SARS-COV-2 VACCINATION WITH BNT162B2 IN RENAL TRANSPLANT PATIENTS: RISK FACTORS FOR IMPAIRED RESPONSE AND IMMUNOLOGICAL IMPLICATIONS

Running Head: SARSCoV2 Vaccination in Renal Transplant Patients

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Abbreviations:

95.0%CI	95.0% Confidence Intervals
COVID-19	CoronaVirus Disease-2019
HLA-DSA	Donor Specific Antibodies against Human Leukocyte Antigens
IQR	Interquartile Ranges
KT	Kidney Transplantation
OR	Odds Ratios
S	Spike Protein

SARS-CoV-2	Severe Acute Respiratory Syndrome-CoronaVirus-2
SOT	Solid Organ Transplant

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ABSTRACT

Solid organ transplant patients are at higher risk for poor CoronaVirus Disease-2019 (COVID-19)-related outcomes and have been included as a priority group in the vaccination strategy worldwide. We assessed the safety and efficacy of a two-dose vaccination cycle with mRNA-based COVID-19 vaccine (BNT162b2) among 82 kidney transplant outpatients followed in our center in Rome, Italy. After a median of 43 post-vaccine days, a SARS-CoV-2 anti-Spike seroprevalence of 52.4% (n=43/82) was observed. No impact of the vaccination on antibody-mediated rejection or graft function was observed, and no significant safety concerns were reported. Moreover, no de-novo HLA-donor-specific antibodies (DSA) were detected during the follow-up period. Only one patient with pre-vaccination HLA-DSA did not experience an increased intensity of the existing HLA-DSA.

During the follow-up, only one infection (mild COVID-19) was observed in a patient after receiving the first vaccine dose.

According to the multivariable logistic regression analysis, lack of seroconversion after two-dose vaccination independently associated with patient age ≥60 years (OR=4.50; P-value=0.02) and use of anti-metabolite as an immunosuppressant drug (OR=5.26; P-value=0.004). Among younger patients not taking anti-metabolites, the seroconversion rate was high (92.9%). Further larger studies are needed to assess the best COVID-19 vaccination strategy in transplanted patients.

Introduction

Several studies on solid organ transplant patients affected by Severe Acute Respiratory Syndrome-CoronaVirus-2 (SARS-CoV-2) infection showed a higher risk for severe CoronaVirus Disease-2019 (COVID-19) with poor outcomes (1-3). Thus, transplanted patients are among the priority population groups for SARS-CoV-2 vaccine-based preventive activities worldwide. It should also be underlined that, in general, vaccine administration in transplanted patients may represent a non-specific trigger factor for developing Donor Specific Antibodies against Human Leukocyte Antigens (HLA-DSA) that are associated with acute organ rejection (4). Moreover, response to various vaccines in transplanted patients is lower than in the general population (5). Furthermore, transplanted patients were not included in the study population to register all approved COVID-19 vaccines, including those based on mRNA technology (BNT162b2 - Pfizer-BioNTech; mRNA1273, Moderna) (6,7).

According to real-life data, transplanted patients receiving mRNA SARS-CoV-2 vaccines show significantly lower seroconversion and anti-spike titres than the general population (8,9). Moreover, to date, there are insufficient data on anti-spike SARS-CoV-2 antibody levels in previously transplanted vaccinees beyond a period of one month after two-dose vaccination.

The main objective of the present study is to assess the safety and efficacy of the mRNA SARS-CoV-2 vaccine (BNT162b2) after the second dose of the vaccine in a population of patients previously undergoing a specific organ transplant, namely the kidney transplantation (KT). The secondary objective is to evaluate the impact of the vaccination on rejection and graft function.

Material and methods

Patients

A retrospective analysis was performed of the data of the KT patients transplanted and followed as outpatients at the Polyclinic Umberto I Hospital, Rome, and receiving COVID-19 vaccination during January - May 2021. No patients presented any of the following exclusion criteria: a) age <18 years, b) pregnancy or lactation status, c) KT performed < one year before vaccination, d) previous COVID-19 positivity, and e) symptomatic status for COVID-19 during the period of the scheduled vaccination. The Local Ethics Board of Sapienza University of Rome approved the present study.

Vaccination policy in Italy for transplanted patients

According to the policy on COVID-19 vaccination in Italy, vulnerable population groups, including solid organ transplant patients, were prioritized to receive mRNA SARS-CoV-2 vaccines. Each Italian region was in charge of the voluntary vaccination of residents in its territory. All KT patients

transplanted at the Polyclinic Umberto I Hospital, Rome, and resident in the Lazio region, Italy, were contacted by phone to propose the vaccination. The vaccine used was the mRNA COVID-19 vaccine (BNT162b2, Comirnaty®, Pfizer- BioNTech) administered in 2 doses given three weeks apart. The vaccine was administered only in a hospital setting after written informed consent.

Among KT vaccinees, only those already followed as outpatients at Polyclinic Umberto I Hospital, Rome, were enrolled in the present study. Routine blood tests were performed as post-transplant outpatient activity, including serum creatinine, serum electrolytes, serum level of calcineurin inhibitors, serum HLA-DSA.

The search for HLA-DSA antibodies was carried out using the multianalyte bead assay with the Luminex platform (Luminex, Austin, TX), including Lifecode Screen and LSA I/II (Immucor, Inc., Norcross, Georgia). The results were expressed as mean fluorescence intensity (MFI); an MFI > 1000 was considered positive.

Following the second dose of the vaccine, serum anti-spike SARS-CoV-2 antibodies were also assessed. LIAISON SARS-CoV-2 S1/S2 IgG chemiluminescent assay against a recombinant Spike (S) protein (S1/S2) (DiaSorin S.p.A., Saluggia, Italy) was used according to the manufacture instructions. Results below 12.0 AU/mL were considered negative. All the post-vaccination adverse events were reported.

Statistical analysis

Continuous variables were reported as medians and interquartile ranges (IQR). Binary variables were reported as numbers and percentages. No missing data were reported in the investigated population. Mann–Whitney U test and Fisher's exact test were used for comparing continuous and categorical variables, respectively.

The last censoring of the investigated population was performed on June 30, 2021.

A logistic regression analysis was adopted for identifying the variables independently associated with a poor anti-spike response after vaccination. Potentially relevant variables were initially investigated using a univariable approach. Therefore, the relevant variables (P-value <0.20) were used to construct a multivariable logistic regression model. A backward wald approach was used for selecting the most relevant variables. Odds ratios (OR) and 95.0% confidence intervals (95.0%CI) were reported. Variables with a P-value <0.05 were considered statistically significant. SPSS statistical package version 25.0 (SPSS Inc., Chicago, IL, USA) was used.

Results

All the 155 KT patients resident in the Lazio region, Italy, accepted and completed the voluntary vaccination against COVID-19 during January-May 2021 (vaccine acceptation rate: 100.0%). Among them, 82 patients (52.9%) were regularly followed as outpatients at the Polyclinic Umberto I, Rome (**Table 1**), while the remaining 73 patients (47.1%) were followed in peripheral nephrology centers. The median age of the enrolled patients was 58.5 years (IQR: 50.3-65.0). Forty-seven (57.3%) patients were male. The median time since the KT was 69 months (IQR: 35-143).

All the patients received some immunosuppressive drugs at the time of vaccination. In detail, 75 patients (91.5%) received steroids, with 24 (29.3%) receiving a weekly dosage of steroids >40 mg.

In 59 cases (72.0%), triple therapy was administrated.

Calcineurin inhibitors represented the cornerstone of the therapy, being administrated in 80 cases (97.6%). Once-daily tacrolimus was the most used drug (n=49, 59.8%), followed by tacrolimus bis in die (n=16, 19.5%), and cyclosporine (n=15, 18.3%).

Everolimus use was reported in 10 patients (12.2%). An anti-metabolite drug (azathioprine or derivatives of mycophenolic acid) was adopted in 57 patients (69.5%).

As for the analysis of the post-vaccine side effects (**Table 2**), pain in the site of vaccine inoculation was reported in 34 (41.5%) and 27 (32.9%) patients after the first and the second dose, respectively. All the other symptoms were only occasionally reported, with only one case (1.2%) of fever reported after the first and the second dose, respectively. Similarly, flu-like symptoms were reported in only four (4.9%) and one (1.2%) case after each dose administration.

In only one case (1.2%), a moderate COVID-19 disease was reported after the first vaccine administration. The patient did not develop anti-spike antibodies after the first vaccine administration. The COVID-19 recovered rapidly after a short-course hospitalization.

As for the graft function, only two cases (2.4%) of transient creatinine increase were reported immediately after the second vaccine dose. The creatinine levels spontaneously repaired in all the cases, excluding any suspect of clinically relevant acute rejection.

As for the immunological aspects, HLA-DSA were not detectable before vaccination in all the patients but one. After the vaccine administration, no *de-novo* HLA-DSA were detected during the follow-up period. Only one patient (1.2%) already presented HLA-DSA before vaccination. In detail, an anti-DQ2 was detected. No *de-novo* HLA-DSA were observed after vaccination, nor increased the intensity of the already existing HLA-DSA. Before vaccination, the last MFI was 3,588, while it was 3,500 two months after the second dose of vaccine.

The median time passing from the second vaccine dose to the anti-spike antibody assessment was 43 days (IQR: 23-63). After this period of follow-up, 43 patients (52.4%) had detectable anti-spike antibodies (Detectable Group), while 39 cases (47.6%) were seronegative (Undetectable Group) (**Table 1**).

Investigating the potential differences between the two groups of patients, we observed that the patients in the Undetectable Group were older with respect to the Detectable Group, with 59.0 vs. 30.2% of the cases aged ≥60 years (P-value=0.03). No statistically relevant differences were observed concerning sex, body mass index, comorbidities, and side effects after the vaccination course. The time of KT only merged statistical relevance, with a more significant number of transplants performed more recently in the Undetectable Group (KT performed within 1-3 years: 35.9 vs. 18.6%; P-value=0.07).

As for the immunosuppressive therapy, no relevant differences were observed in terms of steroid use, steroid dosing, and use of calcineurin inhibitors. In the Undetectable Group, triple therapy (84.6 vs. 60.5%; P-value 0.03) and antimetabolite drugs (84.6 vs. 55.8%; P-value=0.008) were more common.

Variables independently associated with the undetectable titre after vaccination

The potential variables connected with an inadequate titre response after the 2-dose vaccination are reported in **Supplementary Table 1 & Table 3**. At univariable logistic regression analysis, patient age ≥60 years at the time of vaccination increased the odds of inadequate titre response, with an OR=3.29 (95.0%CI=1.05-10.31; P-value=0.04).

On the opposite, the longer was the time from KT, and the lower was the risk of inadequate response (time since KT 6-10 years: OR=0.27, P-value=0.004; time since KT >10 years: OR=0.34, P-value=0.08). Triple immunosuppressive therapy (OR=3.60, 95.0%CI=1.24-10.41; P-value=0.02) and the use of anti-metabolites (OR=4.35, 95.0%CI=1.51-12.54; P-value=0.006) both increased the odds of poor titre detection.

In **Table 3**, the results of the multivariable logistic regression analysis were reported. Only the patient age ≥60 years (OR=4.50, 95.0%CI=1.31-15.46; P-value=0.02) and the use of anti-metabolites (OR=5.26, 95.0%CI=1.69-16.42; P-value=0.004) independently associated with undetectable titre after vaccination. Interestingly, when these two parameters were combined, we observed a vast difference in anti-spike response in the patients with or without these variables (**Figure 1**).

In detail, patients aged <60 years without use for anti-metabolites at the time of vaccination showed a very high seroconversion rate (92.9% of cases), very similar to the general population receiving the mRNA SARS-CoV-2 vaccine. Patients having only one factor showed intermediate rates, with 53.1-54.5% of seropositive cases reported. Lastly, patients having both these factors showed very disappointing results, with only 28.0% of cases showing a post-vaccination serological response.

Discussion

In the present study performed on 82 KT, a seroconversion rate of 52.4% was assessed after a median period of 43 (IQR 23-63) days post-second dose of mRNA-based COVID-19 vaccine (BNT162b2). This result is in line with previously published studies (8-12). Age >60 years and the use of anti-metabolite drugs independently increased the odds of a lower seroconversion after COVID-19 vaccination. Also in this case, the results of our study are in line with previous experiences (8,9).

Interestingly, when both advanced age and anti-metabolites use were absent in our population, a high seroconversion rate (92.9%) was observed, suggesting the utility of a "tailored" use of the vaccine third dose.

Recent studies reported the efficacy for seroconversion of the administration of a third dose (around two months after the second dose) of the COVID-19 vaccine among transplanted patients (13,14). Overall, the seroconversion rate measured 2-4 weeks after the third dose of COVID-19 vaccine improved in both studies, up to 66.7% (13) and 46.7% (14), principally when no admixture of different vaccines was used. Furthermore, the third dose of the mRNA-1273 vaccine induced a serologic response in 49% of 159 KT patients who did not respond after two doses (15). In a randomized controlled trial performed on 120 transplanted patients receiving a third dose of mRNA-1273 vaccine vs. placebo, 55% vs. 18% serologic response rates were reported (relative risk=3.1; P<0.001) (16). However, in light of our results, we can suggest not considering the entire population of solid organ transplant patients as systematically needing a third vaccine administration, mainly considering the small number of studies exploring this field.

As for the potential immunological risk of vaccination in transplanted patients, to the best of our knowledge, the risk of developing HLA-DSA has been assessed among liver and heart transplanted patients receiving COVID-19 vaccines (17) but never in KT ones. Up to now, only a post-vaccine rejection case has been described in the literature, with a biopsy-proven antibody-mediated rejection episode reported in a heart-transplant patient seven days after receiving the third dose of COVID-19 vaccine (14). In the present study, we assessed HLA-DSA in all the participants before and after the vaccination, and no *de-novo* development of HLA-DSA was observed. Similar results were observed in liver and heart transplant patients (17). Larger studies are necessary to clarify this specific aspect. Overall, no significant safety concerns were reported in this study (**Table 2**), similarly

to what was observed in the registration trials of mRNA-based COVID-19 vaccines (6,7), as well as in the studies assessing the efficacy of a third dose of the vaccines (13,14).

In literature, the rate of post-vaccination infections among fully vaccinated transplanted patients has been estimated to be around 0.6% in two US studies (18,19). This datum is substantially higher than the rate of 0.05% reported in the general population (20). Although a limited follow-up, we observed in our study that only one case of mild COVID-19 occurred after the first dose of vaccine. The patient did not have seroconversion at the time of COVID-19 diagnosis and fully recovered after the infection. No case was reported after the second vaccination administration, although only 52.4% of seroconversion rates were reported. This evidence is in line with the few reports of COVID-19 in transplanted patients after two-dose vaccination (18,19,21).

Interestingly, antibodies to SARS-CoV-2 seem not to be a surrogate indicator of the magnitude of memory T cells (22) in immunocompetent individuals, suggesting that antibody levels alone may not be a robust indicator of protection in subjects previously infected with SARS-CoV-2 (23). Thus, a low SARS-CoV-2 antibody titre after infection or vaccination does not necessarily mean a lack of protection. However, studies focused on this specific aspect are necessary to evaluate the impact on protecting the T-cells response elicited by COVID-19 vaccines (23), particularly in the population of transplanted patients. A small study on seven KT non-responders to two-dose BNT162b2 vaccine and receiving triple immunosuppression regimen found SARS-CoV-2 Spike-protein reactive T-helper in all the patients, showing that vaccination might induce cellular immunity despite lack of serological response (24).

The main strengths of this work are: 1) the homogeneity of the study population (i.e., only KT patients); 2) the use of only one type of COVID-19 vaccine; 3) the median availability of SARS-CoV-

2 serology longer than one month after the second dose of the vaccine; 4) the assessment of the graft function; and, 5) the evaluation of HLA-DSA before and after the vaccination. The main limitations are: 1) the lack of an immunocompetent control group; 2) the relatively low number of participants; and, 3) the lack of exploration of T- and B-cells immune response after vaccination.

In conclusion, we identified age >60 years and immunosuppressive anti-rejection regimen containing an anti-metabolite as factors independently increasing the odds of poor serological response to mRNA-based COVID-19 vaccine (BNT162b2) in KT patients. No impact of the vaccination was observed in terms of HLA-DSA appearance and graft function worsening. The administration of the third dose of vaccine should be evaluated in selected transplanted patients. Further larger studies are needed for better clarifying the best COVID-19 vaccination strategy to use in transplanted patients, including new generation vaccines with a broader repertoire of SARS-CoV-2 antigenic stimuli.

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TABLES

Table 1. Demographic characteristics of the investigated population.

Variables	**Entire cohort** (N=82, 100.0%)	**Antibody response**		**P-value**
		Detectable (n=43, 52.4%)	**Undetectable** (n=39, 47.6%)	

	Median (IQR) or n (%)			
Age, years				
18-49	36 (43.9)	13 (30.2)	7 (17.9)	0.03
50-59	26 (31.7)	17 (39.5)	9 (23.1)	
≥60	20 (24.4)	13 (30.2)	23 (59.0)	
Male sex	47 (57.3)	24 (55.8)	23 (59.0)	0.83
BMI	25.8 (23.0-28.4)	26.8 (23.0-28.8)	25.2 (22.9-27.8)	0.41
Time since KT, years				
1-3	22 (26.8)	8 (18.6)	14 (35.9)	0.07
4-5	14 (17.1)	5 (11.6)	9 (23.1)	
6-10	22 (26.8)	15 (34.9)	7 (17.9)	
>10	24 (29.3)	15 (34.9)	9 (23.1)	
T2DM	7 (8.5)	5 (11.6)	2 (5.1)	0.44
Hypertension	70 (85.4)	38 (88.4)	32 (82.1)	0.54
Dyslipidemia	43 (53.4)	22 (51.2)	21 (53.8)	0.83
Hyperuricemia	32 (39.0)	16 (37.2)	16 (41.0)	0.82
Any side effect after vaccination	36 (43.9)	17 (39.5)	19 (48.7)	0.51
Time 2nd dose-Ab dosing, days	43 (23-63)	42 (22-62)	43 (24-63)	0.60
Steroid use	75 (91.5)	39 (90.7)	36 (92.3)	1.00
Weekly steroid dose >40 mg	24 (29.3)	12 (27.9%)	12 (30.8)	0.81
Triple IS therapy	59 (72.0)	26 (60.5)	33 (84.6)	0.03
Everolimus use	10 (12.2)	6 (14.0)	4 (10.3)	0.74
Any CNI use	80 (97.6)	42 (97.7)	38 (97.4)	1.00
Cyclosporine	15 (18.3)	10 (23.3)	5 (12.8)	0.26

Tacrolimus bis-die	16 (19.5)	9 (20.9)	7 (17.9)	0.79
Tacrolimus mono-die	49 (59.8)	24 (55.8)	25 (64.1)	0.50
Anti-metabolite	57 (69.5)	24 (55.8)	33 (84.6)	0.008

Abbreviations: IQR, interquartile ranges; n, number; BMI, body mass index; KT, kidney transplantation; T2DM, type 2 diabetes mellitus; Ab, antibody; IS, immunosuppressive; CNI, calcineurin inhibitor.

Table 2. Self-reported reactions after the two doses of COVID-19 vaccine (BNT162b2) in kidney transplant patients.

Variables	**First dose**	**Second dose**	**Cumulative**
	N (%)		
Pain in the site of inoculation	34 (41.5)	27 (32.9)	36 (43.9)
Fever	1 (1.2)	1 (1.2)	1 (1.2)
Flu-like symptoms	4 (4.9)	1 (1.2)	5 (6.1)

Abbreviations: N, number.

Table 3. Multivariable analysis for the risk factors of undetectable antibody response after COVID-19 vaccination in kidney transplant patients: backward conditional method.

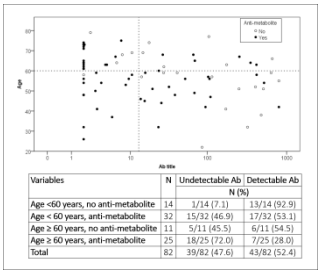
Variables	Beta	SE	Wald	OR	95.0%CI		P-value
					Lower	Upper	
Age, years							
18-49	Ref.	-	-	1.00	-	-	-
50-59	0.26	0.66	0.15	1.29	0.36	4.69	0.70
≥60	1.50	0.63	5.71	4.50	1.31	15.46	0.02
Anti-metabolite	1.66	0.58	8.18	5.26	1.69	16.42	0.004

Constant	-0.53	0.53	1.00	0.59	-	-	0.32

Hosmer-Lameshow Test: 0.861

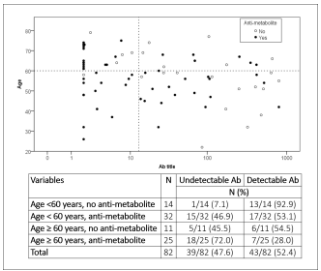
Variables initially tested in the model: male sex, year since KT, age, anti-metabolite, triple IS therapy.

Abbreviations: SE, standard error; OR, odds ratio; 95.0% CI, 95.0% confidence intervals.



Variables	N	Undetectable Ab	Detectable Ab
		N (%)	
Age <60 years, no anti-metabolite	14	1/14 (7.1)	13/14 (92.9)
Age < 60 years, anti-metabolite	32	15/32 (46.9)	17/32 (53.1)
Age ≥ 60 years, no anti-metabolite	11	5/11 (45.5)	6/11 (54.5)
Age ≥ 60 years, anti-metabolite	25	18/25 (72.0)	7/25 (28.0)
Total	82	39/82 (47.6)	43/82 (52.4)

Figure 1. Scatter plot showing the distribution of the vaccinated patients according to their age, the anti-spike title reached after the second vaccine dose, and the use of an anti-metabolite as an immunosuppressive drug at the time of vaccination.



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Variables	**Entire cohort**	**Antibody response**		**P-value**
	(N=82, 100.0%)	**Detectable**	**Undetectable**	
		(n=43, 52.4%)	**(n=39, 47.6%)**	
		Median (IQR) or n (%)		
Age, years				
18-49	36 (43.9)	13 (30.2)	7 (17.9)	0.03
50-59	26 (31.7)	17 (39.5)	9 (23.1)	
≥60	20 (24.4)	13 (30.2)	23 (59.0)	
Male sex	47 (57.3)	24 (55.8)	23 (59.0)	0.83
BMI	25.8 (23.0-28.4)	26.8 (23.0-28.8)	25.2 (22.9-27.8)	0.41
Time since KT, years				

1-3	22 (26.8)	8 (18.6)	14 (35.9)	0.07
4-5	14 (17.1)	5 (11.6)	9 (23.1)	
6-10	22 (26.8)	15 (34.9)	7 (17.9)	
>10	24 (29.3)	15 (34.9)	9 (23.1)	
T2DM	7 (8.5)	5 (11.6)	2 (5.1)	0.44
Hypertension	70 (85.4)	38 (88.4)	32 (82.1)	0.54
Dyslipidemia	43 (53.4)	22 (51.2)	21 (53.8)	0.83
Hyperuricemia	32 (39.0)	16 (37.2)	16 (41.0)	0.82
Any side effect after vaccination	36 (43.9)	17 (39.5)	19 (48.7)	0.51
Time 2nd dose-Ab dosing, days	43 (23-63)	42 (22-62)	43 (24-63)	0.60
Steroid use	75 (91.5)	39 (90.7)	36 (92.3)	1.00
Weekly steroid dose >40 mg	24 (29.3)	12 (27.9%)	12 (30.8)	0.81
Triple IS therapy	59 (72.0)	26 (60.5)	33 (84.6)	0.03
Everolimus use	10 (12.2)	6 (14.0)	4 (10.3)	0.74
Any CNI use	80 (97.6)	42 (97.7)	38 (97.4)	1.00
Cyclosporine	15 (18.3)	10 (23.3)	5 (12.8)	0.26
Tacrolimus bis-die	16 (19.5)	9 (20.9)	7 (17.9)	0.79
Tacrolimus mono-die	49 (59.8)	24 (55.8)	25 (64.1)	0.50
Anti-metabolite	57 (69.5)	24 (55.8)	33 (84.6)	0.008

Abbreviations: IQR, interquartile ranges; n, number; BMI, body mass index; KT, kidney transplantation; T2DM, type 2 diabetes mellitus; Ab, antibody; IS, immunosuppressive; CNI, calcineurin inhibitor.

Variables	First dose	Second dose	Cumulative
	N (%)		
Pain in the site of inoculation	34 (41.5)	27 (32.9)	36 (43.9)
Fever	1 (1.2)	1 (1.2)	1 (1.2)
Flu-like symptoms	4 (4.9)	1 (1.2)	5 (6.1)

Abbreviations: N, number.

Variables	Beta	SE	Wald	OR	95.0%CI		P-value
					Lower	Upper	
Age, years							
18-49	Ref.	-	-	1.00	-	-	-
50-59	0.26	0.66	0.15	1.29	0.36	4.69	0.70
≥60	1.50	0.63	5.71	4.50	1.31	15.46	0.02
Anti-metabolite	1.66	0.58	8.18	5.26	1.69	16.42	0.004
Constant	-0.53	0.53	1.00	0.59	-	-	0.32

Hosmer-Lameshow Test: 0.861

Variables initially tested in the model: male sex, year since KT, age, anti-metabolite, triple IS therapy.

Abbreviations: SE, standard error; OR, odds ratio; 95.0% CI, 95.0% confidence intervals.