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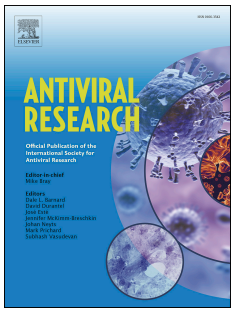

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Increased incidence of herpes zoster in patients on renal replacement therapy cannot be explained by intrinsic defects of cellular or humoral immunity to varicella-zoster virus

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ABSTRACT

Background

Patients in need of long-term renal replacement therapy (RRT) are known to be at increased risk of herpes zoster, occurring when the latently present varicella-zoster virus (VZV) reactivates. In this study we investigated immunity to VZV in patients receiving RRT, with the aim of better understanding the mechanism behind the increased risk.

Methods

Patients treated for at least three months with hemodialysis or peritoneal dialysis, and matched healthy controls (HC) were included. Cellular immunity to varicella-zoster virus (VZV) was studied using an interferon-γ (IFNγ) enzyme-linked immunospot (ELISpot) assay, flow-cytometric analysis of cytokine production and a proliferation assay. Humoral immunity was determined by measuring immunoglobulin (Ig)G antibody levels to VZV using an in-house glycoprotein enzyme-linked immunosorbent assay (ELISA). Multiple regression was used to assess variables of influence on measures of cellular and humoral immunity to VZV in patients receiving RRT.

Results

Similar numbers of IFNγ spot-forming cells and levels of VZV-IgG were found in 97 patients and 89 HC. Age and transplantation history were negatively associated with cellular immunity ($p = 0.001$ and $p = 0.012$, respectively) while treatment modality, gender and urea levels were not. No variables were found to be associated with VZV-IgG levels.

Conclusions

Increased incidence of herpes zoster in patients receiving RRT cannot be explained by intrinsic defects of cellular or humoral immunity to VZV as measured by the methods used in this study, although older age and previous transplantation were associated with decreased cellular immunity to VZV. Herpes zoster susceptibility might be caused by a diminished function of otherwise capable T cells in a uremic environment.

Keywords: varicella-zoster virus; herpes zoster; cellular immunity; humoral immunity; hemodialysis; peritoneal dialysis

ABBREVIATIONS

DMSO:	dimethylsulfoxide
ELISA:	enzyme-linked immunosorbent assay
ELISpot:	enzyme-linked immunospot
FCS:	fetal calf serum
gp:	glycoprotein
HC:	healthy control
IFN-γ :	interferon-γ
Ig:	immunoglobulin
IQR:	interquartile range
IU:	international units
PBMC:	peripheral blood mononuclear cells
RRT:	renal replacement therapy
SEB:	staphylococcal enterotoxin B
TNF-α	tumor necrosis factor alpha
VZV:	varicella-zoster virus

1. INTRODUCTION

In temperate countries, almost the entire adult population has experienced a primary varicella-zoster virus (VZV) infection, known as chickenpox or varicella, after which the virus remains latently present for life in the dorsal root ganglia [1, 2]. When cellular immunity to VZV diminishes, for instance with advancing age or as a result of immunosuppression, the virus is able to reactivate, causing herpes zoster (shingles) [3, 4]. Herpes zoster is characterized by rash in a dermatomal distribution and neuralgia, which can be severe and long-lasting [5]. Pain lasting for at least 90 days after the onset of rash is known as postherpetic neuralgia, the most common complication of herpes zoster [1, 3]. Other complications include bacterial superinfections and an increased risk of stroke [1, 6]. Disseminated zoster, occurring mainly in immunocompromised patients, can be lethal [3].

Uremia, a consequence of renal failure, leads to disturbances of both innate and adaptive immunity. Accordingly, patients in need of long-term renal replacement therapy (RRT) are known to be susceptible to infections, which are a major cause of morbidity and mortality in this group [7-9]. Also, the herpes zoster risk is increased in patients receiving RRT, and is reported to be even higher than the already increased risk of patients with chronic kidney diseases [10-13]. Patients receiving peritoneal dialysis were found to be at higher risk of herpes zoster than hemodialysis patients [12, 13]. Of note, although zoster vaccination was associated with a 50% lower risk of herpes zoster in patients in receiving RRT, the incidence among vaccinated patients aged ≥60 years is still higher than in unvaccinated 80-year olds not receiving dialysis [13-15]. Treating herpes zoster is particularly challenging in patients in need of RRT as reduced renal clearance leads to dosing difficulties of antiviral therapy and analgesics.

To date, the mechanism explaining herpes zoster susceptibility in patients on long-term hemodialysis or peritoneal dialysis treatment is unclear. In the present study, we aimed to evaluate VZV immunity in these patients by determining the cellular and humoral immunity to VZV in patients and matched controls, as this knowledge could aid in the improvement of preventive measures of herpes zoster in these patients.

2. METHODS

2.1 Study population

Eligible patients, receiving renal replacement therapy for at least 3 months, were recruited from the Dialysis Centre Groningen and its regional annexes. Healthy controls were age and sex-matched to patients. They were recruited by using posters in the university buildings and, to be able to include older healthy volunteers, with help from local general practitioners. Exclusion criteria for both patients and controls were pregnancy, malignancy (except for skin malignancies) within the last two years, an auto-immune related cause of renal failure (including systemic lupus erythematosus and ANCA (anti-neutrophil cytoplasmic antibodies)-associated vasculitis), use of immunosuppressive medication other than prednisone ≤5 mg per day (or equivalent) or use of immunostimulatory medication in the last 6 months.

Medical records of patients were reviewed for clinical data including herpes zoster history, serum levels of urea and albumin. Further information on history and timing of varicella and herpes zoster in study participants was collected using a questionnaire. Varicella vaccination is not part of routine immunizations in children in The Netherlands, and zoster vaccination, containing the same viral strain as the varicella vaccine but approximately 14 times more potent, is not recommended for adults.

The study was approved by the institutional review board of the University Medical Centre Groningen (METc 2014/305 and 2012/375). All patients and controls gave written informed consent.

2.2 Isolation, storage and thawing of PBMC and serum

Peripheral blood mononuclear cells (PBMC) were isolated from venous blood, that was collected in lithium heparin containing tubes. After density-gradient centrifugation on

Lymphoprep (Axis-Shield), PBMC were frozen in RPMI 1640 (Lonza) supplemented with gentamicin (Gibco/ThermoFisher Scientific) 10% fetal calf serum (FCS, Sigma-Aldrich) and 10% dimethylsulfoxide (DMSO, Merck) and stored in liquid nitrogen until use. Upon thawing, cell viability was evaluated by trypan blue staining. Serum was stored at -20 °C until use.

2.3 Interferon-γ (IFNγ) ELISpot assay

Interferon-γ (IFNγ) enzyme-linked immunospot (ELISpot) assay was performed as described previously [16]. In brief, stimulations were done with 10 µl UV-inactivated varicella vaccine (Provarivax; MSD, 1350 PFU/0.5ml) or 5 µg/ml of concanavalin A (positive control). A negative control consisted of PBMC in culture medium alone. Except for the positive control, experiments were done in duplicate. After staining, spots were counted using an automated reader (AID EliSpot Reader; Autoimmun Diagnostika GmbH). The mean number of spots in the negative control sample was subtracted from the mean number of spots in the VZV-stimulated wells. Results are referred to as the number of IFNγ spot-forming cells per 2 x 10^5 PBMC.

2.4 Flow cytometric analysis of cytokine production

PBMC (1.2 x 10^6/tube) were stimulated for 18 hours, of which the final 16 hours in presence of 10 µg/ml brefeldin A (Sigma-Aldrich). Next to stimulation with UV-inactivated varicella vaccine, PBMC were stimulated using 5 µg/ml staphylococcal enterotoxin B (SEB; Sigma-Aldrich, positive control), while a negative control consisted of PBMC in medium alone. In all three conditions, 10µg/ml anti-CD28/CD49d was added for co-stimulation (Beckton Dickinson (BD)). Fluorescent T cell barcoding staining and immunostaining was performed as described previously [17]. Immunostaining was done with anti-CD3, anti-CD8, anti-CD69,

anti-IFNγ, anti-tumor necrosis factor alpha (TNFα) and interleukin 2 (IL-2) (all from BD). After incubation and washing, cells were immediately analyzed on an LSR flow cytometer (BD). Results were analyzed using Kaluza software (Beckman Coulter). CD4+ and CD8+ T cell populations were gated as CD3+CD8- and CD3+CD8+, respectively. Results were expressed as the percentage of CD69+ cytokine-producing CD4+ or CD8+ T cells, within the total CD4+ or CD8+ T cell population.

2.5 T cell proliferation assay

Thawed PBMCs were stained with cell proliferation dye eFluor 670 (Thermo Fisher Scientific) at a final concentration of 1 µmol/ml and incubated for 10 minutes in the dark at 37°C. The reaction was stopped by adding RPMI plus 10% FCS. Next, 96-well U-bottomed plates (Greiner Bio-One) were filled with 1 x 10^5 stained PBMCs, which were stimulated with 1.5 µl UV-inactivated varicella vaccine. As a positive control, cells were stimulated with CD3-specific and CD28-specific antibodies (obtained from a hybridoma culture supernatant). Cells were incubated for 7 days at 37°C in an atmosphere containing 5% CO_2. Subsequently, cells were harvested and 5 µl of allophycocyanin-conjugated mouse anti-human CD3 and 5 µl of peridinin chlorophyll protein–conjugated mouse anti-human CD8 (both from BD PharMingen/BD Biosciences) were added to the tubes. Cells were washed and analyzed on a LSR flow cytometer using FACSDiva (both from BD). Using ModFit software (Verity Software House), proliferation indices (sum of the cells in all generations divided by the calculated number of original parent cells) were determined for CD4+ T cells (CD3+CD8-) in response to stimulation with VZV and anti-CD3/CD28.

2.6 Antibody levels to VZV

For quantitative detection of VZV-specific IgG antibodies, an in-house glycoprotein (gp) enzyme-linked immunosorbent assay (ELISA) was previously developed and validated [16]. VZV purified glycoproteins (EastCoastBio) were used as antigen, and pooled human serum with known levels of anti–glycoprotein VZV was used as standard. According to recommendations of Institut Virion/Serion, VZV-IgG levels from 50 to 100 mIU/ml were considered as equivocal, while values above 100 mIU/ml were considered positive.

2.7 Statistical analysis

Comparisons of continuous variables between patient and healthy control group, and within different subgroups of patients, were performed using the Mann-Whitney U test as the tested variables were found not to be normally distributed. A Kruskal-Wallis test was used when comparing more than two groups. Fisher's exact test was used to analyze gender distribution. For correlations, Spearman's rho was used.

Multiple regression analysis was used to assess effects of age, sex, renal replacement therapy modality, previous transplant and urea levels on VZV immunity in patients receiving RRT, using number of IFNγ spot-forming cells or VZV-IgG levels as the dependent variable. To meet assumptions for multiple regression analysis, results of the ELISpot assay were square root transformed and ELISA results (VZV-IgG) were logarithmically transformed.

Statistical analysis was performed using IBM SPSS Statistics 23 (IBM). Figures were made using GraphPad Prism 5.03 (GraphPad Software). P-values ≤ 0.05 (2-sided) were considered significant.

3. RESULTS

3.1 Study population

Characteristics of 97 included patients receiving RRT and 89 healthy controls are summarized in Table 1. There were no significant differences in age and gender between dialysis patients and controls ($p = 0.516$ and $p = 0.146$, respectively). Patients treated with peritoneal dialysis were significantly younger than those treated with hemodialysis (median 55.7 versus 69.5 years, $p = 0.004$) and also patients who previously received a transplant kidney were younger than patients who did not (median 47.0 versus 69.5 years, $p < 0.0001$). No significant differences in gender were found between these groups.

3.2 Similar cellular and humoral immunity to VZV in patients receiving RRT and controls

Similar numbers of IFNγ spot-forming cells per 2 x 10^5 PBMC in response to VZV stimulation were found in patients receiving RRT (median 52, interquartile range [IQR] 18-130) and matched healthy controls (median 55, IQR 20-133) ($p = 0.487$, Figure 1). Results were corrected for results in the negative control wells (median 20, IQR 10-49 and median 25, IQR 14-38 for patients and controls, respectively). Also, no differences were found when comparing results between subgroups with different causes of renal failure (data not shown).

Frequencies of CD4+ T cells producing cytokines upon stimulation were generally higher in patients receiving RRT than in healthy controls. A significant difference was seen for IL-2 in response to VZV ($p = 0.048$), while for TNFα a trend was observed ($p = 0.100$) (Figure 2A). As for polyclonal stimulation with SEB the difference between patients and controls was statistically significant for all three cytokines, the increased cytokine response in dialysis patients was not VZV-specific (Figure 2C). Upon stimulation of CD8+ T cells, no

significant differences in cytokine production were found between patients and controls (Figure 2B and 2D).

An equal capacity of CD4+ cells to proliferate in response to stimulation with VZV and in response to polyclonal stimulation was observed in a subgroup of 25 patients receiving RRT and 20 matched healthy control subjects. Also for CD8+ T cells no significant differences were found in proliferative capacity between patients and control subjects. However, a trend towards a higher response to polyclonal stimulation was observed in patients' cells (Figure 3).

The median VZV-specific IgG level was similar in patients receiving RRT (median 1694 mIU/ml, IQR 924-3767) and in healthy controls (median 1823 mIU/ml, IQR 1034-3002) ($p = 0.931$, Figure 4).

No correlation existed between humoral and cellular immunity to VZV (levels of VZV-IgG and the number of IFNγ spot-forming cells) (data not shown).

3.3 Variables of influence on VZV immunity in dialysis patients

After correcting for the effects of age and gender, a history of previous transplantation was associated with a lower number of IFNγ-spot forming cells (measure of VZV cellular immunity). Age itself was also shown to be negatively associated, meaning that higher age was associated with a lower cellular immunity to VZV. No significant effects were seen for treatment modality, gender or pre-dialysis urea level (Table 2).

The same variables (age, gender, history of previous transplant, treatment modality and pre-dialysis urea levels) did not significantly predict VZV-IgG levels as a measure of humoral immunity (p for the overall model = 0.578) (data not shown).

3.4 History of varicella and herpes zoster

None of the included patients and controls were vaccinated against varicella-zoster virus, which is in line with the absence of routine immunizations against varicella-zoster virus in The Netherlands. As all participants had positive VZV-IgG levels, all can be considered to have experienced a natural primary VZV infection earlier in life.

Questionnaire results (asking about varicella and herpes zoster history) were available for 90 (93%) patients receiving RRT and for 31 (35%) healthy controls subjects. Thirteen patients reported a positive herpes zoster history, and for one extra patient (reporting a negative history) notes on herpes zoster were found in medical records. One patient experienced herpes zoster 10 months before study participation, for 3 it was at least 7 years ago, and 9 could not remember the timing nor were notes found in medical records.

Four healthy control subjects stated to have a positive herpes zoster history. In 3 of them, herpes zoster occurred at least 15 years before participating in the study, while one stated to have experienced herpes zoster only a few months before participating in the study. In this control a very high VZV-IgG of >30,000 mIU/ml was found, while the number of 18 IFNγ spot-forming cells in response to VZV stimulation was below average. No increased levels of humoral and cellular immunity to VZV were found in patients and the other control subjects with a positive herpes zoster history (data not shown).

4. DISCUSSION

An increased risk of herpes zoster in patients receiving long-term renal replacement therapy is acknowledged, but to date the underlying mechanism remains unclear [10-12]. In contrast to our hypothesis, in the present study we found cellular and humoral immunity to VZV to be similar in patients receiving RRT and matched healthy controls. Multiple regression analysis revealed that both age and transplant history were negatively associated with VZV-specific cellular immunity, while gender, urea level and dialysis modality were not found to be significantly associated. None of all these variables were found to be significantly associated with humoral immunity to VZV.

By performing a VZV-specific IFNγ ELISpot assay, we showed that PBMC of patients receiving RRT and healthy controls are equally capable to respond to stimulation with VZV. VZV-specific CD4+ T cells, the main producers of IFNγ in PBMC culture, are of special importance to keep the latently present VZV in check [18, 19]. Previously we demonstrated a decreased cellular immunity to VZV in SLE patients [16], while other research groups reported similar findings for other patient groups at risk for herpes zoster, including transplant recipients, diabetes mellitus patients and HIV-infected patients [20-22].

The results of a multivariable analysis of cellular immunity to VZV in patients receiving RRT for the most part are in line with previous reports. Firstly, advanced age is a well-known risk factor for herpes zoster, corresponding with decreased levels of VZV-specific cellular immunity in the elderly [23]. Secondly, the negative effect of a previous transplantation on cellular immunity to VZV is in accordance with the increased herpes zoster incidence in renal transplant recipients. This increased incidence can be explained by intensive use of immunosuppressant medication, which is elevated even further in case of treatment with anti-rejection therapy [24].

Gender, serum urea levels and dialysis modality were not found to be of significant influence on VZV immunity in multivariable analysis. Serum urea levels were added to the analysis as uremia is considered to be a causative factor of the immune dysfunction in patients receiving RRT [7, 9]. In our analysis the effect of serum urea could have been missed because only pre-dialysis urea levels were taken into account, disregarding dialysis efficiency and fluctuations of serum urea levels within patients. Furthermore, the range of urea levels was limited, as only patients receiving RRT were included in the analysis. All of these patients have urea levels above the normal range.

As stated, we also did not find a significant effect of treatment modality on VZV immunity. Lin et al. observed a higher herpes zoster incidence in patients treated with peritoneal dialysis compared to those treated with hemodialysis, also when adjusting for important risk factors including age and the use of immunosuppressants [12]. This was recently confirmed by Tseng et al.[13]. Apparently, the higher herpes zoster incidence in peritoneal dialysis patients does not seem to be caused by intrinsic differences in the humoral and cellular immunity to VZV.

Although ELISpot is generally regarded to be a sensitive method of studying T cell immunity [25, 26], it does not allow for phenotypical discrimination of individual cytokine producing cells. Therefore, we also performed analyses of T cell cytokine production by flow cytometry. For CD8+ T cells, no significant differences in cytokine production were observed between patients and controls. Similar frequencies of IFNγ producing CD4+ T cells in patients receiving RRT and controls were found in response to VZV stimulation, confirming the ELISpot results. The median frequencies of TNFα and IL-2 producing CD4+ cells were slightly higher in patients receiving RRT, which was only significant for IL-2. This phenomenon does not seem to be VZV-specific, as in response to polyclonal stimulation for all three tested cytokines increased percentages of positive cells were seen in the group of

patients receiving RRT. An increased production of cytokines is a well-known feature of patients with end-stage renal disease, which is thought to result from (but also to add to) the pro-inflammatory state caused by uremia [7, 9].

Because of the possibly distorting effect of hypercytokinemia in patients receiving RRT, we also wanted to study cellular immunity to VZV with a test that is not based on cytokine production. Therefore, we performed a CD4+ T cell proliferation assay. Although previously the proportion of spontaneously preactivated CD4+ T cells was found to be high, proliferative capacity after phytohaemagglutinin stimulation was shown to be blunted in patients receiving RRT [27]. However, in the current study we did not find differences between patients and controls in the proliferative capacity of CD4+ T cells in response to VZV stimulation.

Strengths of our study include the substantial sample size allowing for multivariable analysis and the exclusion criteria used, including (recent) use of immunosuppressant drugs and an autoimmune rheumatic disorder as cause of renal failure. This way, we aimed to reduce confounding influences and to study the intrinsic influence of long-term RRT on immunity to VZV.

The study also has several limitations. Self-reporting of varicella and herpes zoster did not seem completely reliable, with at least 1 patient not reporting a herpes zoster episode that was noted in medical records. Herpes zoster also does not necessarily come to medical attention. As herpes zoster incidence in this study could easily be underestimated, we did not provide incidence numbers. Some of the high VZV-IgG levels in patients receiving RRT may be caused by unreported herpes zoster episodes or may be the consequence of an asymptomatic endogenous viral reactivation, as Smetana et al. previously noted to occur in patients receiving RRT [28].

Another limitation is the lack of more detailed information on general lymphocyte counts and subsets. Only for 37 patients total lymphocyte counts were available, which were within normal limits. However, loss of renal function is associated with a decline in total T cell numbers [7]. Although this mostly affects the naïve T cell and to a lesser degree the memory T cell compartment [7], a decreased number of T cells, which remained uninvestigated in the current study, could contribute to higher herpes zoster susceptibility.

Despite its limitations, the findings presented in this study are important for better understanding herpes zoster susceptibility in patients receiving RRT. Understanding the mechanism underlying the susceptibility may lead to new approaches of herpes zoster prevention in these patients.

As we did not find evidence for impaired humoral or cellular immunity to VZV in patients receiving RRT, another explanation for the increased herpes zoster risk in these patients has to be present. Absence of defects in humoral or cellular immunity in our study might be explained by a different performance of T cells in an *in vivo* uremic environment, while no intrinsic defects are present. Another possible explanation is that the increased herpes zoster risk in patients receiving RRT is for a large part attributable to underlying immunosuppressive conditions or medication use that were excluded in the current study, or by the generally advanced age of these patients. Of note, future clinical studies should keep in mind that an IFNγ ELISpot assay of VZV immunity may not correspond with herpes zoster risk in patients receiving RRT.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interests to disclose.

TABLES

Table 1. Baseline characteristics of patients and controls

	HC n=89	**RRT** n=97
Female gender, no. (%)	50 (56)	44 (45)
Age, median (range) years	64.1 (25.3-82.1)	66.3 (24.9-91.0)
Cause of renal failure, no. (%)	NA	
Vascular		19 (20)
Diabetic nephropathy		15 (15)
Genetic		13 (13)
Glomerulonephritis		24 (25)
Urologic		8 (8)
Congenital		1 (1)
Unknown		17 (18)
RRT modality, no. (%)	NA	
Haemodialysis		76 (78)
Peritoneal dialysis		21 (22)
Duration of RRT, median (range) months[a]	NA	33 (5-140)
Previous kidney transplant, no. (%)	NA	18 (18)
Time since restart RRT, median (range) months		36 (10-203)
Pre-dialysis serum levels, median (IQR)	NA	
Leukocytes, $x10^9$ cells/l		7.3 (6.3-8.7)
Lymphocytes[b], $x10^9$ cells/l		1.8 (1.3-2.1)
Urea, mmol/l		20.8 (17.1-26.3)

Albumin, g/l	40 (35-43)

HC: healthy controls, RRT: renal replacement therapy, IQR: interquartile range

[a] In patients without history of kidney transplantation

[b] Data on lymphocyte count were only available for 37 patients

Table 2. Multiple regression analysis of (square root transformed) number of IFNγ spot-forming cells in response to VZV stimulation

Variable	B (95% CI)	(Standardized) Beta	p-value
Age (years)	**-0.114 (-0.186- -0.038)**	**-0.385**	**0.003**
Gender (female versus male)	1.657 (-0.288-3.602)	0.173	0.094
Previous Tx	**-3.575 (-6.434- -0.716)**	**-0.301**	**0.015**
RRT modality (PD versus HD)	-2.282 (-4.793-0.230)	-0.203	0.074
Duration of RRT (months)	-0.130 (-0.045-0.018)	-0.093	0.398
Urea serum level (mmol/l)	0.093 (-0.051-0.237)	0.143	0.203

Note: Adjusted R^2 = 0.110, significance of overall model: p=0.015. IFNγ: interferon-γ, CI: confidence interval, Tx: transplantation, RRT: renal replacement therapy, PD: peritoneal dialysis, HD: hemodialysis. B and Beta give an indication of the relative size of the effect of a variable

FIGURES LEGENDS

Figure 1. Numbers of interferon-γ (IFNγ) spot-forming cells in response to VZV stimulation in 80 healthy control (HC) subjects and 97 patients receiving renal replacement therapy (RRT). Lines show the median.

Figure 2. Frequencies of cytokine producing CD4+ (**A**) and CD8+ (**B**) T cells upon stimulation with varicella-zoster virus (VZV), and upon stimulation with staphylococcal enterotoxin B (SEB, positive control) (**C** for CD4+ and **D** for CD8+ T cells) in 80 healthy control subjects (HC) and 97 patients receiving renal replacement therapy (RRT). Bars show the median and interquartile range. IFNγ = interferon-γ; TNFα = tumor necrosis factor α; IL-2 = interleukin-2.

Figure 3. Proliferation indices of CD4+ (A and B) and CD8+ (C and D) T cells in response to varicella-zoster virus (VZV) and polyclonal stimulation using anti-CD3/CD28 in 20 healthy control (HC) subjects and 25 patients receiving renal replacement therapy (RRT). Lines show the median.

Figure 4. Levels of IgG antibodies directed against varicella-zoster virus (VZV) glycoprotein (gp) in 89 healthy control (HC) subjects and 97 patients receiving renal replacement therapy (RRT) presented on a log-scale. Lines show the median.

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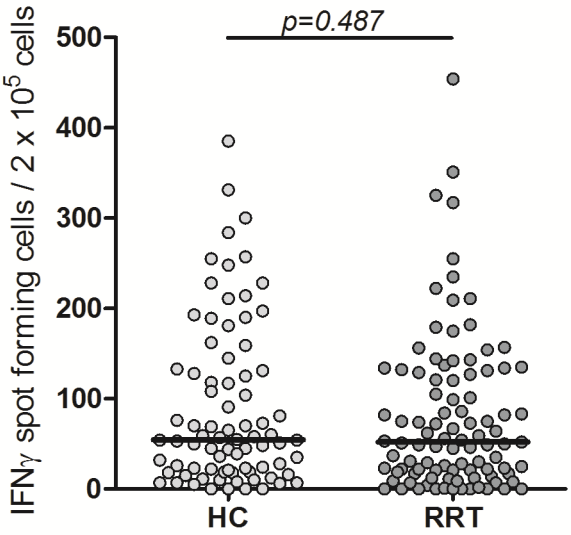
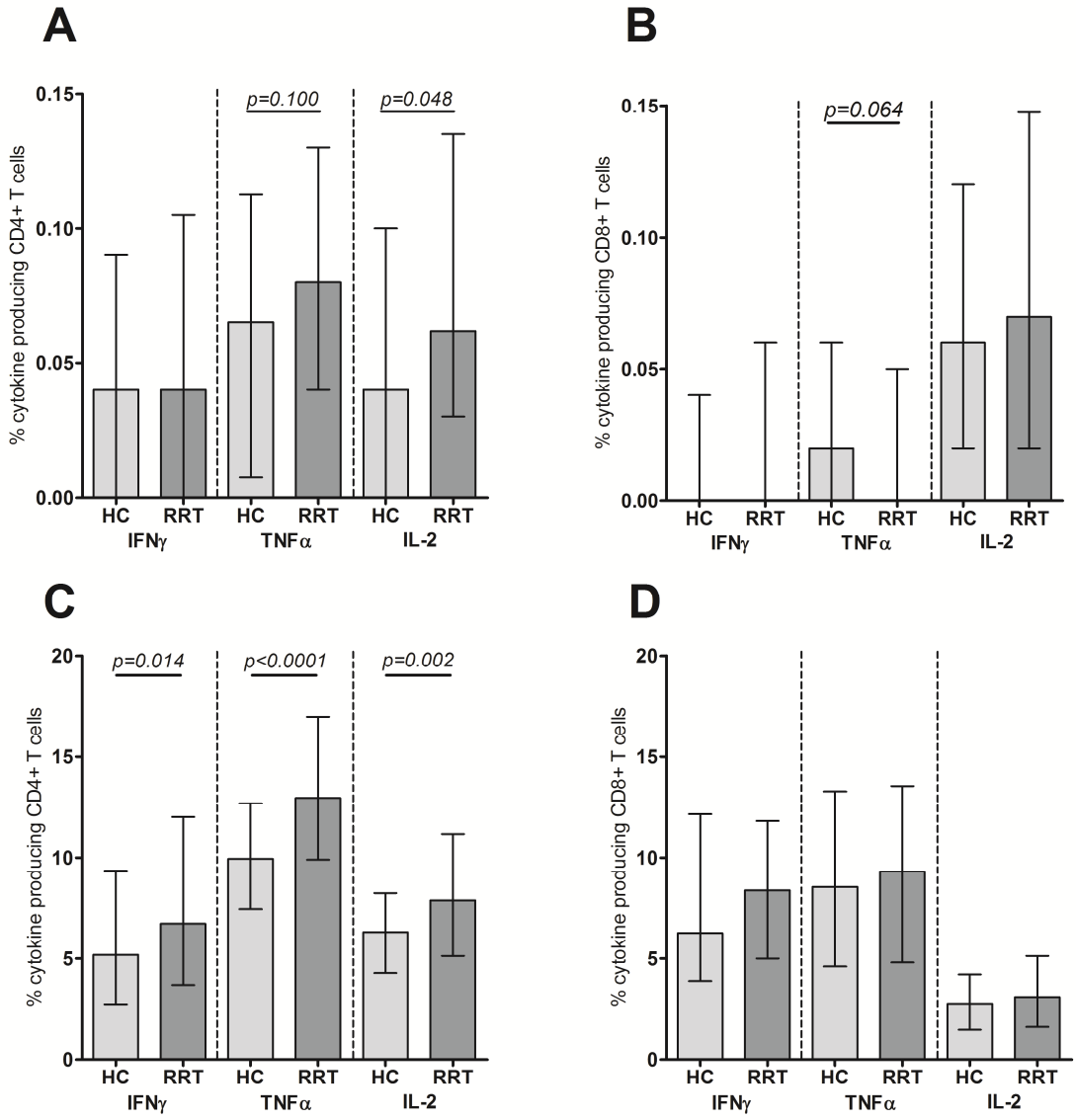
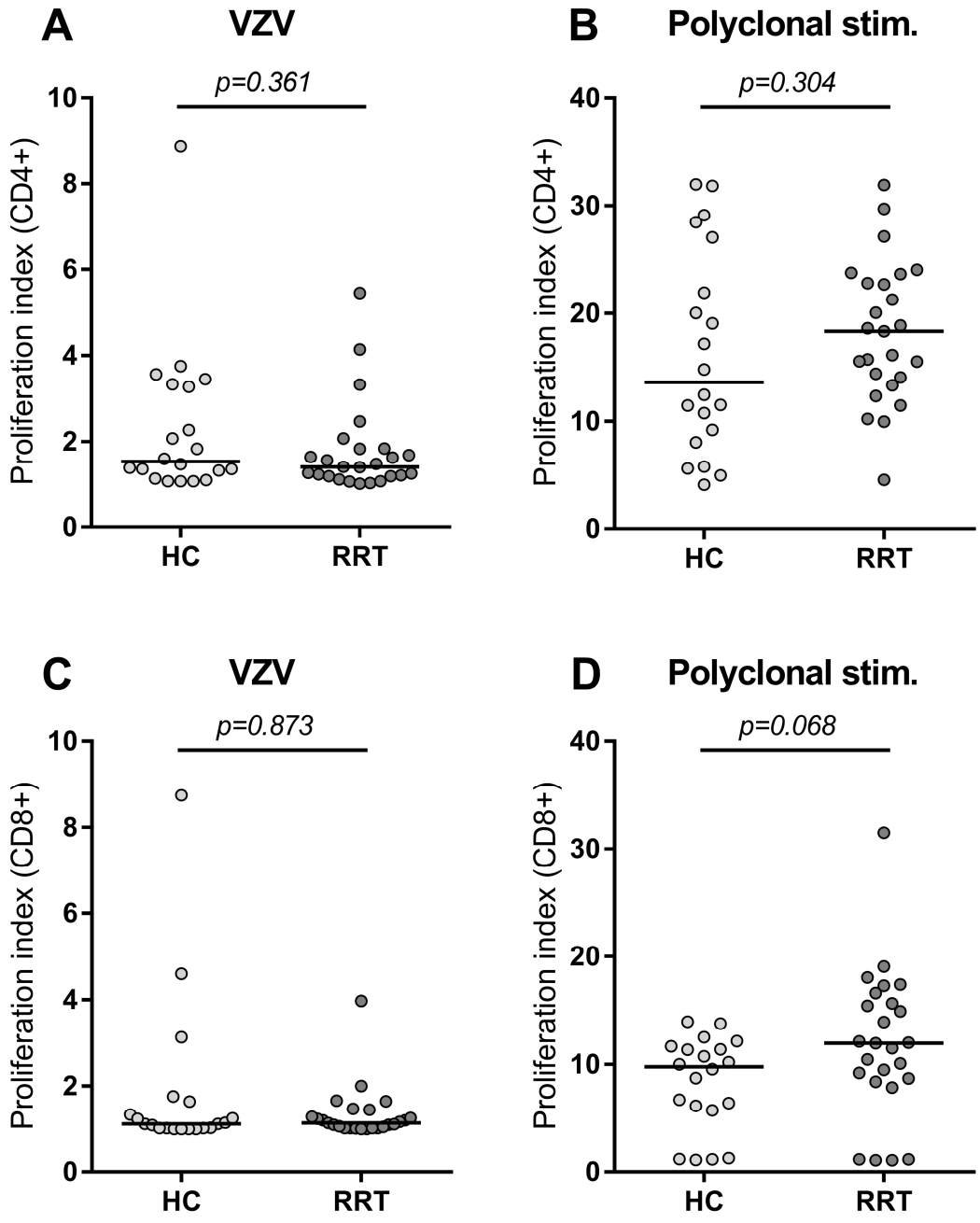
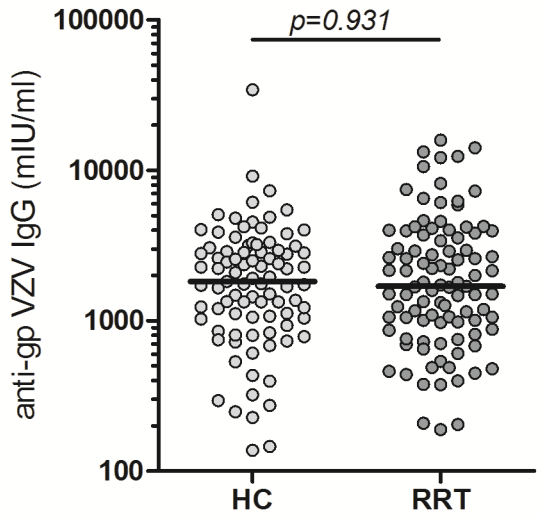



A
B
C
D
% cytokine producing CD4+ T cells
% cytokine producing CD8+ T cells
p=0.100
p=0.048
p=0.064
p=0.014
p<0.0001
p=0.002
HC
RRT
IFNγ
TNFα
IL-2


A
VZV
p=0.361
Proliferation index (CD4+)
0
2
4
6
8
10
HC
RRT
B
Polyclonal stim.
p=0.304
Proliferation index (CD4+)
0
10
20
30
40
HC
RRT
C
VZV
p=0.873
Proliferation index (CD8+)
0
2
4
6
8
10
HC
RRT
D
Polyclonal stim.
p=0.068
Proliferation index (CD8+)
0
10
20
30
40
HC
RRT



Highlights

Rondaan et al. Increased incidence of herpes zoster in patients on renal replacement therapy cannot be explained by intrinsic defects of cellular or humoral immunity to varicella-zoster virus

- Immunity to varicella-zoster virus (VZV) was investigated in renal replacement therapy (RRT) treated patients and controls
- No intrinsic defects of humoral and cellular immunity to VZV were found in patients compared to controls
- Higher age and a previous transplantation are associated with lower VZV specific cellular immunity in patients
- Cytokine production of CD4+ T cells was higher in patients than in controls