

EXPRESSION OF P-GLYCOPROTEIN ON IMMUNE CELLS AFFECTS STEROID RESPONSE IN CHILDHOOD IDIOPATHIC NEPHROTIC SYNDROME

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Introduction

- Idiopathic Nephrotic syndrome (NS) is one of the most common glomerular disease in children.
- About 80-90% NS patients show response to steroids and others develop resistance during the course of disease.

Nasi M et al. Pediatric Kidney Disease 1992

- Almost 50-60% of steroid responsive NS have frequent relapses or steroid dependent and 10-20% patient develops steroid resistance.

Shalhoub RJ, lancet 1974;2:556-603

- Indirect evidences suggest that NS is a consequence of dysfunction of CD4+ T cell function
- Steroid non responsiveness may be because of disturbances in T cell subset population and/ or,
- One of the factors of the acquired steroid resistance could be the factors that modulate the disease response to pharmacological interventions, such as P-gp expression.
- The expression of P-gp on different immune cells suggest that P-gp may influence cell mediated immune response.

Klimecki et al Blood 1994;83:2451-245

- Worse response to steroid or dependency in NS may be due to over expression of P-gp. Further examinations are necessary to establish whether increased P-gp activity is a result of MDR-1 gene polymorphism.

Wasilewska et al. Pediatr Nephrol 2006

- Patients of NS carrying homozygous mutants of single nucleotide polymorphism (SNP) G2677T/A are prone to develop steroid resistance.

Narayan Prasad et al NDT 2011;26:3968-74

- P-gp acts as an efflux pump and removes its substrates from inside the cell to outside.
- P-gp appears to be a double edged sword which protects the cells against the accumulation of xenobiotics and toxins in the cytoplasm

- Simultaneously by limiting intra lymphocytic concentration, P-gp is capable of limiting the ability of steroids to bind to their receptors resulting in corticosteroid resistance.

Arthritis Rheum 2005; 52:1676-1683

Objectives

- To study the P-gp expression on blood lymphocytes and P-gp positive T-regs, Th1 and Th2 cells in NS in sustained remission (SSNS), during relapse, SRNS and healthy controls.

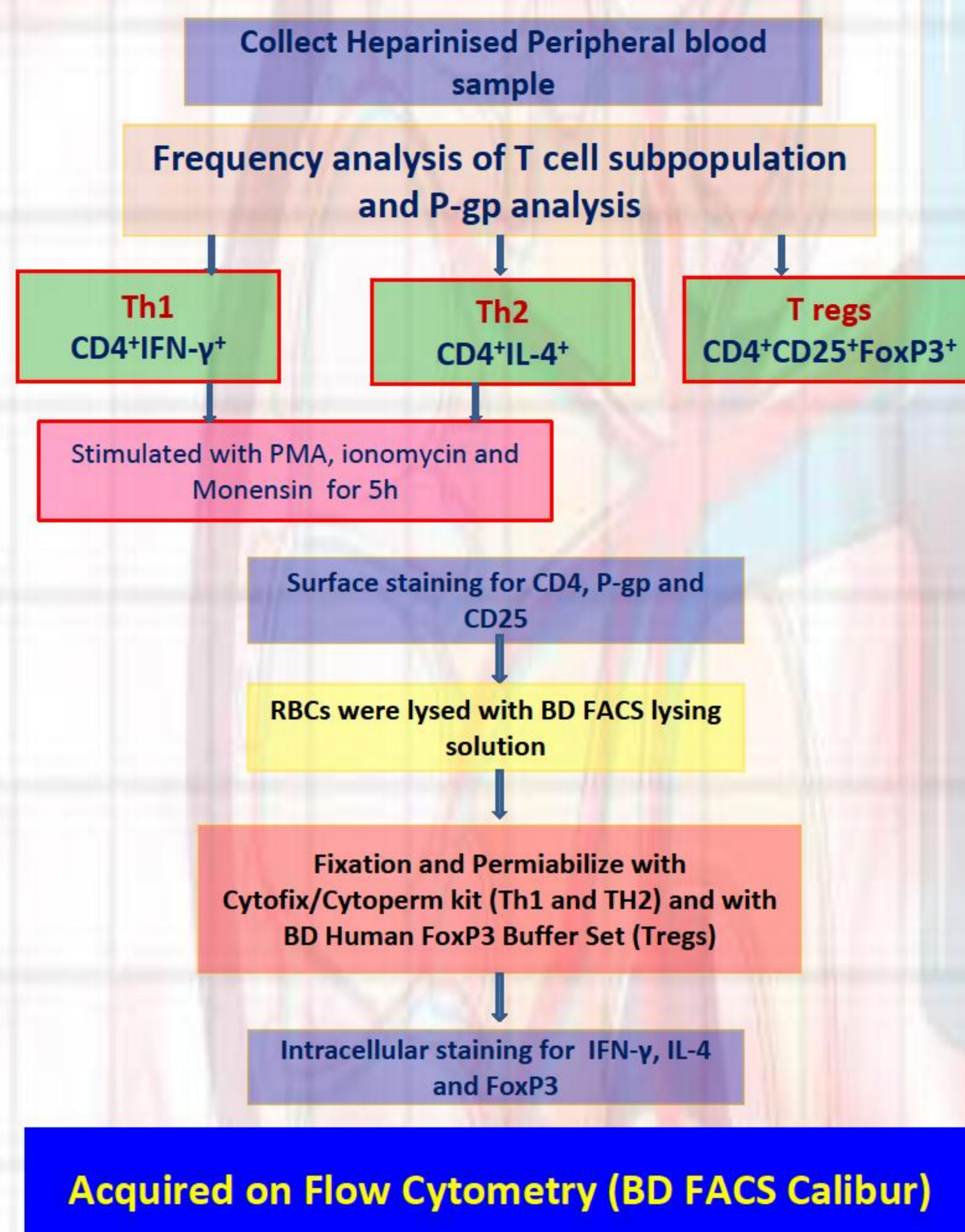
Materials and Methods

Study population (N=81)

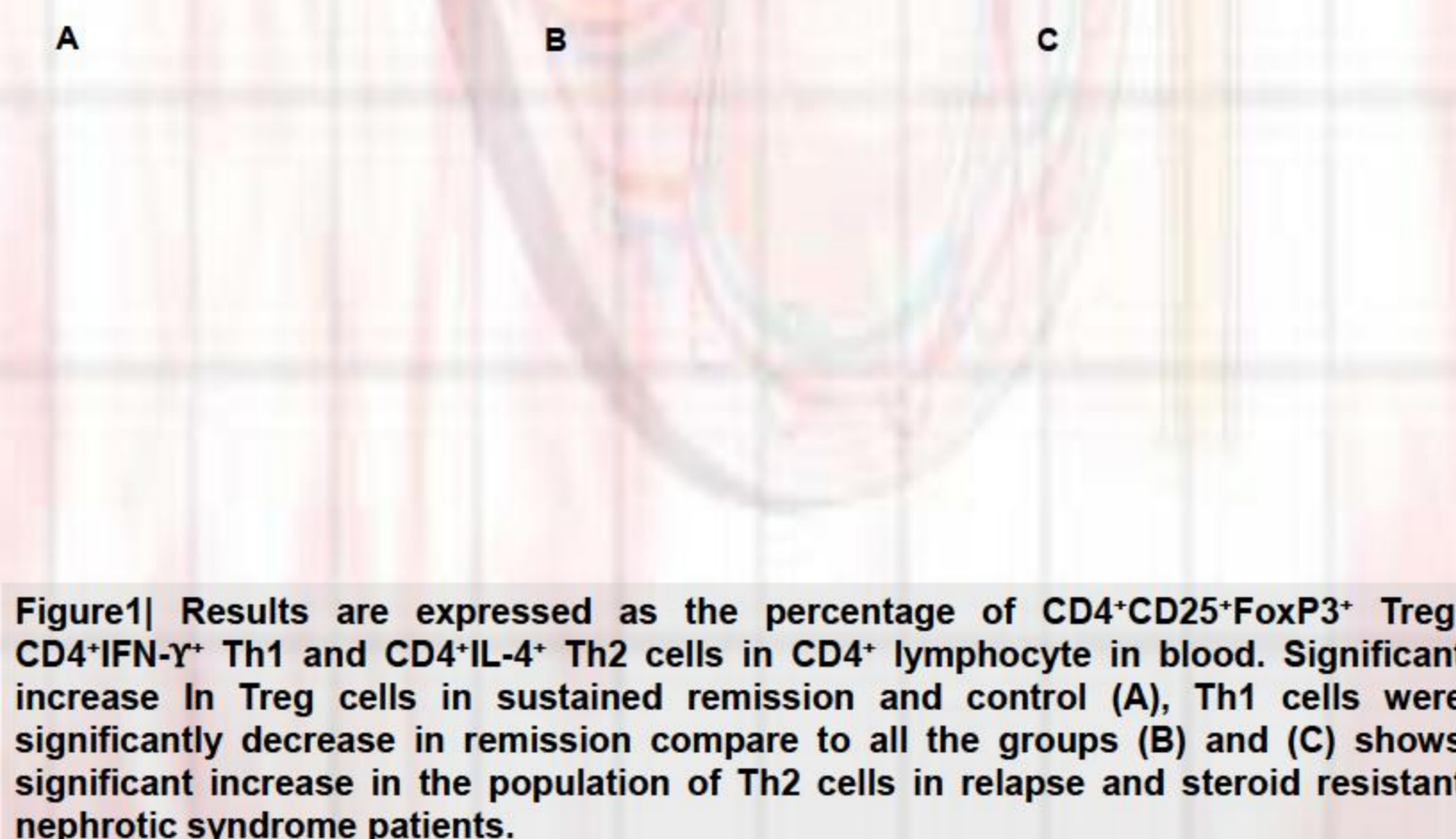
SSNS Remission (n=22, Male-18, MeanAge-8.52±5.8)
SSNS Relapse (n= 24, Male-20, MeanAge-8.5±4.2)
SRNS (n= 21, Male-11, MeanAge-11.7±3.8)
Control (n= 14, Male-11, MeanAge-10.6±4.3)

All patients were recruited as per criteria of ISKDC

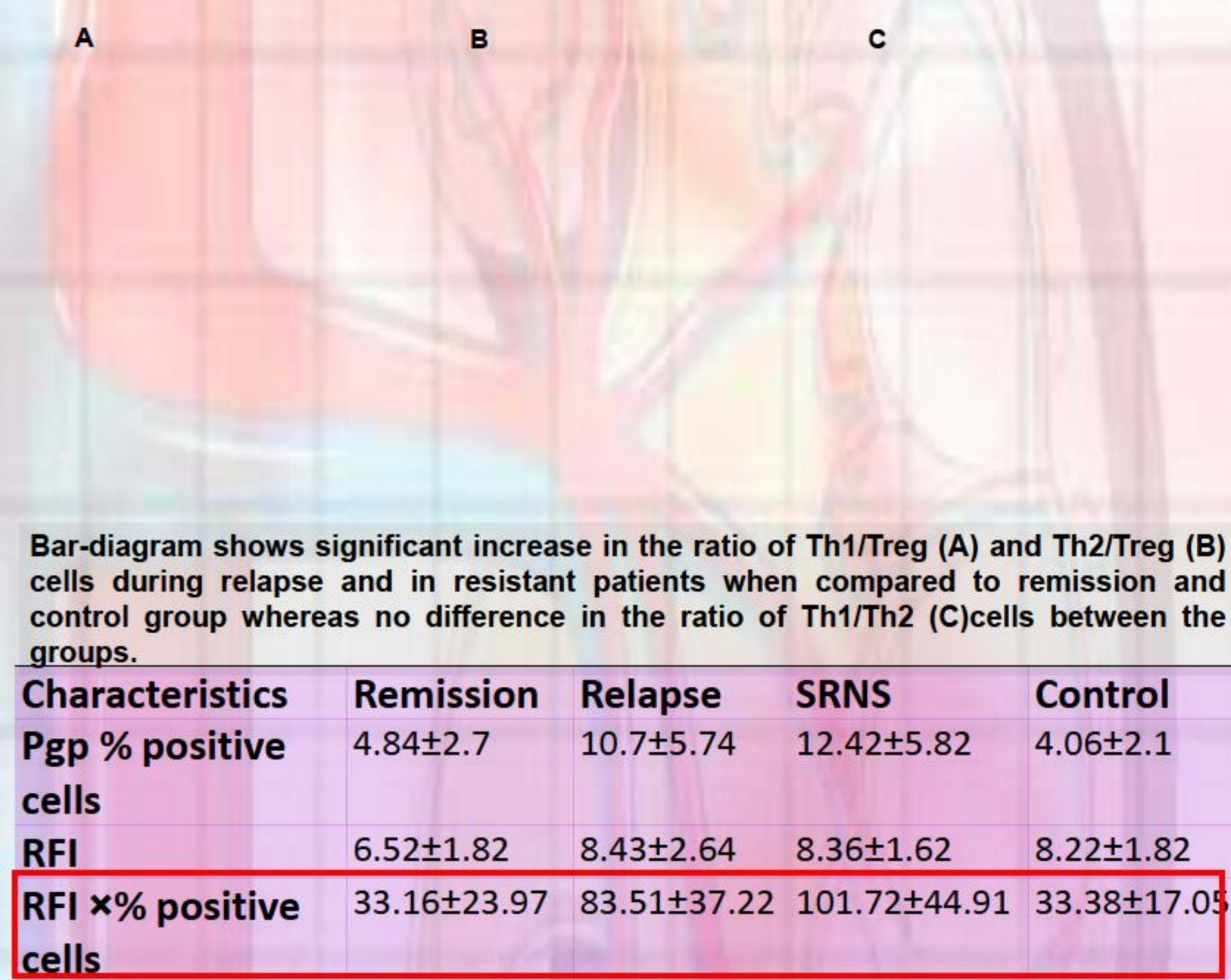
Materials and Methods



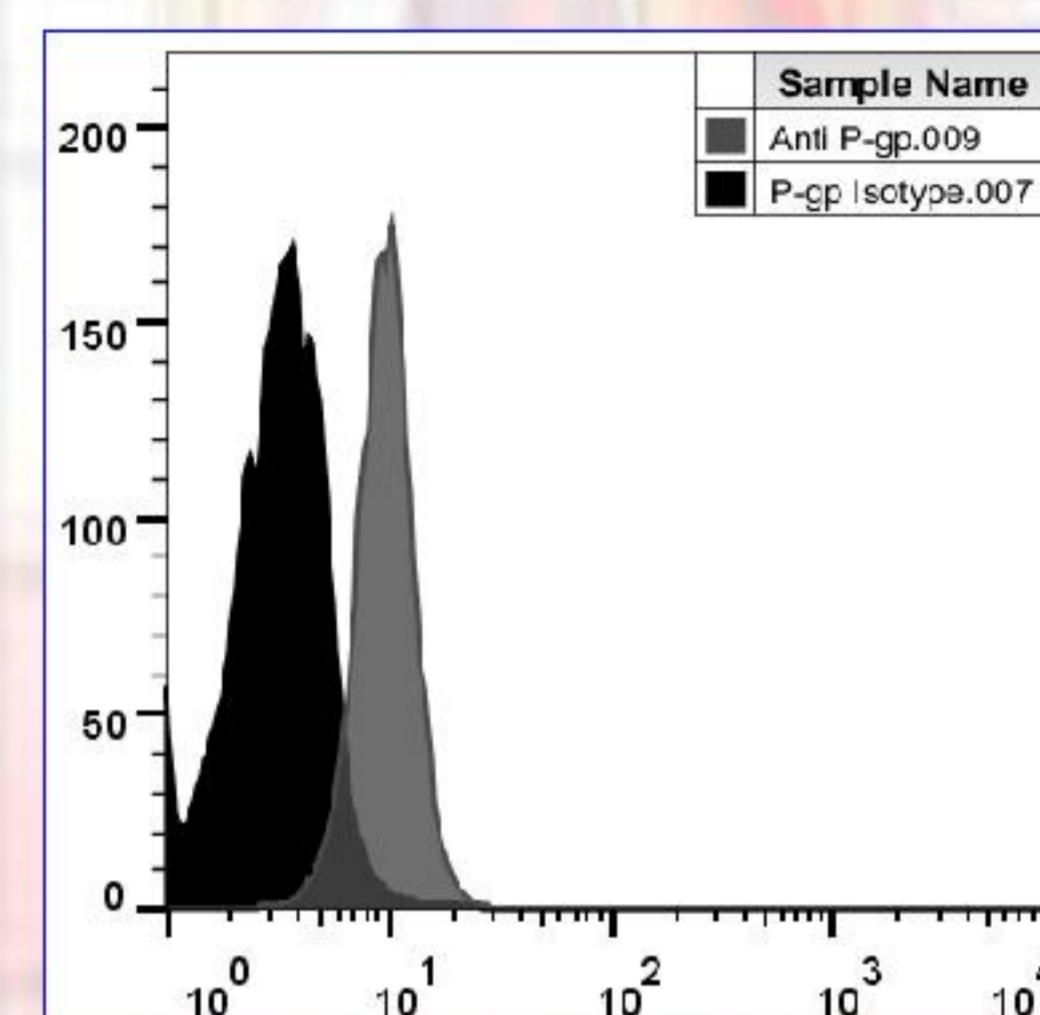
Results



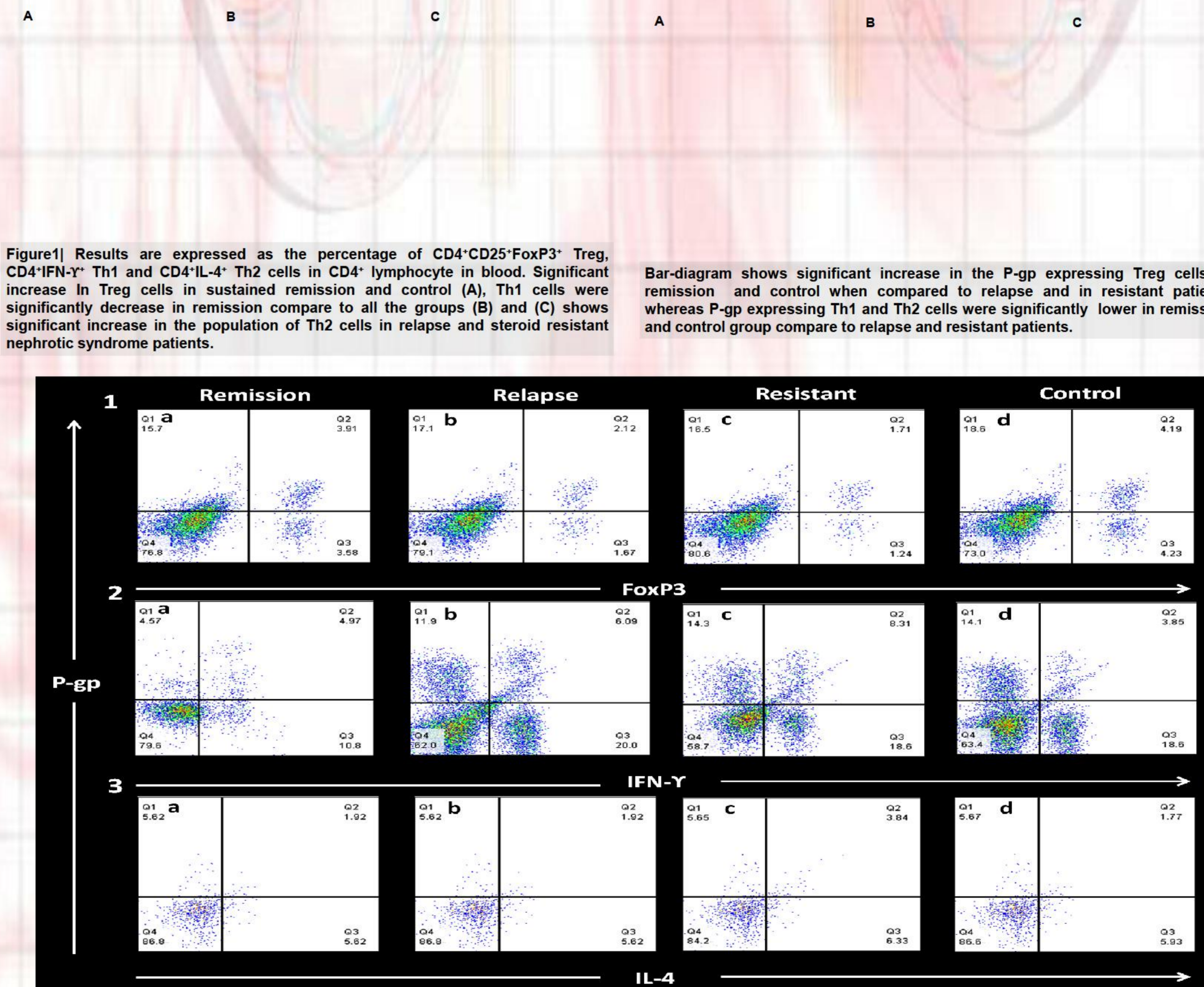
Results



P-glycoprotein, RFI and absolute P-gp expression on lymphocytes in different group of patients.



Relative fluorescence intensity (RFI) in one of the representative sample from a patient with resistant NS.



Representative Flow Cytometric Picture of Different Groups

	Pgp positive×RFI	P-value
%Treg	-0.445	0.001*
Th1/Treg ratio	0.406	0.001*
Th2/Treg ratio	0.431	0.001*
Th1/Th2 ratio	-0.189	0.102
%Th1	0.149	0.199
%Th2	0.318	0.005*

Pearson's Correlation of P-gp expression with different T cell profiles

Conclusions

- ✓ Pgp expression is greater in relapsed and resistant state and may be the cause of resistance in SRNS.
- ✓ The imbalance of Tregs and T eff cells may result in to a state of sustained remission, relapse and resistant in childhood NS patients.
- ✓ Greater T regs ratio to Th1, and Th2 cells results into remission.