Original Paper

Increased Proportion of Circulating T Follicular Helper Cells and Serum Levels of IL-21 in Antibody-Mediated Rejection of Renal Allograft

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Introduction. Antibody-mediated rejection (AMR) is one of the major obstacles to successful kidney transplantation. The T helper cell subset that plays a key role in the activation of B-lymphocytes and antibody production is T follicular helper (Tfh) cell. Therefore, we aimed to compare the percentage of Tfh cells and the serum level of interleukin 21 (IL-21), mainly secreted by this subset, in patients with AMR and stable recipients.

Methods. Peripheral blood samples were taken from 30 patients diagnosed with AMR and 30 stable kidney transplant recipients as well as 10 age- and sex-matched healthy individuals. The percentage of circulating Tfh cells (TCD4+CXCR5+PD1+) and the level of IL-21 were studied by flow cytometry and ELISA techniques, respectively.

Results. The proportion of cTfh cells among circulating TCD4+ cells in AMR patients was markedly elevated compared to the other groups ($P < .0001$). It was also higher in stable recipients than in healthy controls ($P < .0001$). The serum level of IL-21 was increased in AMR patients compared to stable recipients ($P = .03$) and healthy participants ($P = .02$). In addition, there was a significant negative correlation between cTfh percentage and the estimated glomerular filtration rate (eGFR) in transplanted patients ($P = .001$). Moreover, the AUC of cTfh cells in AMR diagnosis was 0.83 [95% CI 0.73-0.93 ($P < .0001$)].

Conclusion. In AMR patients, cTfh cell percentage and IL-21 levels were significantly increased. The significant association between cTfh % and eGFR, with an AUC of 0.83, indicates its potential as a diagnostic and prognostic marker in AMR.

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INTRODUCTION

In recent years, kidney transplantation has been considered as a standard treatment for patients with end-stage kidney disease (ESKD); however, allosensitization and donor-specific antibody (DSA) production resulting in acute antibody-mediated rejection (AMR) continue to pose significant challenges to long-term graft survival. Moreover, the persistent presence of DSAs and repeated episodes of AMR might lead to chronic allograft nephropathy. The problem get worse in sensitized patients particularly those undergoing

second or third kidney transplants.[1] T follicular helper (Tfh) cells are a subset of CD4+ T cells required for germinal center formation and B cell responses.[2] The role of this subset in antibody-mediated disorders such as allergies, infectious and autoimmune diseases as well as vaccine responses is under study.[3] B-lymphocytes play the major role in developing AMR,[4] but the implication of T helper cells, in particular Tfh cells has to be elucidated in the immunopathogenesis of AMR.

One of the main cytokines produced by Tfh cells is interleukin-21 (IL-21). IL-21 is a pleiotropic cytokine secreted by a variety of immune cells, affecting different subtypes, including T, B, natural killer (NK), and dendritic cells (DCs).[5] IL-21 not only mediates the germinal center formation in lymph nodes but also is involved in the differentiation and function of Tfh cells.[6] In recent years, the role of IL-21 in alloimmune responses has been investigated and the findings were suggestive of its implication in graft rejection.[7] A cohort study has demonstrated that the expansion of circulating Tfh (cTfh) cells was associated with a higher risk of developing anti-HLA donor-specific antibodies, graft rejection, and deteriorated graft function.[8] It was also shown that the frequency of circulating CD4+CXCR5+IL-21+ Tfh cells, and serum level of IL-21 were positively correlated with serum creatinine levels and negatively correlated with the eGFR in the patients diagnosed with AMR.[9] Results of one study showed a significant association between the pre-transplant presence of donor-reactive IL-21-producing cells and the development of acute rejection after transplantation.[10] Moreover, a recent study reported increased proportions of cTfh and memory B cells at the onset of AMR, which was associated with serum creatinine levels.[11]

Therefore, quantification and function assay of Tfh cells seem necessary for monitoring and treating antibody-mediated complications after transplantation.[12] In this study, we aimed to compare the percentage of cTfh cells and IL-21 concentrations among stable recipients and patients diagnosed with AMR.

MATERIALS AND METHODS

The study participants

The peripheral blood samples were collected from 30 patients (46.9 ± 13.8-year-old, male to female: 17:13) with acute antibody-mediated kidney transplant rejection (18 biopsy-proven and 12 with clinical AMR diagnosis) before the initiation of treatment. Next, besides, 30 age- and sex-matched stable allograft recipients were recruited and 10 healthy people were included as the basic control group. Clinical criteria for the diagnosis of acute AMR included increased serum creatinine, oliguria or anuria, and positive anti-HLA antibody tests. Pathological criteria of acute AMR (according to the latest update of 2019 Banff) were microvascular inflammation, linear C4d staining in peritubular capillaries, intimal or transmural arteritis, acute thrombotic microangiopathy, and acute tubular injury in the absence of any other apparent causes.[13]

The sampling took place at three hospitals (Labbafinezhad, Imam Khomeini, and Shohadaye-Tajrisj) in Tehran, Iran, between 2021 and 2024. The patients with a medical history of autoimmune disorders, allergies, malignancies, or active infection were excluded from the study. All the study participants gave their informed written consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki, and the study protocol was approved by the Ethics Committee of the Tehran University of Medical Sciences (IR.TUMS.CHMC.REC.1401.024).

Peripheral blood mononuclear cells isolation and Flow Cytometry

Peripheral blood mononuclear cells (PBMCs) were isolated via density gradient centrifugation over Ficoll-Hypaque and diluted to 10^6 cells/ml. PBMCs were stained with mouse FITC anti-human CD4 conjugated Antibody (Zistfanavaran, Iran), mouse PE/Cy5 anti-human CXCR5 conjugated Antibody (Biolegend, United Kingdom), and mouse PE anti-human PD-1 conjugated Antibody (Biolegend, United Kingdom). After delineating the lymphocyte region, CD4+ cells were gated, the CXCR5+PD1+ population was selected within the TCD4+ cells, and the RUQ segment was considered circulating T follicular cells. Flow cytometry was performed with FACSCalibur (BD FacsCalibur Becton Dickinson, USA) and data were analyzed using FlowJo v10.7 (FlowJo, USA) software.

ELISA test

The serum level of IL-21 was measured with a Human IL-21 ELISA Kit (Zellbio, Germany). The

reagents, samples, and standards were prepared according to the manufacturer's instructions. Fifty microliters of standard or sample (including 40 microliters of sample serum plus 10 microliters of anti-IL-21 antibody) were added to the corresponding wells. Only anti-IL-21 antibody was added to the control blank well. Then streptavidin HRP was added to all wells. The plate was sealed and incubated at 37 degree C for one hour. In the next step, the plate was washed five times with 300 microliters of the washing solution and then 100 microliters of chromogen were added. After 10 minutes of incubation, 50 microliters of stop solution was added and ODs were read at a wavelength of 450 nm using Hiperion MPR4++ Microplate Reader (Medizintechnik GmbH & Co.KG Germany). The concentrations were determined according to the standard curve. The detection range of the kit was 10-1000 pg/ml.

Statistical Analysis

SPSS software (SPSS 26.0; SPSS Inc., Chicago, USA) was used for statistical analysis. Data was presented as mean ± standard deviation (SD). The Kolmogorov-Smirnov test was performed to determine the distribution normality between groups. To compare the quantitative variables between three groups the Kruskal-Wallis H test and for comparison between two groups, the Mann-Whitney U tests were used. Pearson correlation and correlation coefficient (R^2) were applied to investigate the correlation between quantitative variables. P-values less than 0.05 were considered significant.

RESULTS

Clinical and paraclinical data of the studied population

The age range of the studied population was 47.1 ± 10.6 years. There was a significant difference in creatinine levels, blood urea nitrogen (BUN), and estimated glomerular filtration rate (eGFR) among the groups ($P < .0001$). The transplantation duration in the AMR group and stable patients were 4.33 ± 2.7 and 3.8 ± 2.2 years, respectively, which did not differ significantly ($P = .8$). All cases underwent their first transplantation. Seventeen of the 60 patients received transplants from living donors, while 43 received transplants from deceased donors. While living donors were more prevalent among stable recipients (n = 10) than in AMR patients (n = 7), the difference was not statistically significant ($P = .3$). Twenty-three out of 30 (76.6%) AMR patients had anti-HLA-I antibodies whereas 11 (36.6%) of stable recipients were anti-HLA-I antibody positive ($P < .0001$). Anti-HLA-II antibodies were detected in 19 (63.3%) AMR patients compared to seven (23.3%) of stable

Table 1. Clinical and laboratory data of AMR patients, stable recipients, and healthy controls

Group	AMR	Stable Recipients	Healthy Controls	*P*
Number	30	30	10	-
Age (year)	46.9 ± 13.8	44.4 ± 12.1	48.8 ± 6.7	NS
Gender Ratio (M:F)	17:13	17:13	6:4	NS
Creatinine (mean ± SD)	2.56 ± 0.94	1.23 ± 0.21	0.89 ± 0.07	< .0001
BUN (mean ± SD)	42.9 ± 15.5	30.7 ± 8.4	14.8 ± 3.2	< .0001
eGFR (mean ± SD)	28.3 ± 8.7	67.5 ± 15.9	97.9 ± 5.1	< .0001
TX years (mean ± SD)	4.33 ± 2.7	3.8 ± 2.2	-	NS
Donor type				
LD	7	10	-	NS
BD	23	20		
Anti-HLA-I Abs	23 (76.6%)	11 (36.6%)	2 (6.6%)	< .0001
Anti-HLA-II Abs	19 (63.3%)	7 (23.3%)	0	< .0001
Anti-HLA-I and II Abs	16 (53.3%)	5 (16.6%)	0	< .0001
IS protocol				
Cyclo/Myco/Pred	4	2	-	
Tac/Myco/Pred	22	25		
Aza/Cyclo/Pred	1	0		
Tac/Rap/Pred	5	3		

AMR: antibody-mediated rejection; eGFR: estimated glomerular filtration rate; TX: transplantation; LD: living donor; BD: brain-dead donor; IS: immunosuppressive; Cyclo: Cyclosporine; Tac: Tacrolimus; Myco: Mycophenolate; Pred: Prednisone; Aza: Azathioprine; Rap: Rapamycin; Ever: Everolimus

patients ($P < .0001$). Sixteen patients in the AMR group had both anti-HLA I and II antibodies but only five in the stable group had both types ($P < .0001$). Two out of 10 healthy individuals had anti-HLA-I antibodies (6.6%) both of which were multiparous women. The presence and levels of donor-specific antibodies have not been checked for the patients because it is not the routine test of the study research centers. The general data of the three groups have been presented in Table 1.

Increased percentage of the circulating T follicular helper cells in the AMR group

The percentage of circulating T follicular helper cells defined as CXCR5+PD1+ population within the TCD4+ cells showed a significant difference between patients with AMR patients, stable recipients, and healthy controls ($P < .0001$) [10 ± 5.4 (mean ± SD)

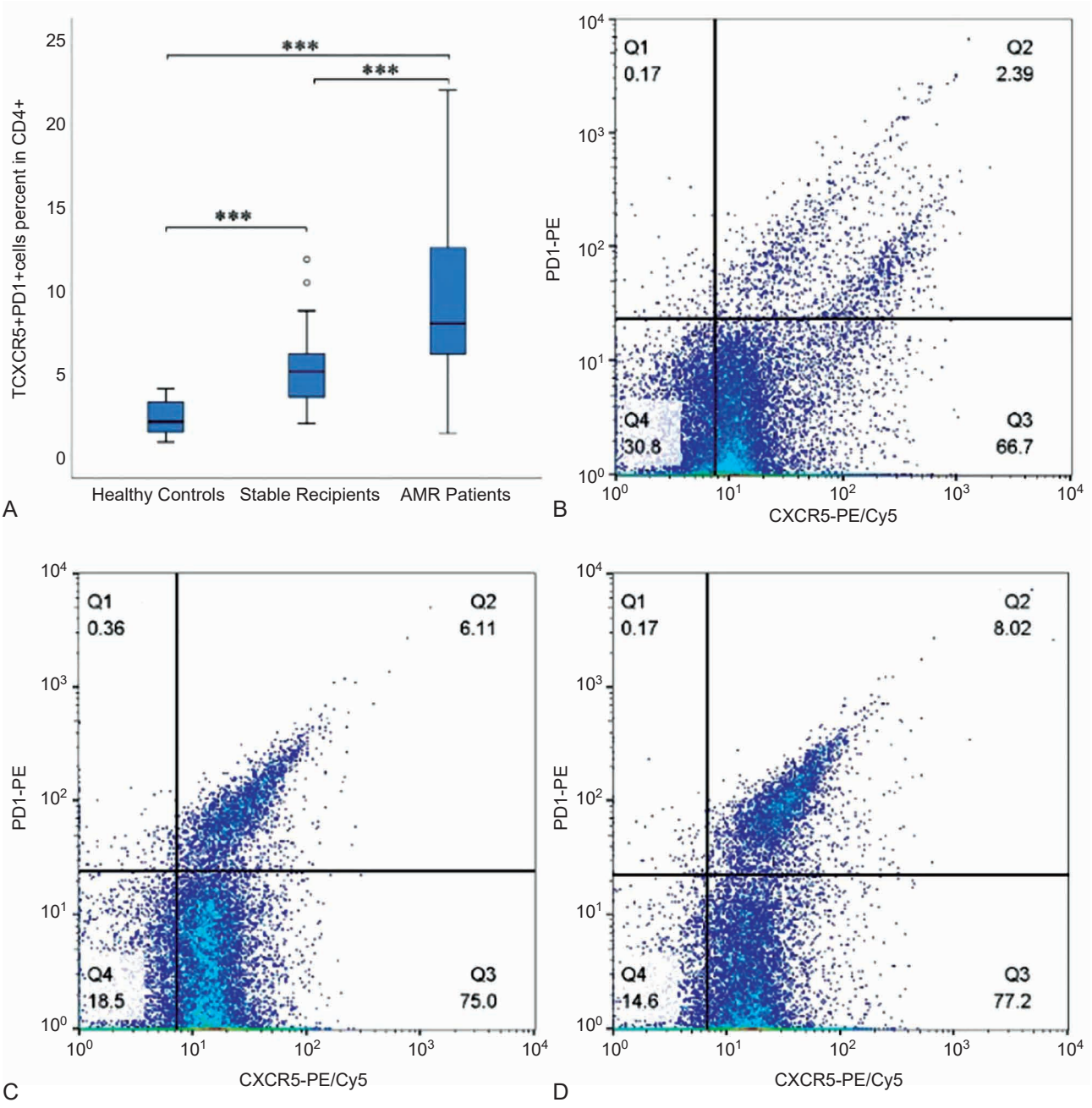

Figure 1. (A) increased percentage of circulating TCD4+CXCR5+PD1+ cells in AMR patients, and stable recipients compared to healthy controls (***: $P < .0001$). (B) CXCR5+PD1+ cells percent in CD4+ population of a healthy individual. (C) CXCR5+PD1+ cells percent in CD4+ population of a stable recipient. (D) CXCR5+PD1+ cells percent in CD4+ population of a patient diagnosed with AMR.

in antibody-mediated rejection vs. 5.17 ± 2.4 in stable recipients and 2.22 ± 1.14 in healthy controls]. CTfh cell frequency was increased in AMR patients compared to the stable recipients ($P < .0001$) and healthy controls ($P < .0001$). Noteworthy, cTfh cell percentage was also significantly higher in stable patients than in healthy individuals ($P < .0001$) (Figure 1).

Increased serum levels of interleukin-21 in AMR patients

Comparison of IL-21 serum levels among the three groups of AMR patients, stable recipients, and healthy controls showed a significant difference between groups [38.9 ± 32.3, 21.2 ± 16.4, 15.9 ± 10.3 pg/ml (mean ± SD), respectively ($P = .024$)]. IL-21 was significantly increased in patients with rejection compared to stable recipients ($P = .03$) and healthy individuals ($P = .02$). However, no statistically significant difference was observed between stable patients and the control group (Figure 2).

Significant correlation between cTfh percentages and eGFR in kidney transplant recipients

The percentage of TCD4+CXCR5+PD1+ cells showed a significant negative correlation with renal allograft function, defined with eGFR in kidney transplant recipients (including both AMR and stable groups) [(Pearson Correlation: -0.43, Correlation Coefficient: -0.18) ($P = .001$)] (Figure 3).

Negative correlation between IL-21 levels and eGFR in kidney transplant recipients

The assessment of the correlation between IL-21 levels and the glomerular filtration rate of the patients revealed a significant negative association; nonetheless, it was not statistically significant [(Pearson Correlation: -0.25, Correlation Coefficient: -0.063) ($P = .053$)] (Figure 4).

Correlation between cTfh cells and serum levels of IL-21

Regression analysis showed a significant correlation between cTfh percentages and serum levels of IL-21 in kidney transplant recipients, including both stable and AMR groups [(Pearson Correlation: 0.59, Correlation Coefficient: 0.34) ($P < .0001$)] (Figure 5).

Diagnostic value of cTfh and IL-21 in antibody-mediated rejection

ROC curve analysis showed a significant diagnostic value for cTfh cells in AMR patients with an AUC of 0.83 [95% confidence interval (CI) 0.73-0.93 ($P < .0001$)]. IL-21 levels showed a lower AUC value of 0.64 [95% CI 0.5-0.78 ($P = .038$)] (Figure 6).

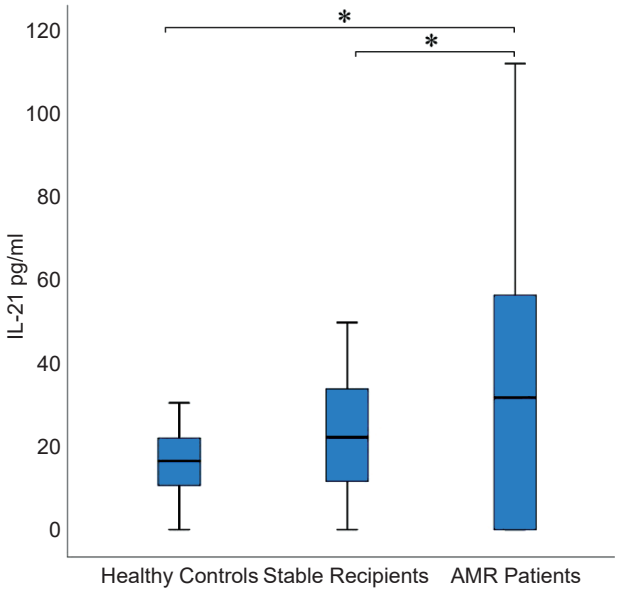

Figure 2. Increased serum levels of IL-21 in patients with antibody-mediated rejection compared to stable recipients ($P = .03$) and healthy individuals ($P = .02$).

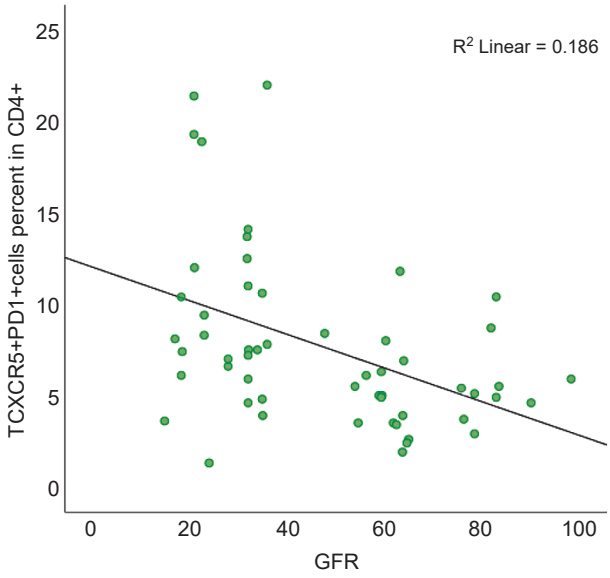

Figure 3. Significant correlation between the percentage of circulating follicular T cells and eGFR in kidney transplant recipients ($P = .001$).

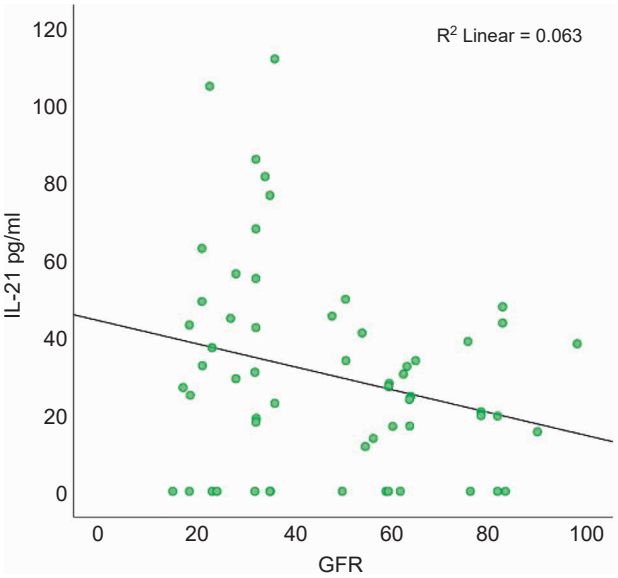

Figure 4. Negative correlation between serum level of IL-21 and glomerular filtration rate in kidney transplant recipients.

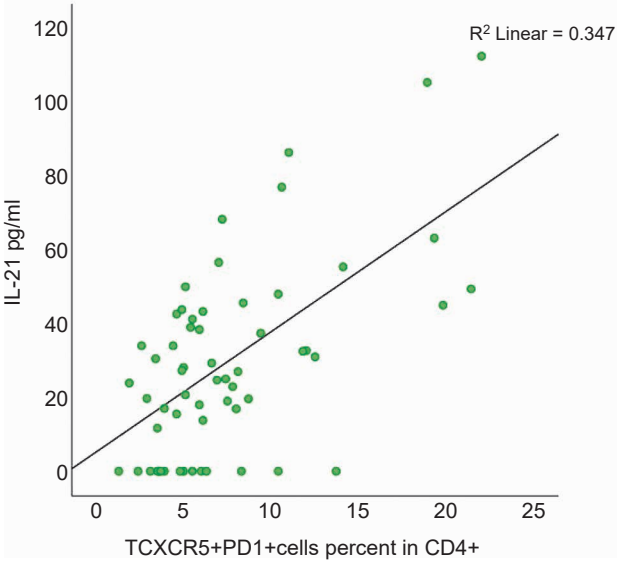

Figure 5. Significant correlation between the percentage of cTfh cells and the serum level of IL-21 in kidney transplant recipients ($P < .0001$).

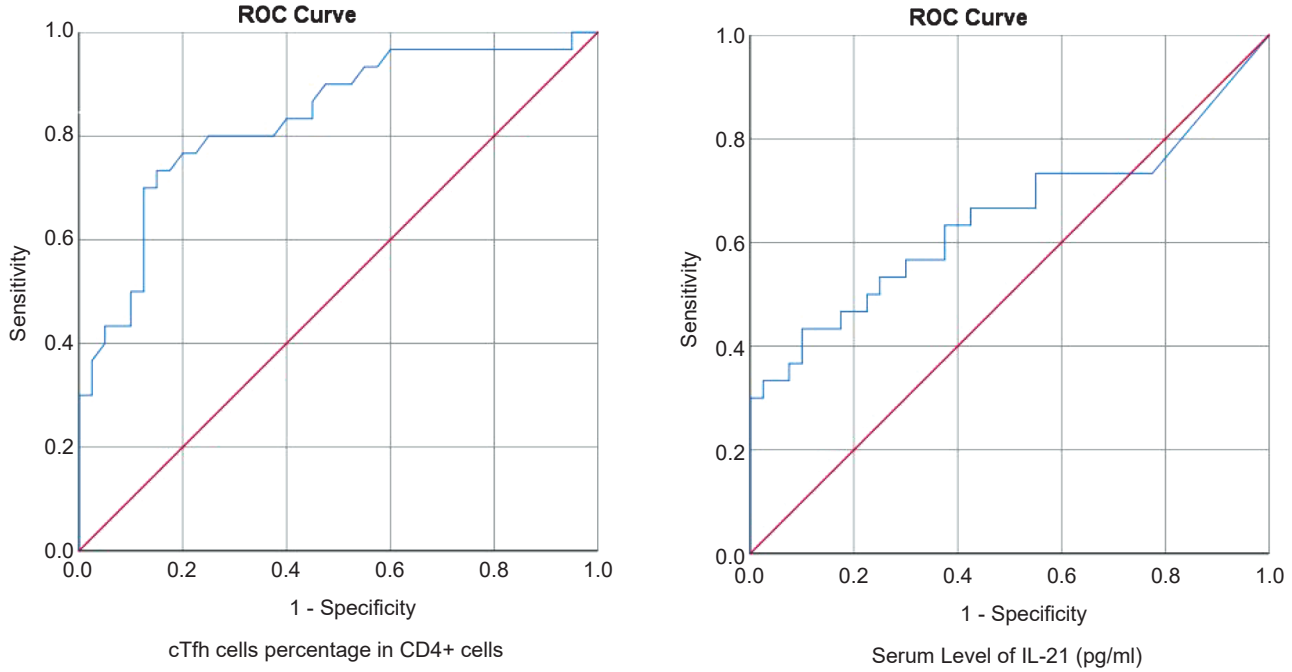

Figure 6. Diagnostic value of cTfh cells ($P < .0001$) and the serum level of IL-21 ($P = .038$) in antibody-mediated rejection

DISCUSSION

T helper follicular cells are the specialized and heterogeneous subset of T helper cells that promote B cell responses in the lymphatic tissue. In response to infectious diseases or vaccination, the interaction between Tfh and B cells mainly results in the production of protective antibodies and humoral immunity memory.[3] However, in transplantation, immune surveillance provided by Tfh cells might put transplant recipients at risk of subclinical or clinical rejection as stimulation of Tfh with non-self HLA and non-HLA antigens might induce antibody-mediated rejection through B cell activation and donor specific antibody (DSA) secretion.[12]

Acute antibody-mediated rejection (AMR) of

renal allograft is a relatively common complication following transplantation that might lead to chronic allograft dysfunction and irreversible tissue damage; nonetheless, there are ambiguities in the underlying mechanism of AMR that need to be elucidated.[14] T follicular helper (Tfh) cells are a subset of TCD+ helper lymphocytes involved in antibody-mediated immune responses. Tfh cells are recruited to the B-lymphocyte zone (containing CXCL13) of lymphoid organs via expression of chemokine receptor CXCR5. T-cell inducible co-stimulatory molecule (ICOS) and programmed cell death protein 1 (PD-1) are also expressed by Tfh cells.[4] Considering the expression of other chemokine receptors, Tfh cells are classified into further subsets such as Tfh1 (CXCR3+CCR6-) and Tfh2 (CXCR3-CCR6) and Tfh17 (CXCR3-CCR6+) cells, suggesting a wide range of function for these cells.[15]

Louis *et al.* investigating kidney transplant recipients with DSA and antibody-mediated rejection showed that the total proportion of cTfh cells in AMR patients was significantly increased and these cells were able to activate B-lymphocytes and stimulate DSA production.[16] Moreover, Chen's study showed that the proportion of Tfh2 cells and Tfh17 as well as IL-21 expression was remarkably increased in AMR patients.[17] Other research reported higher percentages of circulating CXCR5+ICOS+Tfh cells in transplant recipients than in healthy individuals, which further increased during AMR episodes.[18,19] Nonetheless, Shi *et al.* observed increased expression of PD-1 on Tfh cells from patients with chronic kidney rejection whereas, Inducible T-cell co-stimulator (ICOS) did not show a significant difference compared to stable recipient cells, nor did IL-21 serum levels.[20] Recently, in a cohort study, Desy *et al.* showed that CD4+CXCR5+ cells were mostly PD1+ and were in close contact with B cells in lymphatic tissues. In addition, the expansion of cTfh cells was associated with a higher risk of anti-HLA DSA development and allograft rejection.[8] Similarly, Liu *et al.* found an increased number of circulating CD4+CXCR5+, CD4+CXCR5+ICOS+, CD4+CXCR5+PD-1+, CD4+CXCR5+IL-21+ Tfh cells in acute cellular and antibody-mediated rejections as well as chronic rejection of renal allograft. Furthermore, the number of CD4+CXCR5+IL-21+ cTfh cells was negatively associated with GFR in patients diagnosed with AMR.[9] Our study demonstrated a significant increase in CXCR5+PD1+ cTfh cell proportion of TCD4+ cells in patients with acute antibody-mediated rejection. Of note, cTfh cell percentage was also significantly higher in stable patients compared to healthy individuals, due to a subclinical alloimmune activation of Tfh cells in recipients and the presumable resistance of this subset to conventional immunosuppressive regimens.

In addition to IL-4 and chemokine ligand 13 (CXCL13), IL-21 is one of the main cytokines produced by Tfh cells.[21] The role of IL-21 in allograft rejection has also been studied, indicating higher serum levels of this cytokine in patients with rejection, which was negatively correlated with graft function.[9] Rojas *et al.* investigated 114 renal transplant recipients before transplantation and found a higher number of IL-21-producing cells in patients with acute rejection compared to stable recipients; moreover, detectable DSA was more frequently observed in the rejection group than in the non-rejection group, which was correlated with IL-21-expressing cells presence in peripheral blood.[10] Furthermore, a recent study demonstrated a significant correlation between the proportion of memory B cells and cTfh cells, and its related cytokines including IL-12, IL-4, and CXCXL13. In addition, the proportion of cTfh cells increased at the onset of AMR episodes. This study suggested cTfh cell proportion as a diagnostic factor of antibody-mediated rejection.[11] The results of the present study were also indicative of increased IL-21 levels in AMR patients; however, IL-21 levels did not show a significant difference between stable recipients and healthy controls. According to the higher proportion of cTfh cells in stable patients, this finding might suggest a regulated function of Tfh cells in these patients; in the other words, despite the increased proportion of cTfh cells in stable recipients, their function is not augmented; however, this hypothesis requires to be investigated with cTfh lymphocytes' function assay. In line with this, Li *et al.* compared the Tfh percentage between stable recipients receiving tacrolimus, those receiving sirolimus, and healthy controls and showed a significantly higher number of Tfh in the tacrolimus group compared to the sirolimus group.[22] Similar to our study, the proportion of Tfh cells was significantly higher in stable recipients on tacrolimus therapy compared

to healthy individuals. Noteworthy, there was no significant difference in IL-21 levels between the three groups. The higher percentage of circulating Tfh cells in the tacrolimus group was supposed to be related to signal transducer and activator of transcription 3 (STAT3) signaling.[22] It appears that sirolimus is more efficient in suppressing Tfh cells than tacrolimus since a recent study reported that treating cTfh cells with sirolimus can inhibit their B-cell-activating function.[23] Furthermore, a pilot study demonstrated higher efficacy of rituximab/sirolimus therapy on DSA desensitization compared to either sirolimus or rituximab alone, proposing Tfh-targeted treatments in managing sensitized patients.[23] In addition to the therapeutic potential of cTfh cells, the present study showed an acceptable diagnostic value for these cells. Therefore, cTfh cell percentage might be suggested for monitoring sensitized recipients and evaluating treatment response in AMR patients.

THE STUDY LIMITATIONS

Despite the abovementioned findings, the limited number of the studied population might have affected the significance of the results. It was difficult to find patients with a definite diagnosis of AMR because AMR usually occurs mixed with cellular rejection; moreover, many patients had immune-related underlying disorders and thus were excluded from the study. In addition, due to the small number of AMR patients, the rejection stages were not considered in the analysis, and patients were included in the study regardless of the pathological stage of AMR. The other problem was the inability to check the level of donor-specific antibodies in the studied patients, which is not routinely performed in Iran; therefore, it was not possible to investigate the correlation between Tfh frequency and DSA levels.

CONCLUSION

To summarize, it is worth mentioning that in kidney transplant recipients the proportion of cTfh cells is higher than in healthy individuals. This proportion further increases in acute antibody-mediated rejection, along with elevated serum levels of IL-21. Moreover, the percentage of circulating Tfh cells might be considered a diagnostic marker in graft surveillance particularly in sensitized recipients.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHORS' CONTRIBUTION

MF, FP, and AA: evaluated the patient and provided clinical data; MS, HM, and SP: performed lab tests; NS: analyzed the results; SA: designed the study and prepared the manuscript; MH: supervised the study.

ETHICAL APPROVAL

All the study participants gave their informed consent before enrolling in the study. The study was conducted in accordance with the Declaration of Helsinki, and the study protocol was approved by the Ethics Committee of the Tehran University of Medical Sciences (IR.TUMS.CHMC.REC.1401.024).

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