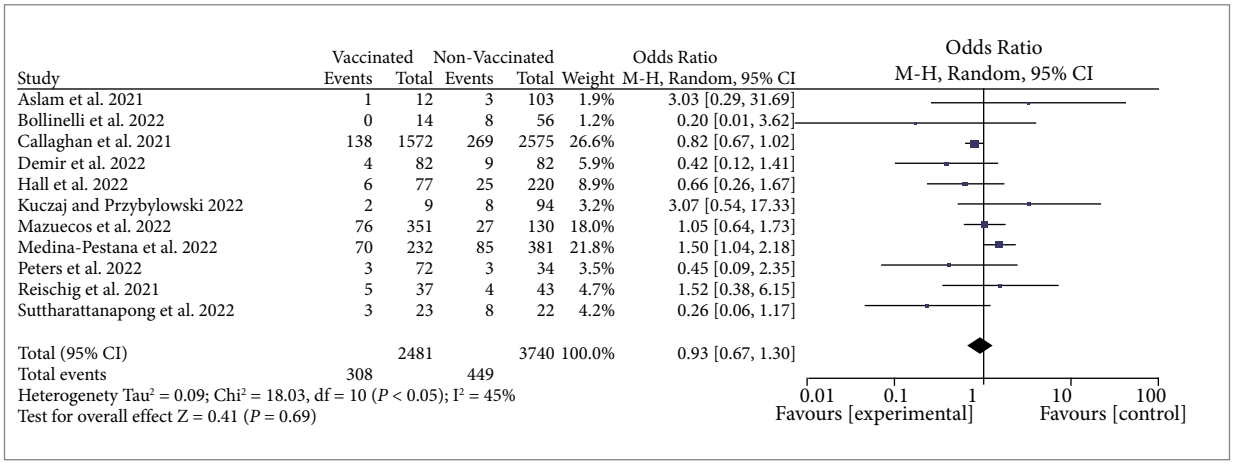
Figure 3. Forest Plot of the overall mortality analysis between vaccinated and unvaccinated patients, excluding data from the articles by Reischig et al.[16] and Medina-Pestana et al.[17].

Table 4, secondary outcomes, presents the numerical representation of the findings of relative mortality and the need for hospitalization or mechanical ventilation. Most of the reports did not explore the need for mechanical ventilation in patients affected by the disease, and when reported, it ranged from no need to up to 36.1% of those infected. As for hospitalization, more studies reported this data, which presented high heterogeneity, ranging from 20.7 to 92.8%. Data regarding relative mortality were compared in more depth in Figs. 4 and 5. However, absolute data varied from 2.9 to 36%.

Table 4. Description of secondary outcomes.

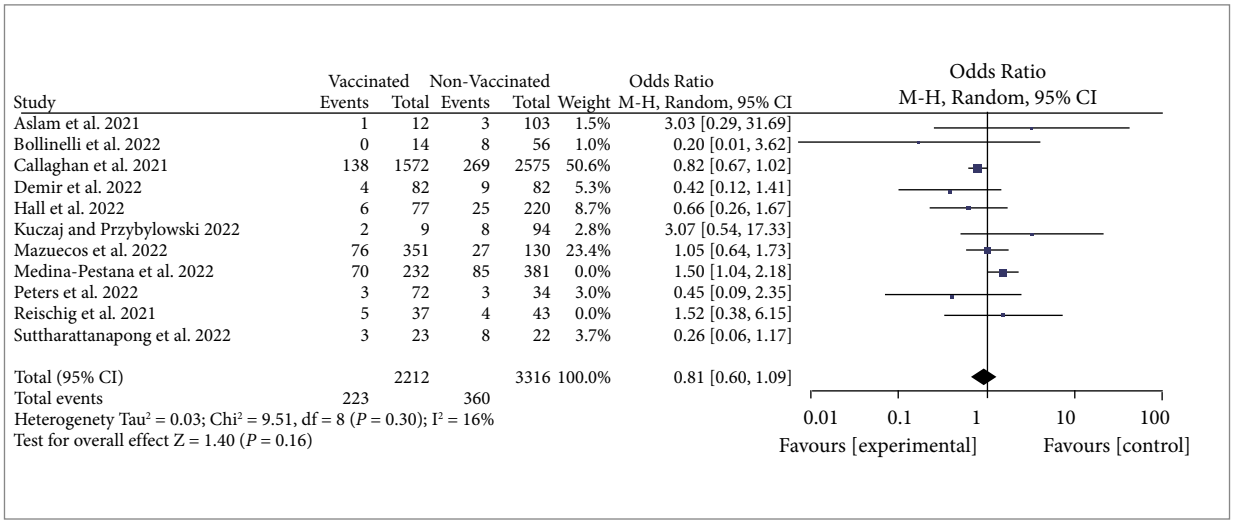
Author	Group	n sample	Relative mortality % (n)	Hospitalization % (n)	Mechanical ventilation % (n)
Demir et al.[8]	Vaccinated	82	4.9 (4)	20.7 (17)	6.1 (5)
	Non-Vaccinated	82	11.0 (9)	41.5 (34)	12.2 (10)
Chavarot et al.[9]	Vaccinated	181	50.0 (6)	67.0 (8)	NR
Bell et al.[10]	Vaccinated	3,119	10.0 (26)	31.0 (81)	NR
Hippisley-Cox et al.[11]	Vaccinated	4,565	n/a	n/a	NR
Callaghan et al.[12]	Non-Vaccinated	3,080	10.4 (269)	NR	NR
	Vaccinated with one dose	1,141	11.6 (30)	NR	NR
	Vaccinated with two doses	39,260	8.2 (108)	NR	NR
Kuczaj and Przybylowski[13]	Vaccinated	440	22.2 (2)	NR	NR
	Non-Vaccinated	112	8.5 (8)	NR	14.3 (11)
Hall et al.[14]	Vaccinated	77	7.8 (6)	50.6 (39)	11.4 (25)
	Non-Vaccinated	220	20,8 (15)	49,1 (108)	11.4 (25)
Peters et al.[15]	Vaccinated	366	4.2 (3)	20.8 (15)	NR
	Non-Vaccinated	70	8.8 (3)	29.4 (10)	NR
Reischig et al.[16]	Vaccinated	226	14.0 (5)	41.0 (15)	NR
	Non-Vaccinated	194	9.0 (4)	40.0 (17)	NR
Medina-Pestana et al.[17]	Vaccinated	232	30.2 (70)	62.9 (146)	36.1 (84)
	Vacinados with two doses	164	24.0 (40)	59.0 (98)	31.0 (51)
	Vacinados with one dose	68	44.0 (30)	71.0 (48)	49.0 (33)
	Non-Vaccinated	341	25.0 (85)	49.0 (168)	28.0 (95)
Sutharattanapong et al.[18]	Vaccinated	23	13.0 (3)	NR	9.0 (2)
	Non-Vaccinated	22	36.0 (8)	NR	18.0 (4)
Mazuecos et al.[19]	Vaccinated	351	21.7 (76)	66.1 (232)	20.2 (71)
	Non-Vaccinated	130	20.8 (27)	63.8 (83)	23.1 (30)
Bollineni et al.[20]	Vaccinated	14	0.0 (0)	85.7 (12)	0.0 (0)
	Non-Vaccinated	56	14.3 (8)	92.8 (52)	19.6 (11)
Aslam et al.[21]	Vaccinated	1,362	8.3 (1)	41.7 (5)	0.0
	Non-Vaccinated	542	2.9 (2)	NR	NR
Saharia et al.[22]	Vaccinated	66	9.1 (6)	54.5 (36)	15.15 (10)

Source: Elaborated by the authors. n/a = not applicable.



Source: Elaborated by the authors.

Figure 4. Forest Plot of the relative mortality analysis between vaccinated and unvaccinated patients.



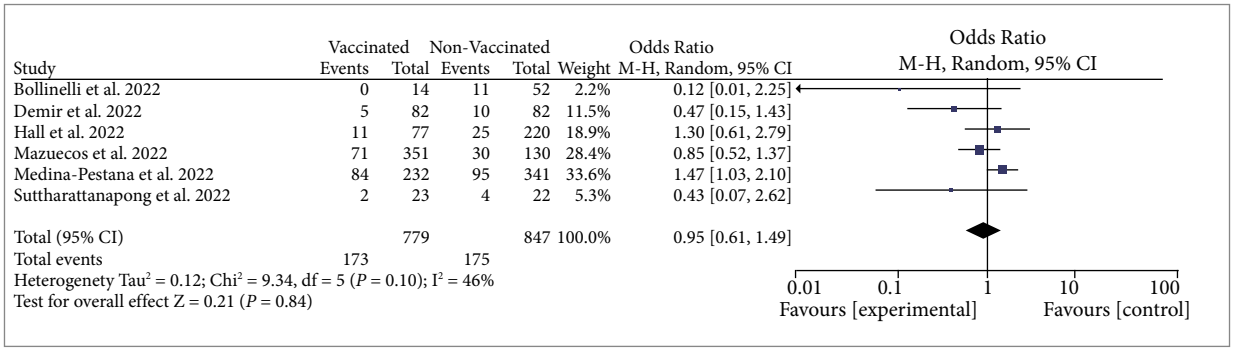
Source: Elaborated by the authors.

Figure 5. Forest Plot of the relative mortality analysis between vaccinated and unvaccinated patients, excluding data from the articles by Reischig et al.[16] and Medina-Pestana et al.[17].

In this article, meta-analyses were also carried out regarding the outcomes sought. The meta-analysis of relative mortality is summarized in Fig. 4, representing the forest graph that evaluated 6,221 patients from 11 articles, generating the odds ratio (OR) of 0.93 (0.67-1.30) and heterogeneity of $I^2 = 45\%$. Fig. 2 represents the synthesis of data referring to general mortality, with 56,643 patients referred to in six documents, which gave an OR of 0.22 (0.02-1.90); however, with the heterogeneity of $I^2 = 99\%$.

We noticed that the article by Medina-Pestana et al.[17] caused high heterogeneity, so an analysis was carried out without this article, both for relative mortality and overall mortality. Data referring to relative mortality without the article by Medina-Pestana et al. [17] are represented in Fig. 5. We then found the forest graph that analyzes 5,528 patients located in 9 articles, generating the OR of 0.81 (0.60-1.09) and heterogeneity of $I^2 = 16\%$. In the analysis of general mortality, we also excluded the article by Reischig et al.[16] because, just as Medina-Pestana et al.[17] produced high heterogeneity, both compare different waves of the pandemic for each group represented. Therefore, for general mortality, we find the forest graph in Fig. 3, which shows the analysis of 42,373 patients analyzed in four documents, generating the OR of 0.06 (0.03-0.14) and heterogeneity of $I^2 = 45\%$.

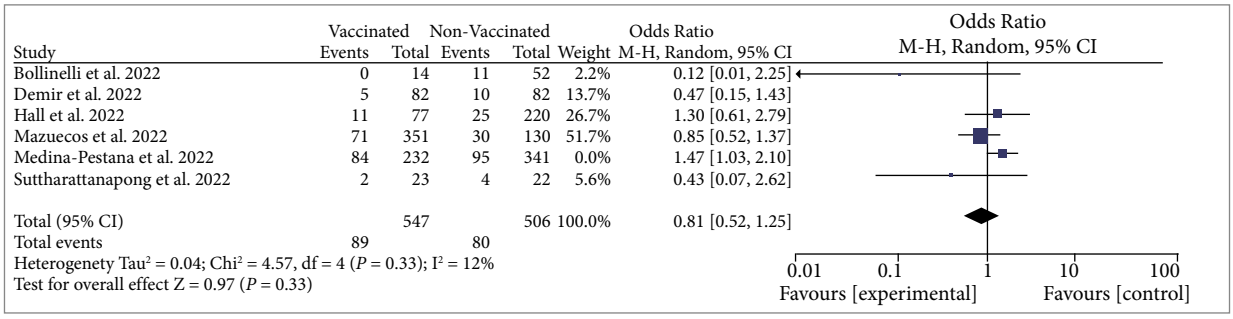
Hospitalization and mechanical ventilation parameters were also analyzed with and without the article by Medina-Pestana et al.[17], the forest graph represented in Fig. 6 was found, analyzing six articles and 1,626 patients, revealing the OR of 0.95 (0.61-1.49) with the heterogeneity of $I^2 = 46\%$. As for ventilation, without including the article by Medina-Pestana et al.[17], the forest graph in Fig. 7 was found, analyzing five articles and 1,053 patients, revealing the OR of 0.81 (0.52-1.25) and heterogeneity of $I^2 = 12\%$.



Source: Elaborated by the authors.

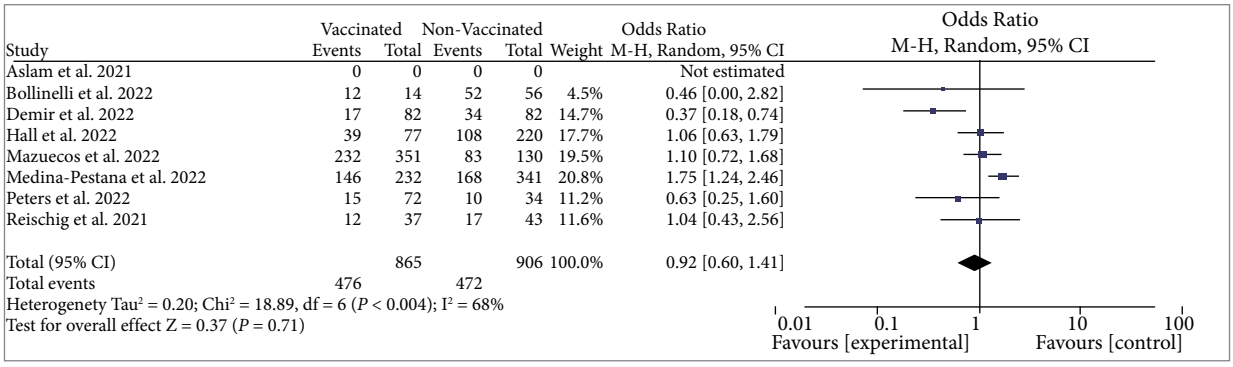
Figure 6. Forest Plot of the analysis of the need for mechanical ventilation between vaccinated and unvaccinated patients.

Hospitalization with the inclusion of the article by Medina-Pestana et al.[17] is represented in Fig. 8. The forest graph resulting from this analysis shows 1,771 patients from eight articles, with an OR of 0.92 (0.60-1.41) and heterogeneity of $I^2 = 68\%$. The same analysis without the article by Reischig et al.[16] and Medina-Pestana et al.[17]. is represented in Fig. 9 through the forest graph that analyzes 1,118 patients and defines the OR as 0.76 (0.48-1.20) with the heterogeneity of $I^2 = 54\%$.



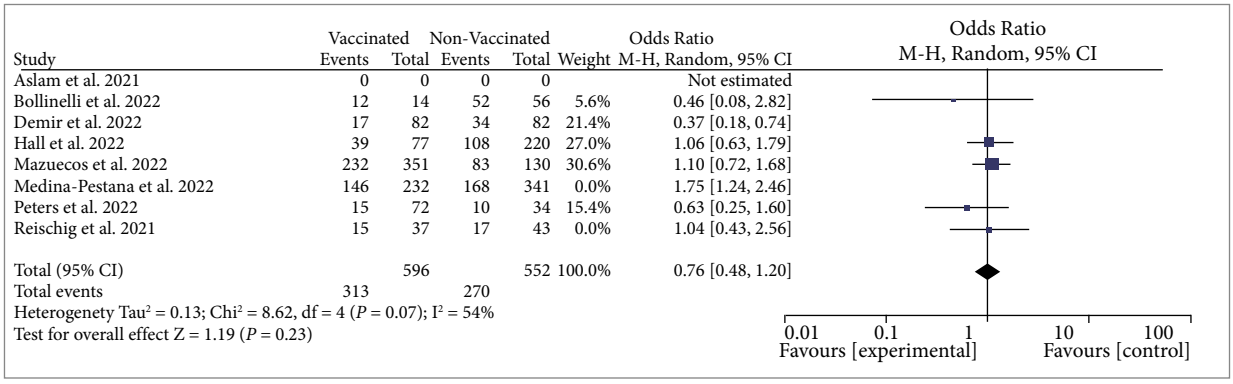
Source: Elaborated by the authors.

Figure 7. Forest Plot of the analysis of the amount of ventilation between vaccinated and unvaccinated patients, excluding data from the article by Medina-Pestana et al.[17].



Source: Elaborated by the authors.

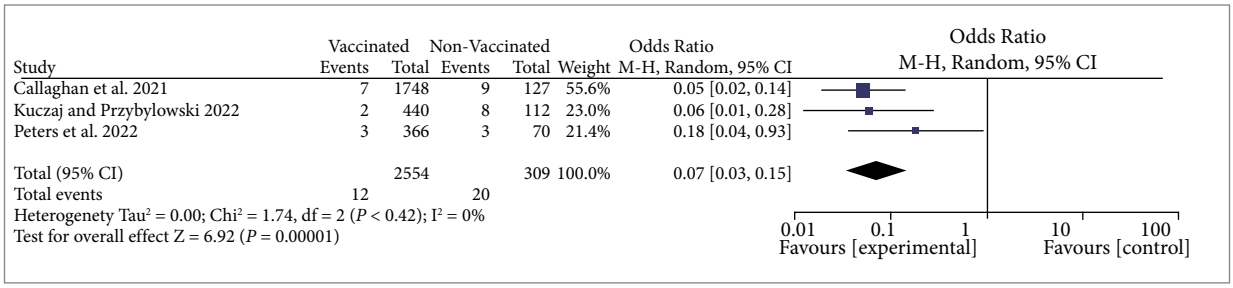
Figure 8. Forest Plot of the analysis of the need for hospitalization between vaccinated and unvaccinated patients.



Source: Elaborated by the authors.

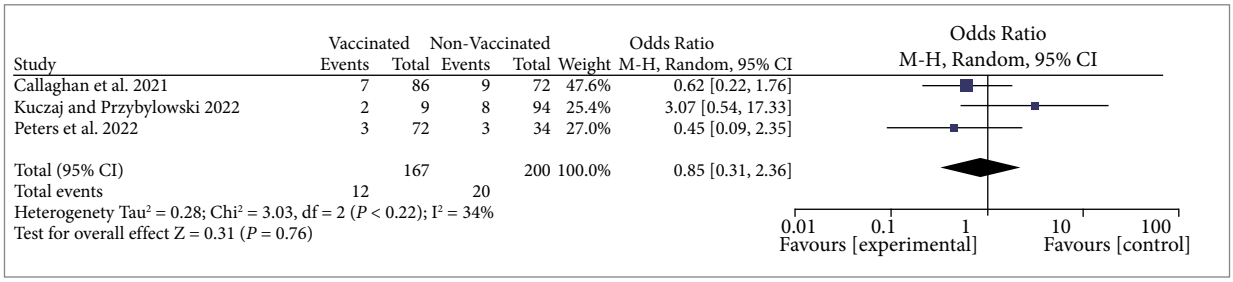
Figure 9. Forest Plot of the analysis of the need for hospitalization between vaccinated and unvaccinated patients, excluding data from the articles by Reischig et al.[16] and Medina-Pestana et al.[17].

An analysis of general and relative mortality data was also carried out with the subgroup of patients with heart transplants. The statistical representation of these data is shown in Figs. 10 and 11. For the general mortality data, a forest graph was created that analyzes 2,863 patients from three articles that generated an OR of 0.07 (0.03-0.15) with heterogeneity of $I^2 = 0\%$. As for the relative mortality data, the forest graph, also by the same three articles, analyzed, this time 367 patients. The OR was 0.85 (0.31, 2.36) with heterogeneity of $I^2 = 34\%$.



Source: Elaborated by the authors.

Figure 10. Forest Plot of the overall mortality analysis in the subgroup of heart transplant patients, vaccinated and unvaccinated.



Source: Elaborated by the authors.

Figure 11. Forest Plot of the relative mortality analysis in the subgroup of heart transplant patients, vaccinated and unvaccinated.

DISCUSSION

The results presented in this meta-analysis allow us to appreciate the combination of results from several studies in different health centers and provide a robust and integrated view of vaccination against COVID-19 in transplant patients. In this sense, it is vital to establish points to be interpreted when analyzing the constructed forest graphs.

In the first analysis, the graph referring to the general mortality of patients is observed. Although the OR indicated a tendency towards the benefit of vaccination [0.22 (0.02-1.90)], heterogeneity was extremely high (I^2 = 99%). The referred is due to studies by Medina-Pestana et al.[17] and Reischig et al.[16], the first having a high weight among the subgroups and the second being to the right of the indifference line. Therefore, both articles provide data demonstrating the non-benefit of vaccinating transplant patients, which aligns with the conclusions at the end of the respective publications.

During the analysis of the articles, it was observed that both the one by Reischig et al.[16] and that of Medina-Pestana et al.[17] compared patient cohorts in different waves of the pandemic. Furthermore, a discrepancy was noted between mortality rates collected in studies and other similar articles, justifiable by the hypothesis suggested by Medina-Pestana et al.[17] reported in its conclusion: the virus-inactivated antigen vaccine (CoronaVac®) may not be able to induce an adequate immune response in transplant patients.

It is essential to highlight that, when it comes to the COVID-19 pandemic, the evolution of the quality of care and treatment has been accentuated over the months. Therefore, patient mortality generally tends to decrease as the pandemic progresses[23]. Consequently, it is interesting that if control and intervention group analyses are carried out during this period, they are framed within the same time interval and compared with equally effective interventions concerning their immunizing potential. Therefore, statistical analyses were included that did not include the data from Reischig et al.[16] and Medina-Pestana et al.[17].

Therefore, we created another forest graph disregarding the studies mentioned above. The result is represented in Fig. 3, which indicated a much more concise OR [0.06 (0.03-0.14)] and heterogeneity of 45%, a much more robust result consistent with the conclusions found in other articles that favor vaccinating transplant patients.

The attenuated virus vaccine is, in fact, an efficient mass immunization mechanism for the general population, with high levels of efficacy when it comes to unrestricted population groups[24]. However, when immunization concerns transplant patients, what is known is the poor capacity to establish a competent response at the humoral level[25]. In this scope, the article by Medina-Pestana et al.[17] also provides highly relevant information: there were no deaths among patients with an adequate humoral response.

Even so, in our comparative analysis, the study presents an OR of 1.62 (1.18-2.30). Therefore, it must be inferred that immunization is effective against COVID-19, but the way to achieve it still needs to be determined. The CoronaVac® vaccine may not be eligible for this portion of the population, given that other immunizers, such as the Messenger RNA BNT162b2 (Pfizer-BioNTech), present seroconversion rates of around 68% among transplant patients[26].

Furthermore, it is notable that some studies analyzed were not included in the forest graph that deals with general mortality. These articles only provide data on already infected and hospitalized patients, comparing vaccinated and unvaccinated patients already in a state of illness, which makes it impossible for us to relate their mortality rates to the general population, which is not included in the articles. To cover this type of study, we created the forest graph called "Relative Mortality" (Fig. 2), which also has its version exempt from studies that included patients vaccinated with CoronaVac®[8,17,18].

When analyzing findings consistent with relative mortality, the OR is 0.93 (0.67-1.30) and heterogeneity of 45%, indicating that, in the meta-analysis, the fact that patients are already COVID-19 patients, whether or not they are vaccinated, is irrelevant to their chances of death. Regarding CoronaVac®-free results, the heterogeneity drops to 41%, and the outcome now has OR rates of 0.99 (0.72-1.36), indicating the tendency towards no difference in mortality by patients. vaccinated patients, but still with marked statistical significance.

This data, although concise, has less weight than general mortality. Therefore, patients who, even when vaccinated, develop COVID-19 and require hospitalization may be seriously affected by the immunosuppression needed for the transplant or already have severe symptoms of their underlying disease. One way to observe this phenomenon is to analyze the study by Kuczaj and Przybyłowski[13], which collected data only from heart transplant patients related to greater fragility in the recipients' health. This study presented the highest OR of the studies analyzed [3.07 (0.54-17.33)].

Furthermore, even in the case of heart transplantation, studies of Callaghan et al.[12], Kuczaj and Przybyłowski[13] and Peters et al.[15] generated meta-analyses with pertinent information. While in "relative mortality," the outcome between vaccinated and unvaccinated patients is indifferent [OR = 0.85 (0.31-2.36)], in "general mortality", vaccines have proven to be very effective in preventing death [OR = 0.07 (0.03-0.15)]. This result brings us to the idea that the vaccination of transplant patients has extreme immunization standards, capable of completely changing the probability of infection in a group. In patients affected by the disease, the vaccine becomes irrelevant. Such assumptions are superficial since only three articles have been analyzed on this issue. However, the data appear consistent for the small number of patients studied.

Regarding the articles included in a systematic review but not in the meta-analyses, it is clear that they did not have a control group of unvaccinated people; therefore, they did not apply to this statistical method. However, during a more detailed observation of these articles, it is possible to relate them to other studies included in the meta-analysis. For example, in the Hippisley-Cox et al.[11] study, the mortality among those vaccinated was just 0.1%, similar to Callaghan et al.[12], of 0,2%.

Similarly, the article by Saharia et al.[22] relates to the study by Callaghan et al.[12] in terms of mortality among vaccinated infected people (9.1 and 8.1%). The studies by Aslam et al.[21] and Bell et al.[10] are close to Peters et al.[15], with overall mortality among those vaccinated at 0.07, 0.8 and 0.8%, respectively. Therefore, such data tells us more about the benefit of vaccinating transplant patients, given the changes in the mortality rate, with overall mortality among those vaccinated at 0.07, 0.8, and 0.8%, respectively. Therefore, such data tells us more about the benefits of vaccinating transplant patients, given the changes in the mortality rate.

Regarding patients' need for mechanical ventilation, according to studies included in the meta-analysis, vaccination was not statistically significant in preventing this outcome. This data can be seen in the graph "Need for mechanical ventilation" (Fig. 6), in which the OR was 0.95 (0.61-1.49), taking CoronaVac® into account, and 0.88 (0.55-1.41) without considering this immunizer. The same phenomenon was observed regarding the hospitalization rate of patients. Both analyses that consider CoronaVac® and those that do not include it were indifferent to the need for hospital admission [0.92 (0.60-1.41) and 1.01 (0.75-1.34), respectively]. Furthermore, when isolated, the article by Chavarot et al.[9] presented a high percentage of relative mortality (50%), which was not related to any study included in the meta-analysis or only in the systematic review.

Therefore, it is essential to highlight some limitations regarding the secondary data retrieved. The different temporality between the studies, the heterogeneity in the number of patients in each group analyzed in the reports, the fact that observational and non-randomized methodologies were considered, and the different interventions in each country were possible biases that could influence the correct generalization of the results. Furthermore, a strong influence of the seroconversion potential on the mortality rate was observed, as well as the influence of the immunizing agent. However, the current search methodology does not present sufficient sensitivity to detect these outcomes, suggesting new future analyses accurately.

CONCLUSION

In short, given the data analyzed, it is clear that vaccination can prevent illness and mortality in transplant patients. However, its ability to protect against hospitalization, mechanical ventilation or death in cases of SARS-CoV-2 infection has not been demonstrated. This research defended the hypothesis that this is due to the low seroconversion rate among some individuals. In this way, vaccination proved to be a capable and plausible way of inducing such an immunological effect. However, given the lower seroconversion rate of this population, other more intense and varied vaccination schedules, together with the measurement of the humoral response, can be allies to establish a clear immunological response, thus minimizing the morbidity and mortality caused by COVID-19 in this portion of the population.

CONFLICT OF INTEREST

Nothing to declare.

AUTHOR'S CONTRIBUTION

Substantive scientific and intellectual contributions to the study: Rocha AL, Milan EP, Caminha ROC, Paiva DFF; **Conception and design:** Rocha AL, Milan EP, Caminha ROC, Paiva DFF; **Data analysis and interpretation:** Rocha AL, Milan EP, Caminha ROC, Paiva DFF; **Article writing:** Rocha AL, Milan EP, Caminha ROC, Paiva DFF; **Critical revision:** Rocha AL, Milan EP, Caminha ROC, Paiva DFF; **Final approval:** Caminha ROC.

DATA AVAILABILITY STATEMENT

All dataset were generated or analyzed in the current study.

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