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Brief report

Similar risk of hospitalization and lethality from COVID-19 in transplant recipients and waitlisted patients: A comparative analysis

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ABSTRACT

Introduction: In 2022, Spanish health authorities recommended passive immunisation against COVID-19 for solid organ transplant recipients (SOT), due to their deficient post-vaccination humoral response. Patients on the transplant waiting list (SOTwl) were excluded from this strategy.
Objective: To compare the risk of hospitalisation, ICU admission, and mortality due to COVID-19 between SOT and SOTwl patients.
Methodology: Patients seen in the Preventive Medicine Department at Ramón y Cajal Hospital between 03/14/2020 and 04/13/2022. The relative risk (RR) of hospitalisation, ICU admission, and mortality was estimated among SOT and SOTwl patients, adjusted for age, sex, and vaccine doses.
Results: A total of 1292 patients were analyzed. SOT patients (n = 1153) were older and had similar risks of hospitalisation (RR 0.97, 95% CI 0.57–1.64), ICU admission (RR 1.74, 95 % CI 0.44–6.86), and death (RR 0.89, 95% CI 0.45–1.77) compared to SOTwl patients (n = 139).
Conclusions: The risks of hospitalisation, ICU admission, and mortality were similar between SOT and SOTwl patients.

Riesgo similar de hospitalización y letalidad por COVID-19 en trasplantados y pacientes en lista de espera: un análisis comparativo

Palabras clave:
Inmunosupresión
COVID-19
Vacunación
Trasplante de órgano sólido

RESUMEN

Introducción: En 2022, las autoridades sanitarias españolas recomendaron la inmunización pasiva frente a COVID-19 a trasplantados de órgano sólido (TOS), con deficiente respuesta humoral postvacunal. Se excluyeron de la estrategia a pacientes en lista de espera de trasplante (LeTOS).
Objetivo: Comparar el riesgo de hospitalización, ingreso en UCI y letalidad por COVID-19 entre pacientes TOS y LeTOS.
Métodos: Pacientes atendidos en Medicina Preventiva del Hospital Ramón y Cajal entre 14-3-2020 y 13-4-2022. Se estimó el riesgo relativo (RR) de hospitalización, ingreso en UCI y letalidad entre pacientes con TOS y LeTOS, ajustado a edad, sexo y dosis vacunales.
Resultados: Se analizaron 1.292 pacientes. Los pacientes TOS (n = 1.153) eran de mayor edad y riesgos similares de hospitalización (RR 0,97, IC95% 0,57–1,64), ingreso en UCI (RR 1,74, IC95% 0,44–6,86) y fallecimiento (RR 0,89, IC95% 0,45–1,77), que los pacientes en LeTOS (n = 139).

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Conclusiones: Los riesgos de hospitalización, ingreso en UCI y letalidad fueron similares entre los pacientes TOS y LeTOS.

Introduction

In February 2021, the Spanish health authorities recommended vaccinating patients with risk conditions for severe illness due to SARS-CoV-2 infection, known as group 7, as a priority. These patients included solid organ transplant recipients (SOT), haematopoietic stem cell transplant recipients, those with chronic kidney disease on replacement therapy, patients with primary immunodeficiencies, cancer patients on chemotherapy or radiotherapy, people with HIV and CD4 counts <200, people with Down syndrome, patients with cystic fibrosis and those undergoing treatment with immunosuppressants and immunomodulators.[1–3]

Subsequently, in March 2022, a strategy of quantifying antibodies against the SARS-CoV-2 S protein plus passive immunisation with Evusheld® was recommended for some patients in group 7, specifically: haematopoietic stem cell transplant or CAR-T cell recipients; SOT recipients; patients with certain primary immunodeficiencies; and patients with cancer on chemotherapy or immunosuppressants.[4–7] This strategy excluded part of group 7, which included patients on the waiting list for solid organ transplantation (SOTwl).[8–11] This restricted list of risk conditions was established in order of priority due to the limited availability of the medication,[3] although it caused concern among healthcare professionals who treated both types of patients.[8] Until June 2022, the Ministry of Health's strategy did not include the whole of group 7 in passive immunisation. In February 2023, due to the circulation of new SARS-CoV-2 variants, the use of Evusheld® was no longer recommended.

However, studies and clinical experience do not seem to demonstrate a categorical difference in hospital burden between SOT and SOTwl patients. Furthermore, some research has shown that even if the serological response were adequate, the cellular response of T lymphocytes may be limited.[12] Emphasis has been placed on the importance of individually assessing patients' clinical risk, independent of the serological assessment, in order to indicate alternatives to vaccination, such as passive pre-exposure immunisation.[13]

The main aim of this study is to describe and compare the risk of hospitalisation, admission to the Intensive Care Unit (ICU) and death due to COVID-19 in patients with SOT and SOTwl.

Methods

This was an observational follow-up study of patient cohorts.

The study period covered the first two years of the pandemic: from 14 March 2020 to 13 April 2022.

The study population included patients over 18 years of age vaccinated against COVID-19 with mRNA vaccines (Moderna or Pfizer) at Hospital Ramón y Cajal. Two groups of patients were selected: those with more than one year since SOT, and patients on SOTwl, from the first day of inclusion on the waiting list. None of the patients included in the study received passive immunisation during the period studied. The Preventive Medicine Department, for logistical reasons of availability, began administering Evusheld® from June 2022. We excluded patients who had allergic reactions to the COVID-19 vaccine which prevented them from completing the vaccination schedule, those vaccinated with vaccines other than those designed on the mRNA platform, and those vaccinated outside Madrid Region.

Sources of information

Data collection was carried out by exploiting existing databases. The information regarding the clinical-epidemiological variables was reviewed by physicians from the Preventive Medicine Department. To minimise the number of missing data, electronic medical records were consulted.

By reviewing medical records, the investigators confirmed the reason for hospitalisation, ICU admission, and death from COVID-19. Attribution to SARS-COV-2 infection was based on the definitions of the European Centre for Disease Prevention and Control.[1]

Definition of hospitalised COVID-19 case: patient who has tested positive for COVID-19 by PCR or antigen test (in the 14 days prior to admission or during the current admission) who develops serious COVID-19-related symptoms/complications requiring hospitalisation. Patients admitted to the hospital for isolation purposes and not for clinical necessity should not be counted as hospitalised cases when it is possible to distinguish between them.

Definition of case admitted to an ICU: patient who has tested positive for COVID-19 by PCR or antigen test (in the 14 days prior to admission or during the current admission) who develops serious COVID-19-related symptoms/complications which require admission to an ICU. The stay in the ICU is a consequence of the COVID-19 infection.

Definition of COVID-19 death: a COVID-19 death is defined, for surveillance purposes, as a death resulting from clinically compatible illness in a probable or confirmed case of COVID-19 unless there is a clear alternative cause of death that cannot be related to COVID-19 disease (for example, trauma). There should not be a period of complete recovery between illness and death.

Statistical analysis

We show the distribution of the clinical-epidemiological characteristics of the two groups of patients studied (SOT and SOTwl): gender, age (categories: 18−29; 30−59; >60), number of vaccine doses. The incidence of hospitalisation due to COVID-19, ICU admission due to COVID-19 and death due to COVID-19 during the study period is also shown for SOT and SOTwl. We analysed differences in the distribution of these variables in SOT and SOTwl using the Chi^2 test.

To estimate the risk of hospitalisation, ICU admission and death in SOT versus SOTwl, the relative risk (RR) was used, considering SOT patients as the reference group and calculating the 95% confidence interval (95% CI) from the RR.

To take into account the effect of age, gender and number of vaccination doses as adjustment variables, a multivariate analysis

Table 1
Sociodemographic and clinical characteristics.

	SOT (n = 1153)	SOTwl (n = 139)	RR	95% CI	p
Age (years), n (%)					
18–29	25 (2.17)	7 (5.04)			
30–59	524 (45.45)	81 (58.27)			0.001[a]
≥60	604 (52.39)	51 (36.69)			
Gender, n (%)					
Female	378 (32.78)	48 (34.53)			0.679[a]
Male	775 (67.22)	91 (65.47)			
Hospitalised, n (%)					
Yes	148 (12.84)	18 (12.95)	0.99	0.58–1.67	0.528
ICU, n (%)					
Yes	31 (2.69)	2 (1.44)	1.05	0.96–1.15	0.292
Death, n (%)					
Yes	68 (5.90)	8 (5.76)	1.00	0.93–1.09	0.566
Vaccine doses, n (%)					
0	78 (6.77)	5 (3.60)			
1	11 (0.95)	2 (1.44)			
2	94 (8.15)	16 (11.51)			0.001[a]
3	514 (44.58)	94 (61.63)			
4	456 (39.55)	22 (15.83)			

95% CI: 95% confidence interval; SOTwl: patient on the waiting list for solid organ transplant; RR: relative risk (crude, unadjusted); SOT: solid organ transplant; ICU: Intensive Care Unit.
[a] Chi^2.

(Poisson) was performed. We used inverse treatment probability weighting to improve the power of the study and balance the difference in sample size between patients with SOT and SOTwl. Three multivariate regression models were performed, where the dependent variable was hospitalisation (model 1), ICU admission (model 2) and death (model 3). The main exposure variable for all three models was dichotomous (SOT [1]/SOTwl [0]), and the adjustment variables: age, gender and number of vaccine doses. The adjusted RR (RRa) was calculated with a 95% CI.

Statistical analysis was performed using Stata® software version 16.

Results

We followed up 1292 patients during the study period, 1153 SOT and 139 SOTwl.

SOT patients were older than patients on the SOTwl (median age: 60.7 vs 55.4). A predominance of men was found in both study groups.

The number of patients who had three or more doses of SARS-CoV-2 vaccine was similar in the two groups (84%), although their distribution was different; there was a higher proportion of patients with four doses in the SOT group (Table 1).

The incidence of hospitalisation was similar in the two groups (13%). The incidence of ICU admission and death was slightly higher in SOT patients, although the difference was not statistically significant.

Univariate analysis showed that the crude RR of hospitalisation (RR 0.99, 95% CI 0.59–1.67), ICU admission (RR 1.05, 95 % CI 0.96–1.15) and death (RR 1.00, 95% CI 0.93–1.09) was similar in both groups, with no significant differences.

The distribution of COVID-19 hospitalisations was similar in the two patient groups: 39% (n = 57) of SOT and 44% (n = 8) of SOTwl were admitted to hospital in 2020; 26% (n = 38) of SOT and 33% (n = 6) of SOTwl were admitted in 2021; and 36% (n = 53) of SOT and 22% (n = 4) of SOTwl were admitted in 2022.

The distribution of deaths was similar between the two groups: 54% (n = 37) of SOT and 75% (n = 6) of SOTwl died in 2021; 31% (n = 2) of SOT and 25% (n = 2) of SOTwl died in 2022.

Multivariate analysis also revealed no significant differences in the adjusted relative risk (RRa) of hospitalisation, admission to ICU, and death between patients with SOT and SOTwl, considering the adjustment variables (age, gender, and number of vaccine doses). The RRa of admission to ICU and death was found to increase with age (the RRa of hospitalisation *did not* increase with age). A greater number of vaccine doses was associated with a reduction in the RRa of hospitalisation, admission to ICU and death, which is statistically significant for death from the third dose and admission to ICU from the fourth dose (Table 2).

Discussion

This study shows that there are no significant differences in the risk of hospitalisation, admission to ICU or death between patients with SOT and SOTwl. Patients with both clinical conditions are part of the high-risk group for severe COVID-19 disease. However, health authorities initially prioritised the study of humoral immunity in SOT patients, considering they had a worse prognosis for COVID-19 and could benefit from passive immunisation if their antibody count did not reach an adequate level. Our results indicate that both SOT and SOTwl had the same risk of severe disease, so other factors, not only humoural immunity, could influence a worse COVID-19 outcome in immunocompromised patients.[2]

One of the key findings of this study is the inverse association between the number of COVID-19 vaccine doses and the risk of hospitalisation, admission to ICU and death in both groups of patients. This underscores the importance of completing vaccination schedules to reduce severe COVID-19 outcomes in high-risk populations. The greatest protection was detected after completing four vaccine doses.[4,12]

The study also found that older age was associated with higher mortality rates and admission to ICU, which is consistent with general epidemiological data on COVID-19. These findings reinforce the need for interventions targeting older adults within these high-risk categories.[14]

SOTwl patients, despite not being classified as at very high risk of becoming seriously ill with COVID-19 by some health authorities, such as in Spain, show considerable susceptibility to severe forms

Table 2
Multivariate analysis of risk of hospitalisation, admission to ICU and death among SOT and SOTwl patients.

	Hospitalisation (model 1)			Admission to ICU (model 2)			Death (model 3)		
	RRa	95% CI		RRa	95% CI		RRa	95% CI	
SOT/SOTwl	0.97	0.573	1.642	1.738	0.44	6.86	0.893	0.452	1.765
Age (years)									
18–29	1.00			1.00			1.00		
30–59	0.512	0.194	1.352	0.55	0.073	4.11	1.119	0.176	7.1
≥60	0.801	0.31	2.07	1.327	0.165	10.637	3.281	0.518	20.728
Gender	1.183	0.727	1.925	1.056	0.316	3.522	0.733	0.346	1.553
No. COVID-19 vaccine doses									
1	2.511	0.8	7.878	3.21	0.611	16.846	1.721	0.473	6.26
2	0.697	0.262	1.851	1.736	0.458	6.575	0.578	0.277	1.206
3	0.617	0.282	1.348	0.439	0.142	1.36	0.127	0.055	0.291
4	0.426	0.177	1.027	0.192	0.057	0.641	0.004	0.000	0.325

Adjustment variables: age, gender and number of vaccine doses.
95% CI: 95% confidence interval; SOTwl: patient on the waiting list for solid organ transplant; RRa: adjusted relative risk; SOT: solid organ transplant; ICU: Intensive Care Unit.

of COVID-19. This calls for a re-assessment of current public health strategies and possibly extending high-risk designations to include SOTwl patients, ensuring they receive appropriate protection and care.[2,15]

This study is observational and was limited to patients vaccinated at a single hospital, which may limit the ability to generalise the results. One limitation of the study was not considering the time since SOT at the time of hospitalisation and/or death as an adjustment variable in the analyses. Another limitation of the study was not considering the presence of serological values and/or death from COVID-19 prior to hospitalisation as an adjustment variable, which would indicate immunisation by natural infection or vaccination.

The findings argue for continued adaptation of public health policies to address the evolving challenges posed by COVID-19, particularly for immunocompromised individuals.

CRediT authorship contribution statement

Abelardo Fernández Chávez: study design, data collection, data interpretation, writing, review and editing. Literature search.

Guillermo Ordoñez León: study design, data analysis, writing, data collection and data interpretation.

Eva Elisa Álvarez León, Paloma Moreno Núñez and José Porto Tomás: data analysis, writing and literature search.

Jesús María Aranaz Andrés: conceptualisation, study design, literature search, data analysis, data interpretation, writing, supervision.

Ethics

This study was submitted to the Hospital Universitario Ramón y Cajal Ethics Committee, receiving approval with the reference number: 159/22.

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Declaration of competing interest

The authors declare that there are no conflicts of interest.

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