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Long-term immune response after SARS-CoV2 vaccination in solid organ transplant recipients

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Abstract

Background Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) vaccination in solid organ transplant (SOT) recipients is associated with suboptimal antibody response (AbR) favouring breakthrough infection (BI). The role of cell-mediated immunity (CMI) remains uncertain.

Methods Single-center prospective longitudinal cohort study of adult SOT recipients monitored for both AbR and CMI at 6 ± 2 months after booster dosage of SARS-CoV-2 vaccine. Primary end-point was BI diagnosis and CMI was the main risk factor. Relationship between CMI and BI was investigated by bivariate tests and multivariable logistic regression.

Results CMI was performed in 139 patients. In 66 patients BI was documented before CMI, thus 73 (33 kidney, 24 liver, 14 lung, 2 heart) were analysed. The first 2 vaccine doses consisted of BNT162b2 and mRNA-1273 in 69.1% and 30.9% of cases, respectively. Whereas mRNA-1273 was used as for third dose in 91.2% of patients. At a median of 215 (IQR 181–252) days after booster dose, 40 (54.8%) patients displayed both AbR and CMI, 21 (28.8%) only AbR and 12 (16.4%) neither AbR or CMI; there were no patients showing negative AbR and positive CMI. Overall, 22 (30.1%) patients reported BI with no significant differences between those with positive vs. negative CMI (59.1% vs. 40.9%, $p = 0.798$), confirmed by multiple logistic regression after adjusting for age, type of vaccine and organs, high AbR and time from transplant.

Conclusion Our data suggest that in the solid organ transplant population of our cohort, cell-mediated immunity does not appear to be a strong predictor of BI.

Keywords Sars-CoV2 vaccine, Solid organ transplant, Cellular mediated immunity, Antibody response

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Background

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) vaccination in solid organ transplant (SOT) recipients is associated with poorer antibody response (AbR) compared with general population [1–5]. Prior studies have shown a correlation between negative or low-level AbR after booster doses and higher likelihood of developing breakthrough infection (BI) in SOT recipients, as well as of having a more severe infection course [6]. However, the role of only AbR in predicting the vulnerability of SOT recipients to SARS-CoV2 infection and its severity has been debated due to the potential protection from cell-mediated immune (CMI) response [4]. Indeed, some authors have reported that although CMI appears lower in SOT compared with the general population, it seems to be more robust and ss than the humoral response [7–10]. Unfortunately, studies investigating the relationship between the presence of long-term AbR, CMI and/or both, with the rate and severity of SARS-CoV-2 infection in SOT recipients are limited. Consequently, the best immune surrogate in predicting long-term clinical effectiveness of vaccination needs to be clarified.

Given this background, in this prospective longitudinal study, we aimed to assess the development of SARS-CoV-2 breakthrough infections according to the long-term immune response pattern (negative or positive AbR combined with negative or positive CMI).

Methods

Study design

CONTRAST (The impact of COvid-19 pandemic on the saNt'orsola TRAnSplant and cancer cohorT: an observational study) is a single-center prospective longitudinal cohort study of SOT recipients who underwent SARS-CoV-2 vaccination within the Horizon 2020 ORCHESTRA project (https://orchestra-cohort.eu/). The recruitment period was from 1 February 2021 to January 2022. All patients were followed up until 31st August 2022. Data were recorded anonymously and managed using REDCap electronic data capture tools hosted at the University of Bologna [11]. The study was approved by the local institutional review board and informed consent was obtained before enrollment.

Setting

The IRCCS Azienda Ospedaliero-Universitaria di Bologna is a 1400-bed tertiary teaching hospital with 4 active transplant programs: kidney, liver, heart, and lung with an average volume of transplantation of 120, 90, 25 and 10 per year, respectively.

Study population

All adult (aged ≥ 18 years) SOT recipients who received ≥ 1booster dose of a SARS-CoV-2 vaccine, which provided consent to participate in the study, and who performed AbR and CMI determination at 6 ± 2 months after booster dosage were included.

Primary end point was BI diagnosis defined as the detection of SARS-CoV-2 RNA or antigen in a respiratory specimen collected ≥ 14 days after the administration of the last vaccine dose (https://www.cdc.gov/coronavirus/2019-ncov/vaccines/effectiveness/why-measure-effectiveness/breakthroughcases.html). Diagnostic testing for SARS-CoV-2 infection was performed according to local policy and clinical judgment and was not dictated by study protocol.

AbR was determined using the Elecsys Anti-SARS-CoV-2 Electrochemiluminescence Immunoassay (ECLIA) assay (Roche Diagnostics AG, Rotkreuz, Switzerland). Minimum and maximum thresholds for detection of anti–receptor binding domain (RBD) antibody levels were 0.4 and 2500 UI/mL, respectively. Positive AbR was defined as an anti-RBD titer of ≥ 5 UI/mL [12].

Cell-mediated immune response was investigated using the COVID-19 T-spot test (Oxford Immunotec, Abingdon-on-Thames, U.K) based on the ELISPOT (Enzyme Linked ImmunoSpot) method. This test quantifies effective T-cells capable of secreting IFN-gamma in response to interaction with SARS-CoV-2 S viral antigens.

Anti-N CMI was positive only in patients with history of SARS-CoV2 infection, thus only anti-S CMI analysis was conducted in this study. Results were quantified according to the number of positive spots as follow: negative for ≤ 4 positive spot; borderline for 5 to 7 positive spot, low-positive for 8 to 19 positive spots and positive if ≥ 20 spots.

AbR and CMI were assessed at multiple timepoints including the administration of the first vaccine dose (t_0), second dose (t_1), 3 ± 1 months after the first dose (t_2), and 6 ± 2 months after the first dose (t_3), 1 ± 1 month after the third dose (t_4) and 6 ± 2 months after the third dose (t_5).

Data on sex, age, comorbidities according to the Charlson score, type of transplant and time from transplant to first vaccine dose administration, basal (t_0 or t_1) immune parameters including lymphocyte subpopulations and immunoglobulin G (IgG) levels, type of each vaccine dose administration, exposure to an induction regimen within 6 months before the administration of the last vaccine dose, immunosuppressive drugs (calcineurin inhibitors, antimetabolites, mammalian target of rapamycin inhibitors, steroids) at the time of the last vaccine dose administration, and graft function were also collected.

Table 1 Characteristics of the population

	Total	Cell-Mediated Immunity (CMI)		
		Negative	Positive	Test
	N **= 73**	***n*** **= 33 (45.2%)**	***n*** **= 40 (54.8%)**	
Age at 1st dose	56.0 [48.0;65.0]	59.0 [49.0;68.0]	56.0 [41.0;64.5]	0.448
Females	30 (41.1%)	13 (39.4%)	17 (42.5%)	0.816
Time from transplant and 1st dose (years)	4.4 [1.5;8.6]	4.4 [1.1;9.2]	4.6 [2.6;8.4]	0.273
Time from previous vaccination and CMI (days)	215.0 [181.0;252.0]	210.0 [172.0;238.0]	216.5 [181.0;253.0]	0.369
Time from previous vaccination and AbR (days)	225.0 [190.0;264.0]	210.0 [172.0;238.0]	216.5 [181.0;253.0]	0.400
SOT group				
Heart	2 (2.7%)	1 (3.0%)	1 (2.5%)	0.479
Liver	24 (32.9%)	8 (24.2%)	16 (40.0%)	
Lung	14 (19.2%)	8 (24.2%)	6 (15.0%)	
Kidney	33 (45.2%)	16 (48.5%)	17 (42.5%)	
Presence of comorbidities				
No	53 (72.6%)	23 (69.7%)	30 (75.0%)	0.793
Yes	20 (27.4%)	10 (30.3%)	10 (25.0%)	
Type of Vaccine				
Pf-Pf-Mo	41 (60.3%)	15 (50.0%)	26 (68.4%)	0.253
Mo-Mo-Mo	21 (30.9%)	11 (36.7%)	10 (26.3%)	
Pf-Pf-Pf	6 (8.8%)	4 (13.3%)	2 (5.3%)	
Graft function at 1st dose				
Good	69 (94.5%)	32 (97.0%)	37 (92.5%)	0.622
Impaired, failure or other	4 (5.5%)	1 (3.0%)	3 (7.5%)	
Immunosuppressive therapy				
Yes	72 (98.6%)	32 (97.0%)	40 (100.0%)	0.452
No	1 (1.4%)	1 (3.0%)	0 (0.0%)	
Calcineurin Inibithors				
No	1 (1.4%)	0 (0.0%)	1 (2.5%)	1.000
Yes	72 (98.6%)	33 (100.0%)	39 (97.5%)	
MMF				
No	40 (54.8%)	16 (48.5%)	24 (60.0%)	0.354
Yes	33 (45.2%)	17 (51.5%)	16 (40.0%)	
mTOR				
No	64 (87.7%)	28 (84.8%)	36 (90.0%)	0.723
Yes	9 (12.3%)	5 (15.2%)	4 (10.0%)	
Steroids				
No	28 (38.4%)	9 (27.3%)	19 (47.5%)	0.094
Yes	45 (61.6%)	24 (72.7%)	21 (52.5%)	
CD4	(*n* = 27) 566.0 [392.0;836.0]	(*n* = 13) 697.0 [236.0;836.0]	(*n* = 14) 546.5 [454.0;803.0]	0.865
CD4 > 500				

Table 1 (continued)

	Total	Cell-Mediated Immunity (CMI)		
		Negative	Positive	Test
	N **= 73**	***n*** **= 33 (45.2%)**	***n*** **= 40 (54.8%)**	
No	12 (44.4%)	6 (46.2%)	6 (42.9%)	1.000
Yes	15 (55.6%)	7 (53.8%)	8 (57.1%)	
CD8	(*n* = 27) 472.0 [324.0;703.0]	(*n* = 13) 420.0 [319.0;952.0]	(*n* = 14) 510.0 [346.0;604.0]	0.923
IgG (mg/dL)	(*n* = 26) 996.5 [827.0;1,095.0]	(*n* = 14) 928.0 [727.0;1000.0]	(*n* = 12) 1043.5 [983.5;1205.0]	0.024
IgG > 600				
No	2 (7.7%)	2 (14.3%)	0 (0.0%)	0.483
Yes	24 (92.3%)	12 (85.7%)	12 (100.0%)	
Leukocytes	(*n* = 36) 6.2 [4.7;8.4]	(*n* = 18) 7.2 [5.1;8.6]	(*n* = 18) 5.8 [4.3;6.9]	0.304
AbR				< 0.001
Positive	61 (83.6%)	21 (63.6%)	40 (100%)	
Negative	12 (16.4%)	12 (36.4%)	0	
Positive AbR				0.588
Very low	1 (1.7%)	1 (4.8%)	0	
Low	4 (6.6%)	1 (4.8%)	1 (2.5%)	
Medium	4 (6.6%)	1 (4.8%)	3 (7.55%)	
High	52 (85.2%)	18 (85.7%)	36 (90.0%)	

Median [iqr]: p-value from Kruskal-Wallis test

Frequency (Percent%): p-value from Fisher's exact test

Abbreviation: Cellular-mediated Immunity (CMI), Antibody Response (AbR), BNT162b2 Pfizer Vaccine (Pf), mRNA-1273 Moderna Vaccine (Mo), Mycophenolate Mofetil (MMF), Mechanistic Target of Rapamycin (mTOR), Immunoglobulin G (IgG)

Statistical analysis

Patients' characteristics represented by categorical variables were described as absolute numbers and percentages. Continuous variables were presented as mean ± standard deviation (SD) if normally distributed and as median and interquartile range (IQR) if non-normally distributed. To investigate whether CMI could affect the onset of BI, a multivariable logistic regression of BI on anti-S CMI response as main exposure was performed, adjusting for the main clinical variables (age, high AbR, type of organ transplanted (kidney vs. other organs), type of vaccine and time from transplant to the first vaccine dose) that may act as confounders. Finally, the immune response pattern of AbR and CMI was obtained by combining the two binary responses, and the clinical characteristics of patients in each subgroup were described and compared using Kruskal-Wallis test. Stata v.18 was used for all analyses.

Results

Overall, CMI was performed in 139 patients (60 kidney, 42 liver, 18 lung, 19 heart). Sixty-six were excluded as CMI was determined after BI. Thus, 73 SOT (33 kidney, 24 liver, 14 lung, 2 heart) recipients were analysed: 30 (41.1%) female, median age was 56 (IQR, 48–65) years (Table 1). All 73 patients received messenger RNA (mRNA)-based vaccines and h and had negative anti-N serology at baseline. The median time from transplantation to the first dose was 4.4 years (IQR, 1.5–8.6). The first 2 vaccine doses consisted of BNT162b2 and mRNA-1273 in 69.1% and 30.9% of cases, respectively; mRNA-1273 was frequently used for the third dose ($n = 62$, 84.9%). Almost all patients had a good graft function at baseline ($n = 69$, 94.5%). Immunosuppression regimen consisted of calcineurin inhibitors, mycophenolate mofetil, mTOR inhibitors and steroids in 98.6%, 45.2%, 12.3% and 61.6%, respectively.

Long-term (median time 225 days [IQR 190–264] after booster dosage) positive AbR was observed in 61 patients (83.6%). In these, anti-RBD levels were classified as very low, low, medium, and high level in 1 (1.7%), 4 (6.6%), 4 (6.6%) and 52 (85.2%) patients, respectively. Long-term (median time 215 days [181–252] after booster dosage) positive CMI was observed in 40 (54.8%). There were not significant differences between positive and negative CMI patients (see Table 1), except for basal IgG (1043.5 vs. 928 mg/dL) and long-term positive AbR rates (100% vs. 63.6%).

Overall, 22 (30.1%) patients reported BI (Table 2) in a similar proportion between those with positive vs. negative CMI [13/40 (32.5%) vs. 9/33 (27.3%), $p = 0.798$]. The time from transplantation to the first vaccine dose was not associated to BI either when analyzed in years or in classes (< 1 year, 1–5 years, > 5 years). No severe cases of COVID-19 were observed in out cohort. Multivariable logistic regression analysis showed no impact of anti-S CMI response on BI development (OR = 1.012, $p = 0.790$) after adjusting for age, high-level AbR, type of vaccine, organ and time from transplant (Table 3).

Combining the immune response patterns, 40 (54.8%) patients displayed long-term positive AbR and positive CMI (group 1), 21 (28.8%) positive AbR and negative CMI (group 2), and 12 (16.4%) negative AbR and negative CMI (group 3). Notably, there were no patients showing negative AbR and positive CMI. Comparison of the three immune response pattern groups showed that higher IgG were associated with positive AbR and positive CMI, a trend toward higher liver transplant rates in group 1, while more frequent use of mycophenolate and steroids in patients with negative AbR and negative CMI were observed (data shown in Supplementary Table1).

In a sensitivity analysis, the matching of CMI and AbR response was used as a composite indicator in the multivariable logistic regression model, confirming no evidence of association with BI (data not shown).

Discussion

Our study suggests that long-term immune response after booster dose of SARS-CoV2 vaccine is characterized by high rates of positive AbR (83.6%), while CMI was positive in 54.8%. There were not patients with negative AbR and positive CMI. Younger age, more than the pattern of immune response, was associated with BI.

Although the vaccines administered in our cohort are first-generation vaccines, it is well established that they provide effective protection against the Omicron variant, as demonstrated in recent studies. Research by Lau et al. [13] and Link-Gelles et al. [14] confirm that first-generation vaccines continue to offer significant protection against Omicron, particularly in preventing severe COVID-19 outcomes. This reinforces the idea that, despite the evolution of SARS-CoV-2, the first-generation vaccines are likely to remain effective in preventing the progression to severe disease. Furthermore, it is plausible to expect that these vaccines will retain some degree of effectiveness against emerging variants, continuing to mitigate the risk of hospitalization and death, which is a critical consideration for vulnerable populations such as solid organ transplant recipients.

Assessing humoral and/or cellular immune response is often used as surrogate of vaccine response in general population and, even more, in immunocompromised hosts. Indeed, AbR has been assessed in several studies on SOT recipients after SARS-CoV2 vaccination, showing a lower positivity compared to control groups [1–3, 5]. In addition, suboptimal AbR in this setting was related with higher risk of BI. However, the use of AbR in clinical practice to stratify patients at low or high risk for BI, in order to individualize

Table 2 Characteristics of breakthrough infection

	Breakthrough Infection		
	Absent	**Present**	**Test**
	***n* = 51 (69.9%)**	***n* = 22 (30.1%)**	
Age at 1st dose	60.0 [55.0;69.0]	40.5 [38.0;53.0]	< 0.001
Females	20 (39.2%)	10 (45.5%)	0.796
Time from transplant and 1st dose (years)	5.0 [1.2;10.0]	3.3 [1.7;8.1]	0.709
< 1 year	8 (15.7%)	2 (9.1%)	
1–5 years	17 (33.3%)	11 (50.0%)	
> 5 years	26 (51.0%)	9 (40.9%)	
Time from previous vaccination and CMI (days)	213.0 [183.0;242.0]	232.5 [159.0;272.0]	0.327
Time from previous vaccination and AbR (days)	213.0 [183.0;242.0]	232.5 [159.0;272.0]	0.336
CMI			
Negative	24 (47.1%)	9 (40.9%)	0.798
Positive	27 (52.9%)	13 (59.1%)	
SOT group			
Heart	1 (2.0%)	1 (4.5%)	0.010
Liver	22 (43.1%)	2 (9.1%)	
Lung	10 (19.6%)	4 (18.2%)	
Kidney	18 (35.3%)	15 (68.2%)	
Presence of comorbidities			
No	37 (72.5%)	16 (72.7%)	1.000
Yes	14 (27.5%)	6 (27.3%)	
Type of Vaccine			
Pf-Pf-Mo	27 (54.0%)	14 (77.8%)	0.154
Mo-Mo-Mo	17 (34.0%)	4 (22.2%)	
Pf-Pf-Pf	6 (12.0%)	0 (0.0%)	
Graft function at 1st dose			
Good	48 (94.1%)	21 (95.5%)	1.000
Impaired, failure or other	3 (5.9%)	1 (4.5%)	
Immunosuppressive Therapy			
Yes	50 (98.0%)	22 (100.0%)	1.000
No	1 (2.0%)	0 (0.0%)	
Calcineurin Inibithors			
No	1 (2.0%)	0 (0.0%)	1.000
Yes	50 (98.0%)	22 (100.0%)	
MMF			
No	28 (54.9%)	12 (54.5%)	1.000
Yes	23 (45.1%)	10 (45.5%)	
mTOR			
No	46 (90.2%)	18 (81.8%)	0.439
Yes	5 (9.8%)	4 (18.2%)	
Steroids			
No	26 (51.0%)	2 (9.1%)	< 0.001
Yes	25 (49.0%)	20 (90.9%)	
CD4	(*n* = 24) 628.5 [465.0;838.0]	(*n* = 3) 236.0 [213.0;392.0]	0.034
CD4 > 500			
No	9 (37.5%)	3 (100.0%)	0.075
Yes	15 (62.5%)	0 (0.0%)	
CD8	(*n* = 24) 455.0 [321.5;710.5]	(*n* = 3) 472.0 [388.0;604.0]	0.939
IgG (mg/dL)	(*n* = 22) 983.5 [824.0;1093.0]	*n* = 4 1077.0 [913.5;1384.0]	0.286
IgG > 600			
No	2 (9.1%)	0 (0.0%)	1.000
Yes	20 (90.9%)	4 (100.0%)	
Leukocytes	(*n* = 29) 6.5 [5.1;8.6]	(*n* = 7) 5.8 [3.9;6.6]	0.145

Table 2 (continued)

	Breakthrough Infection		
	Absent	**Present**	**Test**
	n **= 51 (69.9%)**	***n*** **= 22 (30.1%)**	
AbR			1.000
Positive	42 (82.4%)	19 (86.4%)	
Negative	9 (17.6%)	3 (13.6%)	
Positive AbR			0.497
Very low	0	1 (5.3%)	
Low	2(4.8%)	0 (0%)	
Medium	3 (78.1%)	1 (5.3%)	
High	37 (88.1%)	17 (89.5%)	

Median [iqr]: p-value from Kruskal-Wallis test

Frequency (Percent%): p-value from Fisher's exact test

Abbreviation: Breakthrough Infection (BI), Cellular-mediated Immunity (CMI), Antibody Response (AbR), BNT162b2 Pfizer Vaccine (Pf), mRNA-1273 Moderna Vaccine (Mo), Mycophenolate Mofetil (MMF), Mechanistic Target of Rapamycin (mTOR), Immunoglobulin G (IgG)

Table 3 Multivariable logistic regression analysis of Breakthrough Infection (BI)

	OR (95% IC)	***p*-value**
Anti-S ELISPOT CMI	1.012 (0.928–1.103)	0.790
High AbR	0.674 (0.142–3.213)	0.621
Age (years)	0.886 (0.832–0.942)	< 0.001
Organ transplanted (kidney vs. other)	4.871 (1.166–20.359)	0.030
Vaccination (mRNA-1273)	0.208 (0.043–1.019)	0.053
Time from transplant to vaccination (years)	1.009 (0.892– 1.142)	0.884

Abbreviation: Cellular-mediated Immunity (CMI), Antibody Response (AbR), mRNA-1273: Moderna Vaccine

preventive management, has been criticised due to the potential concomitant role of CMI, which is more difficult to assess in clinical laboratories [4]. Indeed, studies assessing both AbR and CMI few weeks after receiving the first two vaccine doses showed that in some cases CMI was positive despite low ore negative level of AbR [7–9]. However, to date few data are available about the long-term immune response pattern and how this could predict the risk of BI.

Most of prior studies included patients with intercurrent BI between vaccination and CMI/AbR determination. It is known that more than vaccination, the virus contact is able to stimulate both humoral and cellular immunity [15, 16] giving the highest protection to the patient. We excluded patients with BI prior CMI in order to limit this bias. Moreover, as a result of the period in which the study was conducted, patients had received only one vaccine booster dose, differently from other studies where patients were vaccinated with fourth or fifth doses [17]. These additional doses could have boosted humoral and cellular immunity which would therefore reach higher values [17]. Another singular finding that comes from our study is that no patients were showing negative AbR and positive CMI. These notable findings suggest that AbR might have a stronger association with long-term vaccine responses compared to CMI.

In multivariable logistic regression analysis, surprisingly, neither immunosuppressive drugs, AbR nor CMI were associated with an increased risk of BI.

However, some limitations of our study should be taken into consideration. Firstly, the small number of patients and the single-centre design may limit the generalizability of our results. This is an ancillary study from a protocol whose main objective was designed on a larger, multicentric cohort of patients, thus its sample size was not obtained by power analysis. Furthermore, using EliSpot assays to determine CMI there is an intrinsic risk of inaccuracy due to the nature of the method and the absence of information about the phenotype of responding cells. Moreover, given the absence of genotype analysis of viral variants, we were not able to provide information about a possible variant role influencing BI risk.

Despite these limitations, this is one of the largest studies investigating both AbR and CMI at 6 months after booster dosage in SOT patients, suggesting that in solid organ transplant population of our cohort, cell-mediated immunity does not appear to be a strong predictor of BI. We advocate our findings could be confirmed in further studies with larger populations.

Abbreviations

SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SOT	Solid Organ Transplant
AbR	Antibody Response
BI	Breakthrough Infection
CMI	Cell-Mediated Immunity
IQR	Interquartile Range
mRNA	Messenger Ribonucleic Acid
UI/mL	International Units per Milliliter
RBD	Receptor Binding Domain
ELISPOT	Enzyme-Linked ImmunoSpot
IFN-gamma	Interferon-gamma
IgG	Immunoglobulin G
OR	Odds Ratio
SD	Standard Deviation
t0, t1, t2, t3, t4, t5	Time points
COVID-19	Coronavirus Disease 2019
mTOR	Mammalian Target of Rapamycin
REDCap	Research Electronic Data Capture

ECLIA	Electrochemiluminescence Immunoassay
CDC	Centers for Disease Control and Prevention

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12879-024-10377-1.

Supplementary Material 1

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Author contributions
Drs. Bonazzetti, Drs. Toschi, Prof. Giannella and Prof. Viale designed the study. Dr. Gibertoni, Drs. Caroccia and Drs. Di Chiara were responsible for the statistical analysis. Drs. Bonazzetti, Drs. Toschi, Drs. Vitulliano, Drs. Lanna, Dr. Croci, Drs. Tazza, Dr. Amicucci contributed to patient enrolment, data collection and interpretation. Drs. Bonazzetti drew up a preliminary draft of the manuscript, which was critically reviewed by Drs Morelli, Drs. Comai, Drs Salvaterra, Dr Potena, Professor Giannella, Professor Viale and Professor Lazzarotto. All of the authors approved the final version of the manuscript.

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Data availability
The dataset generated and analysed during the current study is not yet publicly available due the fact that the study has been conducted within the European Union's Horizon 2020 project named "ORCHESTRA" (grant agreement No 101016167), which will end on 30 November 2024. Thus, raw data will be available only after the end of the EU H2020 project on reasonable request.

Declarations

Ethics approval and consent to participate
The study was approved by the local institutional review board ethics committee "Comitato Etico Area Vasta Emilia Centro (AVEC)", IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy. Informed consent was obtained before enrollment. This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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