



**HAL**  
open science

## **SARS-CoV-2 T-cell responses after one or two COVID-19 vaccine boosters in allogeneic transplant recipients**

Béatrice Clémenceau, Amandine Le Bourgeois, Thierry Guillaume, Marianne Coste-Burel, Pierre Peterlin, Alice Garnier, Maxime Jullien, Jocelyn Ollier, Marie C Béné, Patrice Chevallier

► **To cite this version:**

Béatrice Clémenceau, Amandine Le Bourgeois, Thierry Guillaume, Marianne Coste-Burel, Pierre Peterlin, et al.. SARS-CoV-2 T-cell responses after one or two COVID-19 vaccine boosters in allogeneic transplant recipients. Société Francophone de Greffe de Moelle et de Thérapie Cellulaire - SFGM-TC 2022, Nov 2022, Bordeaux, France. inserm-03887197

**HAL Id: inserm-03887197**

**<https://inserm.hal.science/inserm-03887197v1>**

Submitted on 6 Dec 2022

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Béatrice Clémenceau, PhD,<sup>1</sup> Amandine Le Bourgeois, MD,<sup>2</sup> Thierry Guillaume, MD PhD,<sup>1,2</sup> Marianne Coste-Burel, PharmD,<sup>3</sup> Pierre Peterlin, MD,<sup>2</sup> Alice Garnier, MD,<sup>2</sup> Maxime Jullien, MD,<sup>2</sup> Jocelyn Ollier,<sup>1</sup> Marie C Béné, PharmSciD, PhD,<sup>1,4</sup> Patrice Chevallier, MD, PhD.<sup>1,2</sup>

(1) Nantes Université, Inserm UMR 1307, 1- Nantes Université, Inserm UMR 1307, CNRS UMR 6075, Université d'Angers, CIRCI2NA, F-44000 Nantes - France, 2-Hematology Department, Nantes University Hospital, Nantes, France, 3-Virology Department, Nantes University Hospital, Nantes, France. 4- Hematology Biology, Nantes University Hospital, Nantes, France.

## Introduction:

A full exploration of immune responses is deserved after anti-SARS-CoV-2 vaccination and boosters, especially in the context of allogeneic hematopoietic stem-cell transplantation (Allo-HSCT). Although several reports indicate successful humoral responses in such patients, the literature is scarce on cellular specific immunity. We recently reported a strong response of specific anti-SARS-CoV-2- CD4+ T-cells, with a IFN $\gamma$ -/TNF $\alpha$ + cytokine profile, in 89% of humoral responders and 40% of non-humoral responders (Clémenceau B, et al. *Vaccines (Basel)*. 2022 Mar 14;10(3):448).

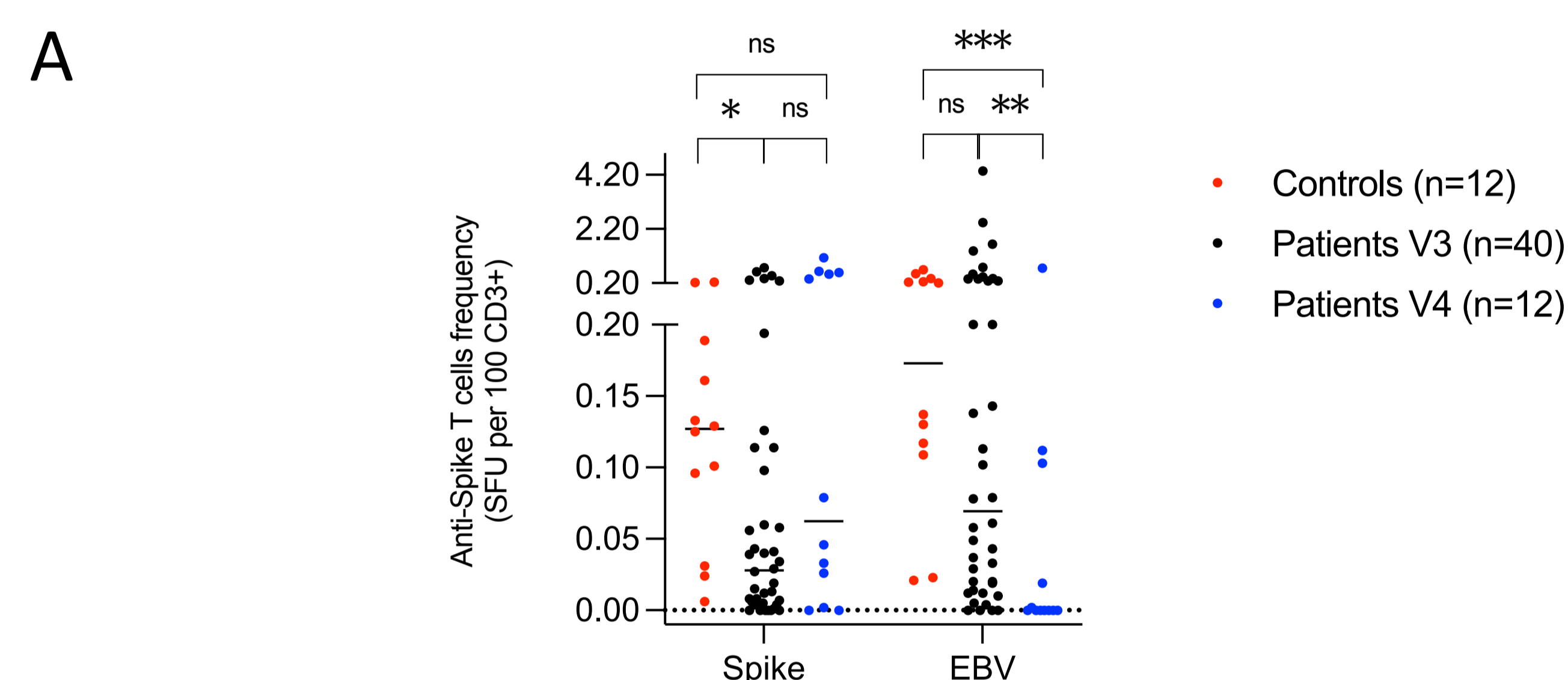
In this study, we have evaluated humoral and T-cell responses **after one (V3 group n=40) or two (V4 group n=12) BNT162b2 mRNA vaccine boosters in 52 Allo-HSCT patients** and in 12 healthy donors. For V3 group, the median time between allo-HCT and V3 vaccination was 869 days (167-5160). For V4 group, the median time between allo-HCT and V3 vaccination was 267 days (143-1090) and 459 days (239-1306) between allo-HCT and V4 vaccination.

## Methods:

Blood samples were collected between January 18th and March 3rd 2022 during the Omicron wave in France. Anti-spike antibodies were tested using anti-SARS-CoV-2 immunoassay Elecsys® (Roche, Rotkreuz, Switzerland). Anti-SARS-CoV-2 Spike and anti-EBV (as positive control) specific CD3+ T-cell responses were evaluated using Human INF $\gamma$  ELISpot (Mabtech, Nacka Strand, Sweden) and intracellular cytokine staining after peptide stimulation (PepTivator Prot\_S Complete, Miltenyi Biotec, Bergisch Gladbach, Germany).

## Results :

All controls (100%) and **81% of the whole patient cohort have developed a protective anti-S antibody level (>250 BAU/mL) after the boost vaccinations**. The rate of subject reaching the highest antibody concentration (>2500 BAU/mL) was significantly higher in controls than the whole patient cohort (100% vs 52%, p=0.005).

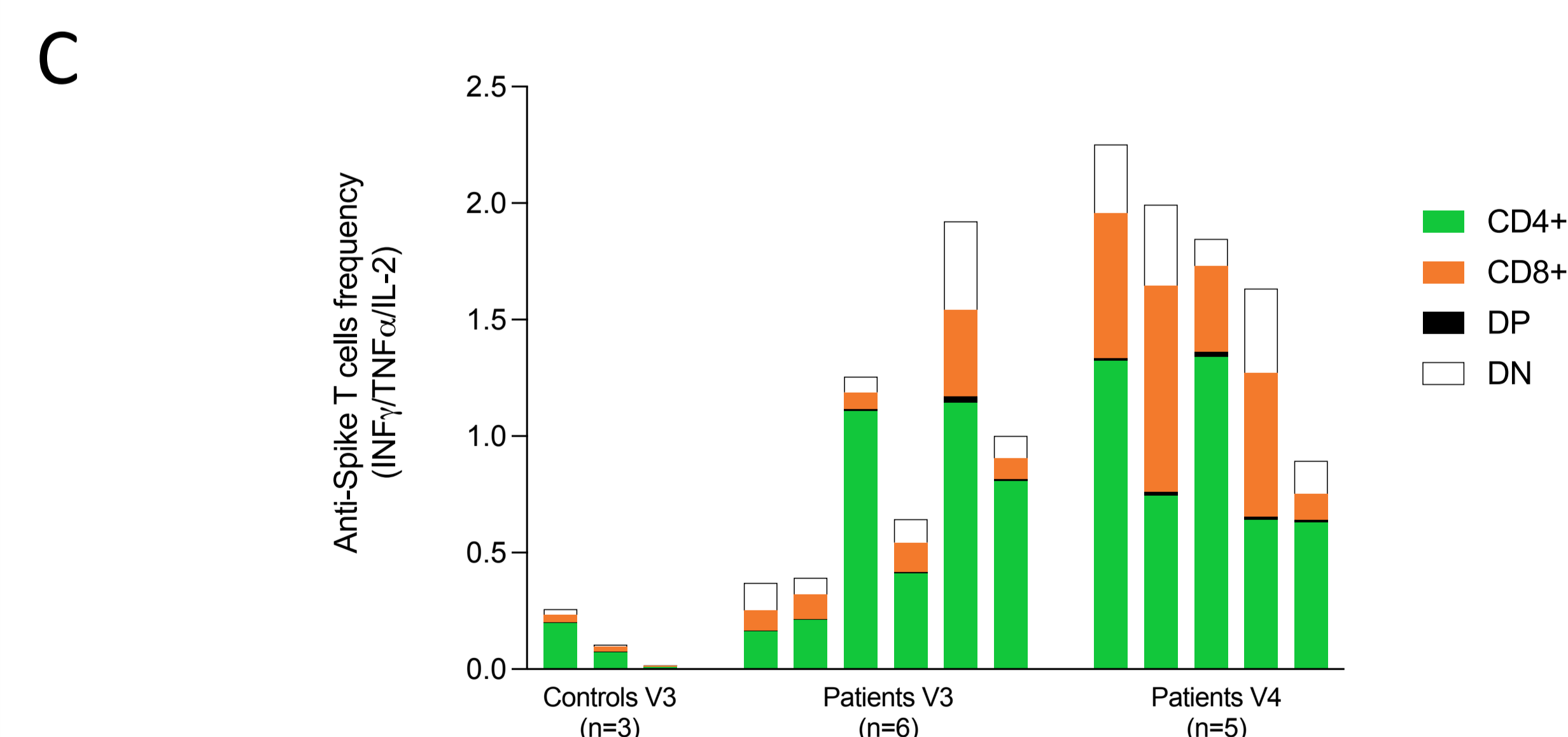


**After the booster vaccination, 85% of patients and 100% of controls developed a specific-T cell response.** The median frequency of anti-Spike T-cells was significantly lower for patients with one vaccine boosters (V3, median = 0.028%) compared to controls (0.127%) but not significantly different between V3 patients and V4 patients (median = 0.063%). Importantly, considering the patients with no antibody response (n=5) or not reaching a protective antibody level after boosts (n=5), 8/10 (80%) had a measurable T-cell response.

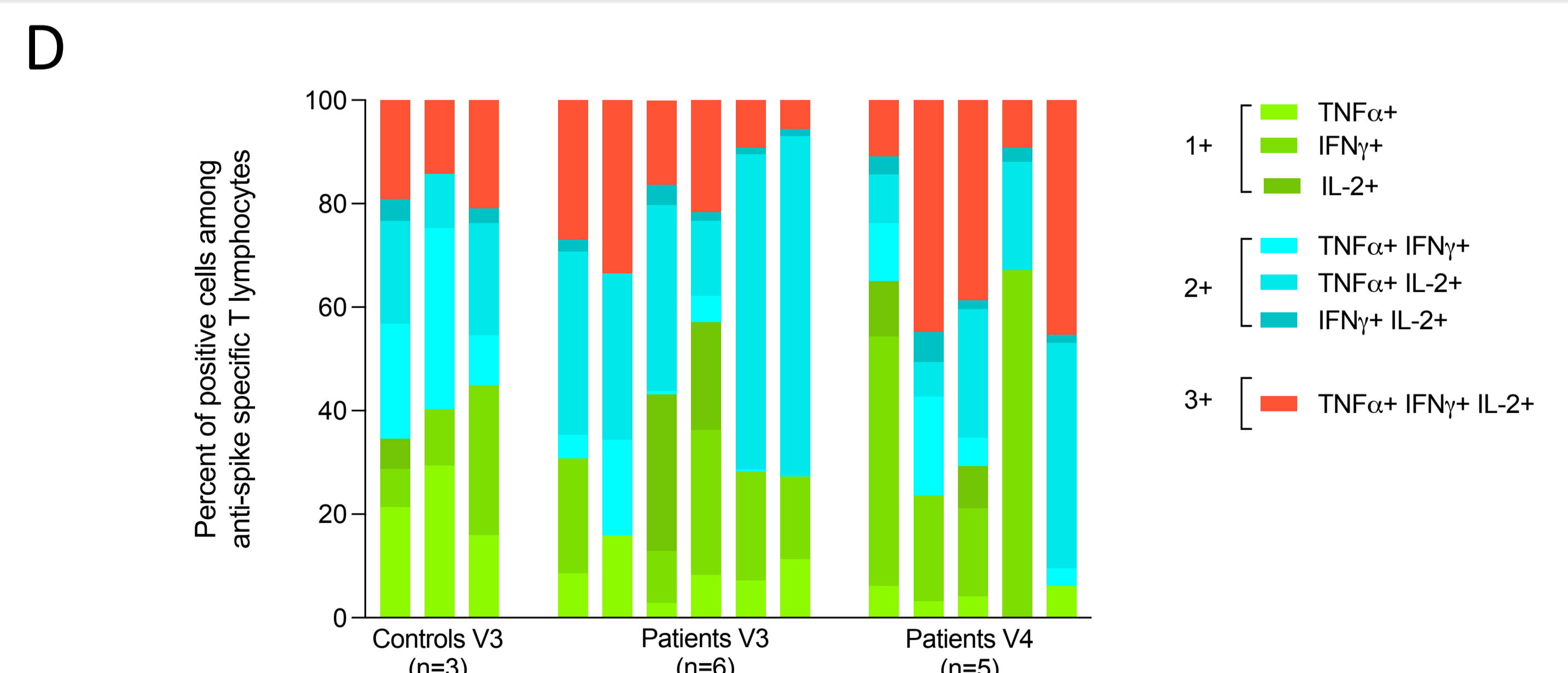
**Table 1. Factors predicting T-cell response: Univariate analysis**

Factors	No responders n=8	Responders N=44	P value
Number of vaccines received: 3/4	6/2	34/10	1
Anti-spike antibody rate: <=250/<250 BAU/ml	2/6	8/36	1
Gender: male/female	8/0	25/19	0.053
Median age: years (range)	57 (49-71)	53 (20-74)	0.84
Disease: lymphoid/myeloid	3/5	13/31	0.97
Donor type: geno/MUD/haplo/mis-m	1/5/2/0	14/17/11/2	0.54
Conditioning: MAC/RIC/Sequential	2/6/0	6/35/3	0.56
GVHD prophylaxis:		23/11/10	0.79
ATG/Csa+MMF+PTCY/PTCY alone	5/2/1		
Previous GVHD: no/yes	3/5	17/27	1
On-going treatment: no/yes	7/1	34/10	0.85
Median delay V3/V4-analyses: days (range)	94 (12-295)	136 (16-298)	0.46
Median delay graft-analyses: days (range)	703 (356-4047)	755 (189-5293)	0.70
Lymphocytes: Giga/L (range)	2.66 (0.75-3.96)	1.37 (0.12-7.14)	0.053
CD3+ T cells: Giga/L (range)	1.58 (0.23-2.25)	0.68 (0.09-3.90)	0.09
CD4+ T cells: Giga/L (range)	0.38 (0.07-1.04)	0.34 (0.04-2.05)	0.77
<b>CD8+ T cells: Giga/L (range)</b>	<b>0.84 (0.13-1.56)</b>	<b>0.34 (0-1.94)</b>	<b>0.03</b>
B cells: Giga/L (range)	0.28 (0-0.65)	0.27 (0-1.61)	0.75
<b>NK cells: Giga/L (range)</b>	<b>0.35 (0.15-0.51)</b>	<b>0.18 (0.04-1.03)</b>	<b>0.02</b>
Gamma globulins: g/l (range)	7.7 (3.4-17.3)	6.75 (1.1-13.9)	0.53

The only factors predicting T-cell response were CD8+ and NK cells counts at time of analyses. For CD8+, this data was also recently reported by Meyer T et al (*Vaccines*. 2022 oct, 10, 1782).



For 14 individuals with the highest frequencies of anti-Spike CD3+ T cells (> 0.180 SFU/100 CD3+ T-cells), the Th1 cytokine of CD3+ T-cell subsets were assessed by INF $\gamma$ , TNF $\alpha$  and IL-2 intracellular staining and a **predominance of anti-spike CD4+ T-cell response was observed.**



Seven cytokine secretion profiles were analysed on specific anti-spike CD3+ T-cells and interestingly, **polyfunctionality T-cells (3+ : INF $\gamma$ , TNF $\alpha$  and IL-2 positives) were observed in both controls (n=3), and patients (n=11).**

At time of last follow-up (June 1st 2022), two V3 patients have presented a non-severe COVID 19 infections (one with a negative serology and 0.039 SFU/100 CD3+ T-cells and the second with a serology >2500 BAU/mL and 0.040 SFU/100 CD3+ T-cells). One V3 patient with negative serology and 0.367 SFU/100 CD3+ T-cells at time of analysis have died of COVID-19 infection.

**Conclusion: In this cohort after one or two booster vaccination, 81% of patient achieved a protective humoral response while 85% achieved a T-cell response. The median frequency of anti-Spike T-cells among CD3+ T-cells was lower in the cohort patients (0.034%) than in controls (0.127%) but not statistically significantly different. Interestingly, polyfunctionality T-cells were observed in both controls and patients. Higher CD8+ and NK lymphocytes counts negatively influenced anti-Spike T-cells response. COVID-19 infections were solely observed in individuals having received only one booster. These results indicate that four vaccine injections help to achieve a satisfactory level of both humoral and cellular immune protection in Allo-HSCT patients.**