신장 삼차 림프 조직의 임상적 의의 연구

2020-07-22

분당차병원 신장내과

이유호

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- **Introduction: tertiary lymphoid tissues (TLTs)**

- **Clinical relevance of renal TLTs in kidney diseases**

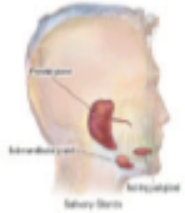
Tertiary lymphoid tissue (TLT)

- Inducible lymphoid tissues that arise in non-lymphoid organs
- Predisposing factor: **chronic sustained inflammation**
- Structure: similar to secondary lymphoid organ (spleen, lymph node)
  - Hematopoietic component (90%)
    - **T and B lymphocytes**
    - Dendritic cell
  - Stromal component (10%)
    - **Fibroblast-lineage cell: Follicular dendritic cells (FDCs)**, fibroblastic reticular cells (FRCs)
    - High endothelial venule, lymphatic duct

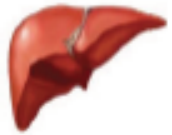
Tertiary lymphoid tissue (TLT)

TLTs can be found in virtually all organs with chronic inflammation

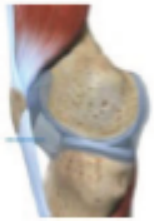
Sjögren's syndrome
(salivary glands and lacrimal glands)



Primary biliary cirrhosis, primary sclerosis cholangitis (liver)

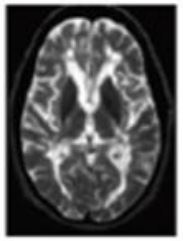


Rheumatoid arthritis (joints)



Atherosclerosis (arteries)

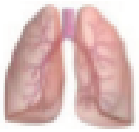
Autoimmune encephalitis/
multiple sclerosis (central nervous system)



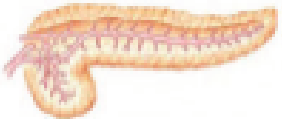
Inflammatory bowel diseases (colon and small intestine)

Helicobacter pylori gastritis (stomach)

Inducible bronchus-associated lymphoid tissue (iBALT) (lungs)



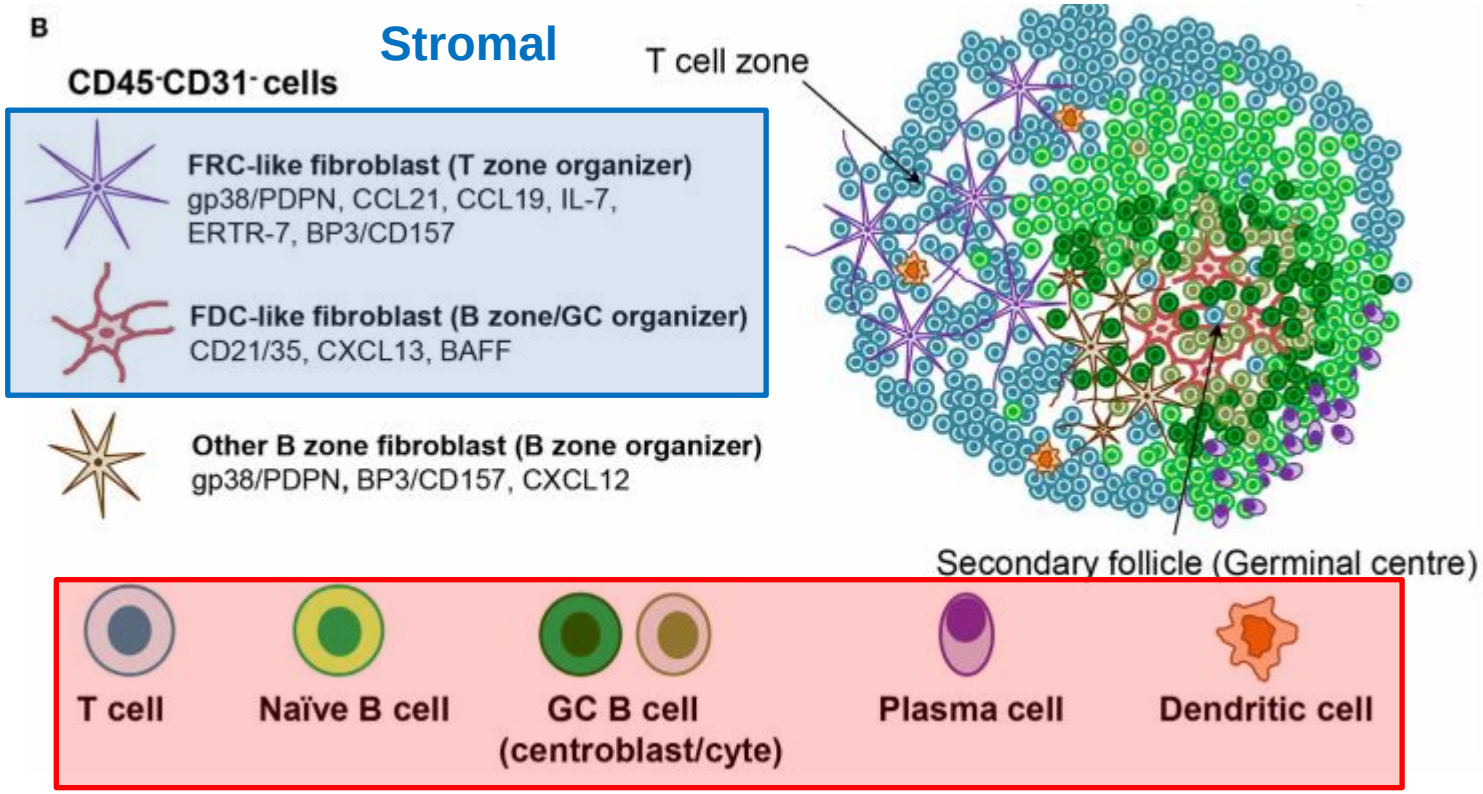
Diabetes (pancreas)

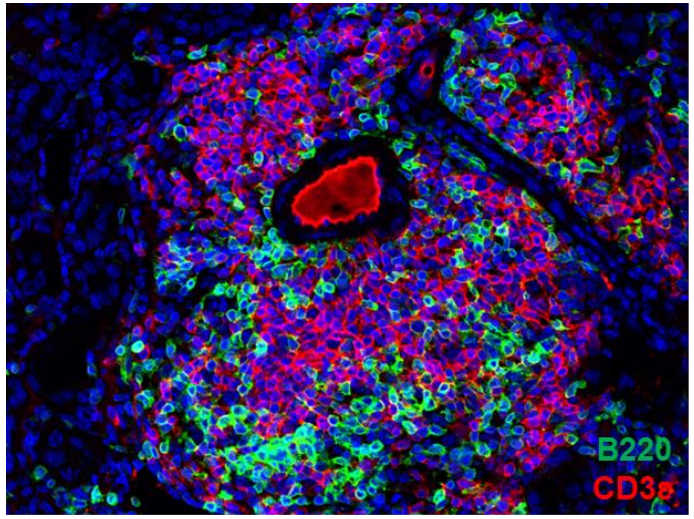


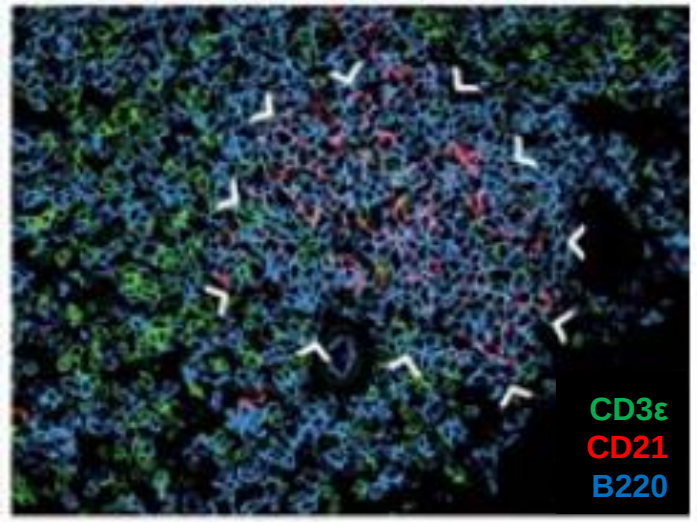
- **Cancer, transplanted organ, etc**

Front Immunol 2016 Nov 8;7:477

Tertiary lymphoid tissue (TLT)

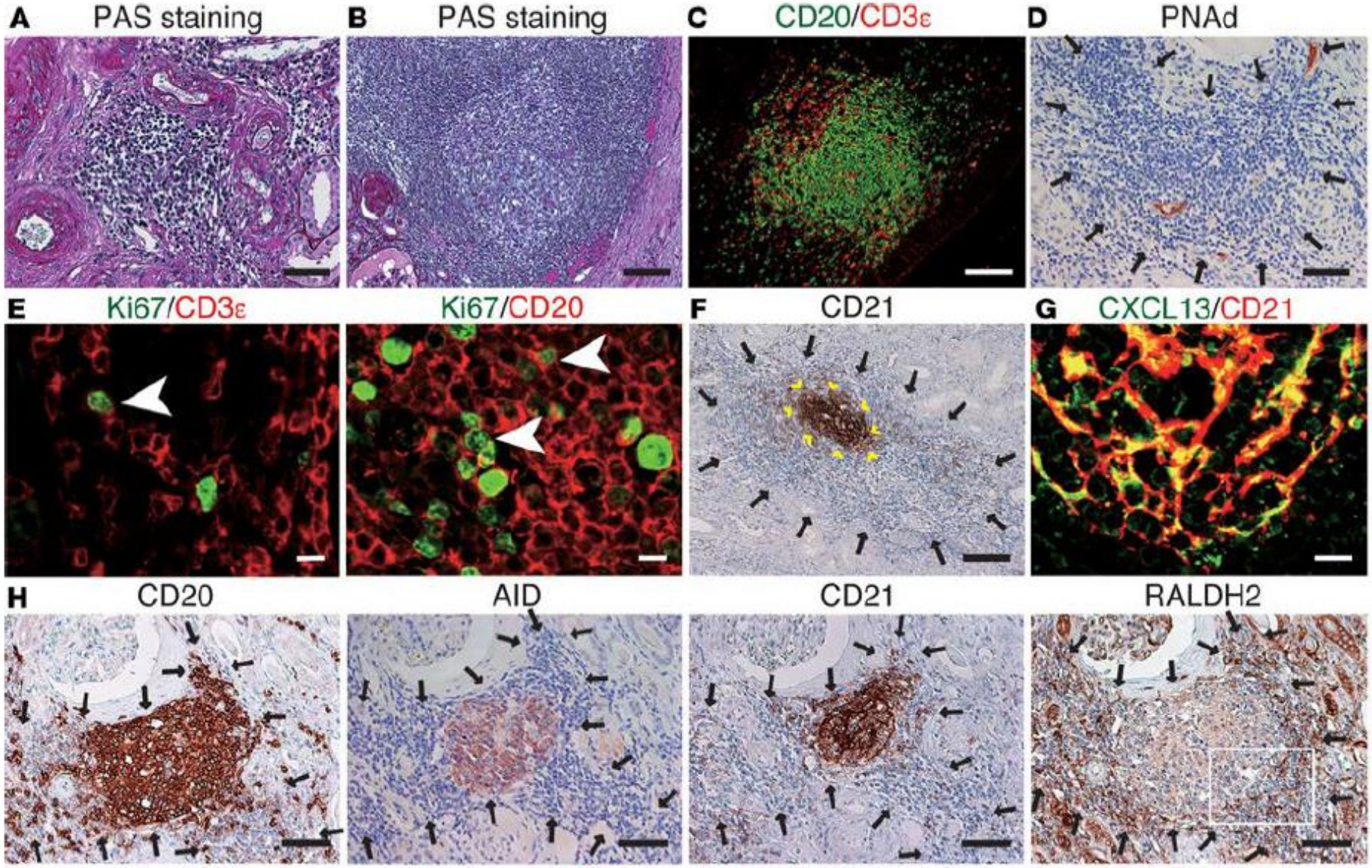


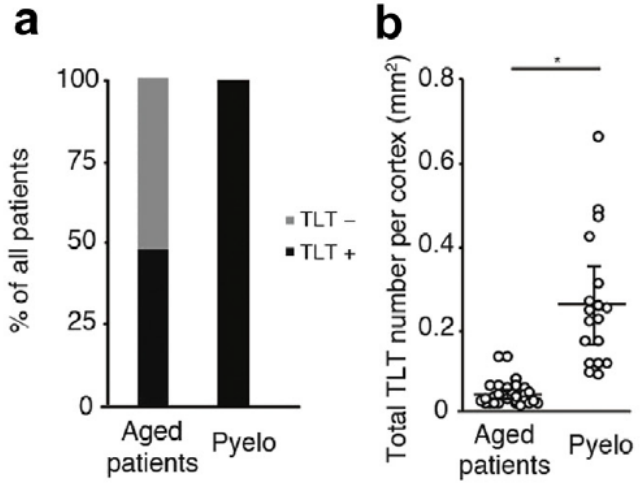


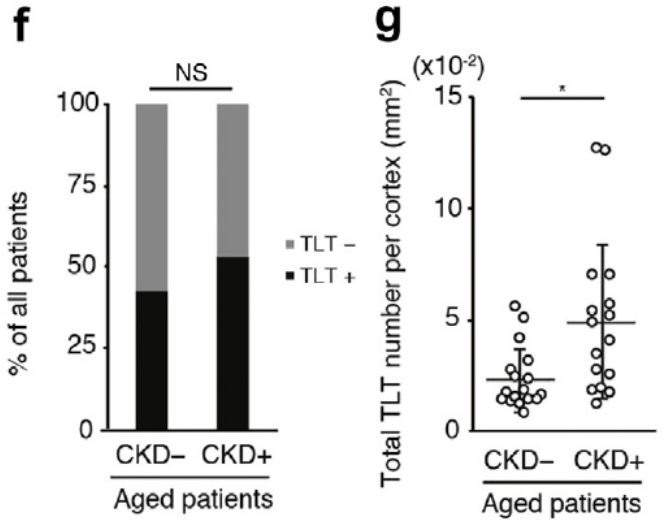


Front Immunol 2016, JCI insight 2016

TLTs in kidney





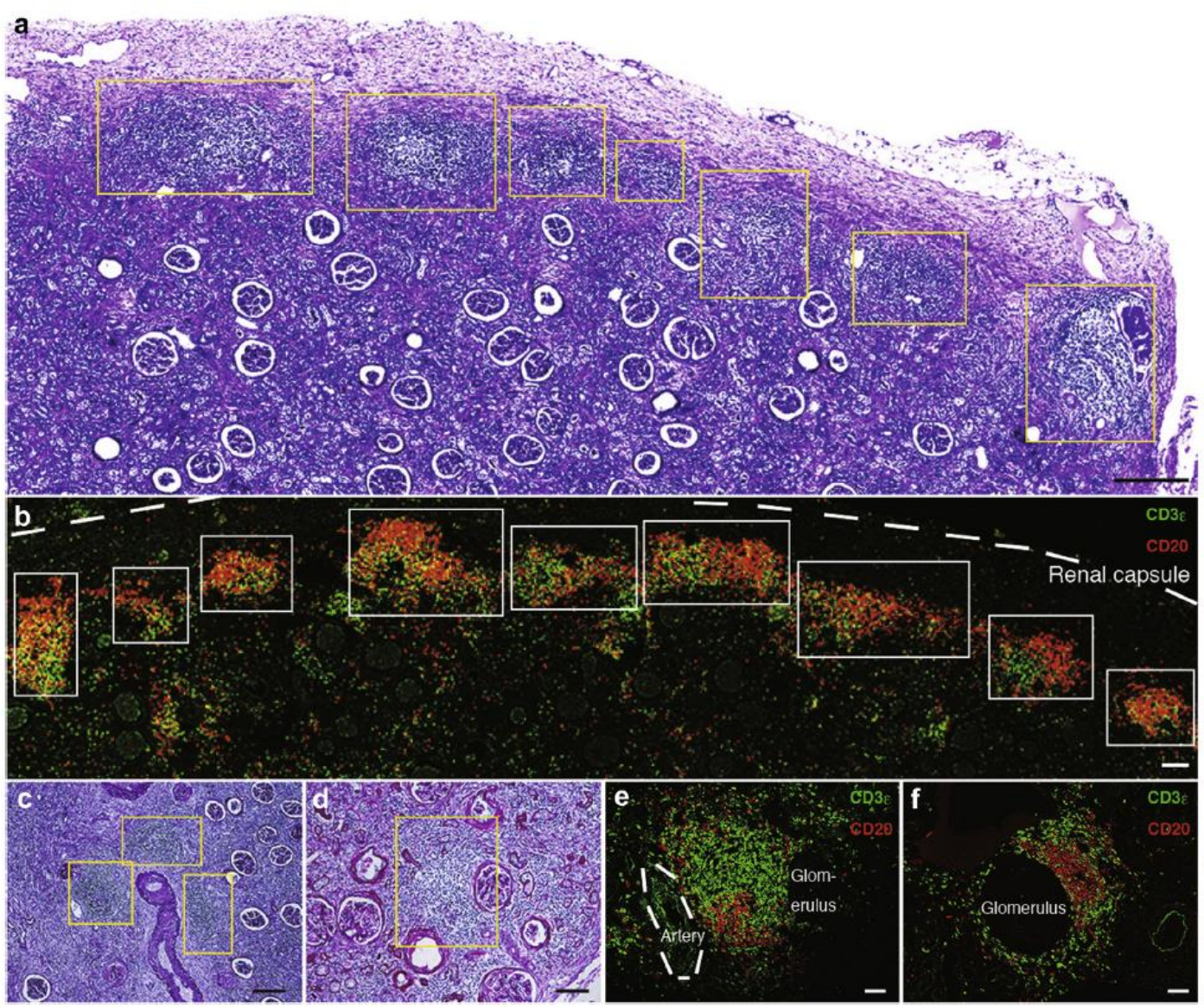


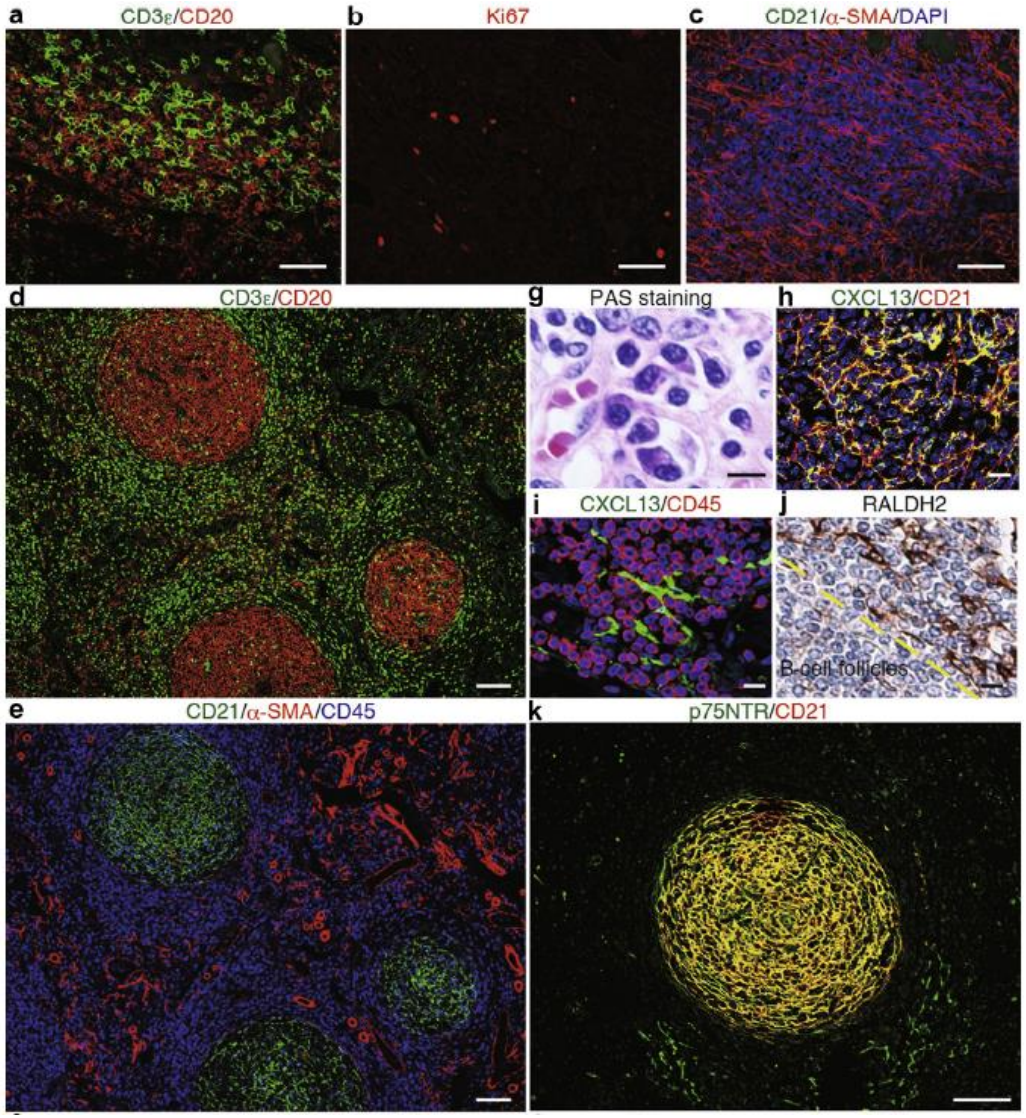
JCI insight 2016
KI 2020

Tertiary lymphoid tissue (TLT)

- **What is the clinical meaning of TLTs?**
  - **Controversial !**
    - Associated with enhanced local immune response OR immune tolerance
    - Organ- and disease-dependent
      - TLTs in cancer: protective ? (e.g. melanoma)
      - TLTs in transplanted organ, autoimmune disease: harmful ?

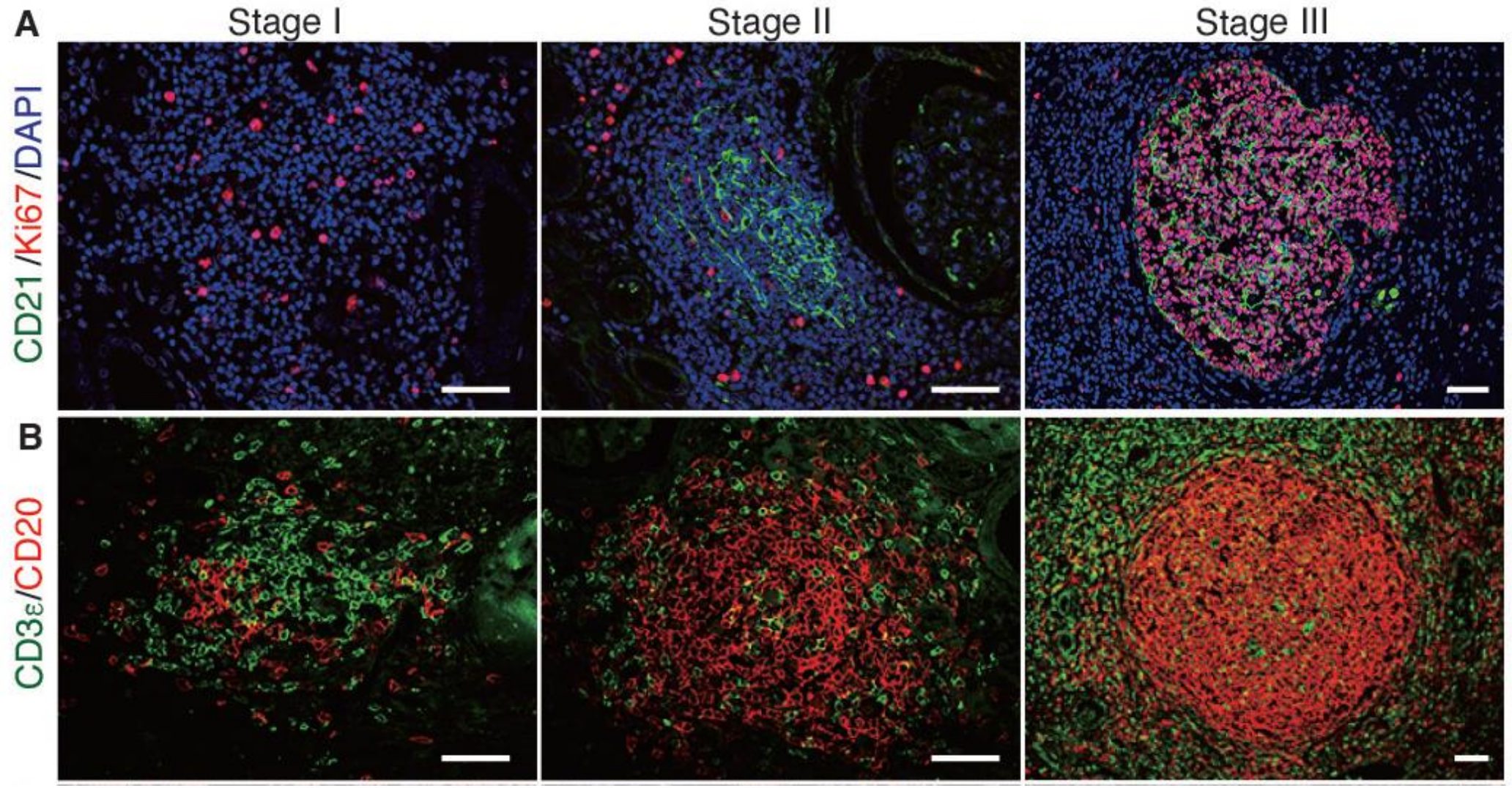
Heterogeneity of TLTs





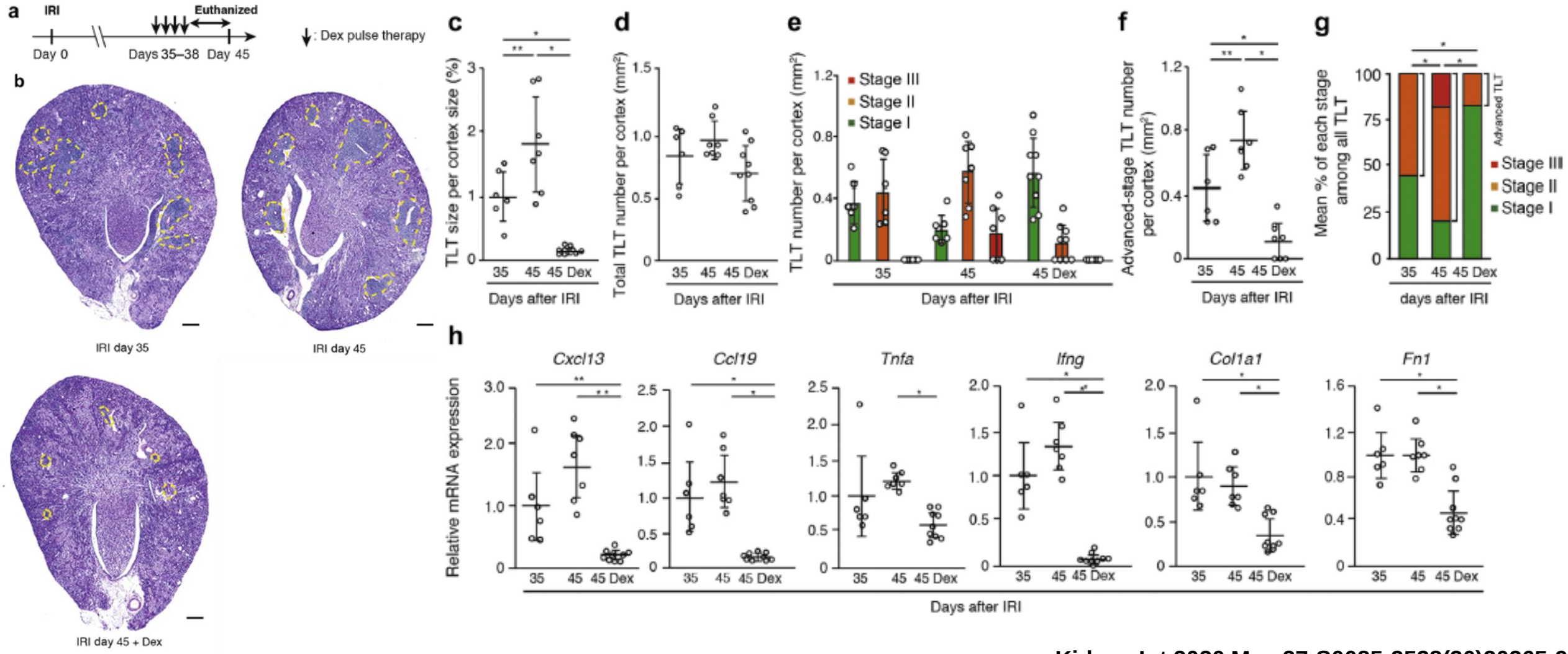
Kidney Int 2020 May 27:S0085-2538(20)30265-9

TLT staging



Kidney Int 2020 May 27:S0085-2538(20)30265-9

TLT staging reflects renal inflammation and injury



Kidney Int 2020 May 27:S0085-2538(20)30265-9

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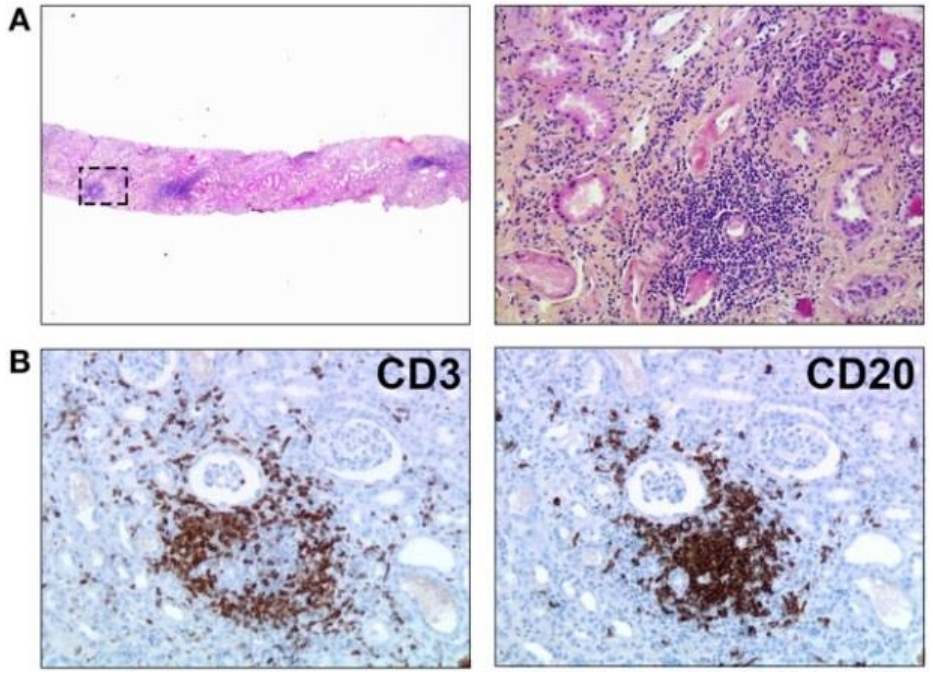
- Introduction: tertiary lymphoid tissues (TLTs)

- **Clinical relevance of renal TLTs in kidney diseases**
  - Kidney transplantation
  - Diabetic kidney disease

TLTs in transplanted kidney

- **Solid organ transplantation**
  - Exposed to continuous immunologic stimulation by recipients' immune system

→ **Vulnerable to the formation of TLTs**



Koenig A et al, Front Immunol 2016 27;7:646

Conflicting significance of TLTs in KT

Reference	Population	Biopsy indication	Histologic criteria	Key findings
KIDNEY RECIPIENTS				
Sarwal et al. (39)	51 patients	Biopsy with acute graft rejection	CD20+ cell count >275/HPF	B cell clusters associated with glucocorticoid resistance and graft loss
Hippen et al. (58)	27 patients	Biopsy with Banff 1A or 1B acute rejection	CD20+ if "strong and diffuse staining"	CD20+ correlated with steroid-resistance rejection and reduced graft survival
Kayler et al. (59)	120 patients	Biopsy with first episode of acute cellular rejection	Cluster of ≥15 CD20+ cells in the tubulo-interstitial compartment	CD20+ clusters are not prognostic factors for glucocorticoid resistance and graft loss
Bagnasco et al. (60)	58 patients (74 biopsies)	Biopsy with type 1 and type 2 acute cellular rejection during the first year post-Tx	B cell-rich when ≥1 cluster containing 100 CD20+ cells/HPF	No correlation between B cell-rich biopsies and worst graft outcome
Scheepstra et al. (61)	50 patients (54 biopsies)	Biopsy with clinically suspect and histologically confirmed acute rejection	B cell (CD20+) count >275/HPF CD20+ cluster if >30 cells CD20+ without the interposition of tubules	Presence of B cells does not correlate with response to conventional therapy or graft outcome
Hwang et al. (62)	54 patients (67 biopsies)	Biopsy with acute cellular rejection	CD20+ count >275/HPF CD38+ if >30% infiltration	CD38+ B cells ± CD20+ B cells correlated with poor clinical outcomes
Martin et al. (63)	18 patients	Serial biopsies for 10 recipients with chronic dysfunction and 8 with long-term normal graft function	Plasma cells count Cd4 deposits DSA elution from biopsy	Patients developing chronic rejection present plasma cells, DSA, and C4d depositions more often than control group on their biopsy
Abbas et al. (64)	50 patients	Biopsy for cause	Plasma cell-rich acute rejection if >10% plasma cells	Plasma cell-rich acute rejection correlated with a poor graft outcome when associated with DSA

Detrimental

Irrelevant

Koenig A et al Front Immunol 2016 27;7:646

Purpose of the study

- **To elucidate the clinical relevance of TLTs in transplanted kidney**
- **Major differences in comparison with previous studies**
  - Analysis of biopsy samples with concurrent evidences of **rejection**

    → Analysis of protocol biopsy samples without rejection
  - Lack of consistency in the **definition of TLTs**

    → Application of new TLT staging system

Study design and patient selection

Patients who underwent **living donor KT** between 2004 and 2014 in Akita University **(N=204)**

Excluded **(N=23)**

- Presence of preformed donor specific antibody before KT(n=1)
- **Biopsy-proven acute rejection** or BK virus associated nephropathy within 1 year after KT (n=17)
- Non-recovery of renal allograft function (eGFR < 30 ml/min/1.73 m^2) over 1 year after KT (n=2)
- Lost to follow-up within 1 year after KT (n=3)

Study participants **(N=181)**

- **Pathologic data**: serial protocol biopsy samples (**0-hour, 1-month, 6-month, and 12-month**)
- Clinical data: baseline characteristics and graft function over 5 years of follow-up

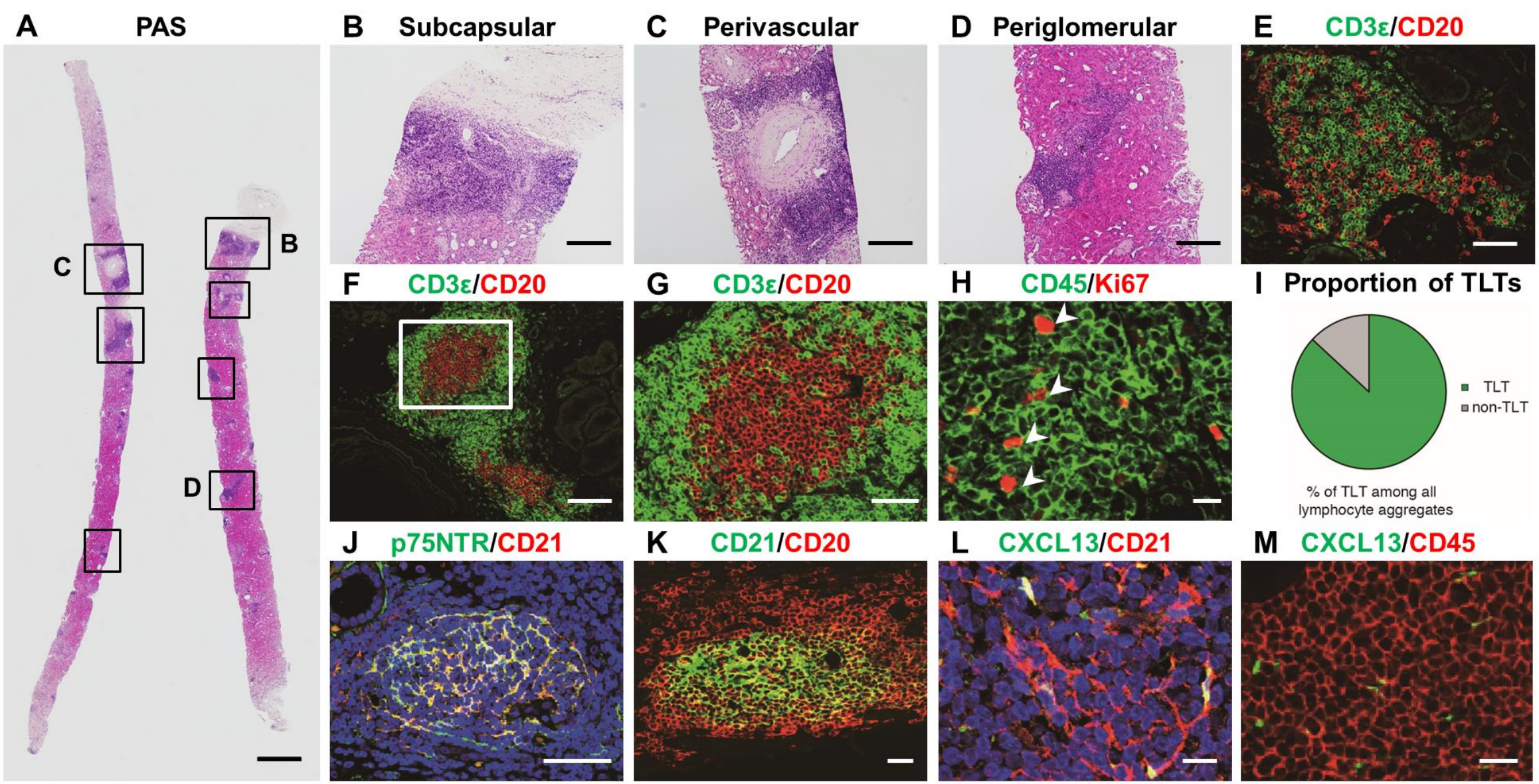
Baseline characteristics of enrolled patients

Recipient information	
Age (year)	48.0 ± 12.4
Gender (Male, %)	114 (63.0)
BMI (kg/m^2)	22.5 ± 3.6
Etiology of ESRD (n, %)	
Chronic glomerulonephritis	112 (61.9)
Diabetes mellitus	26 (14.4)
Hypertension	12 (6.6)
Polycystic kidney disease	11 (6.1)
Others	20 (11.0)
Time on dialysis (month)	42.1 ± 57.4
Preemptive KT (n, %)	28 (15.5)
Number of HLA mismatching (n)	3.2 ± 1.5

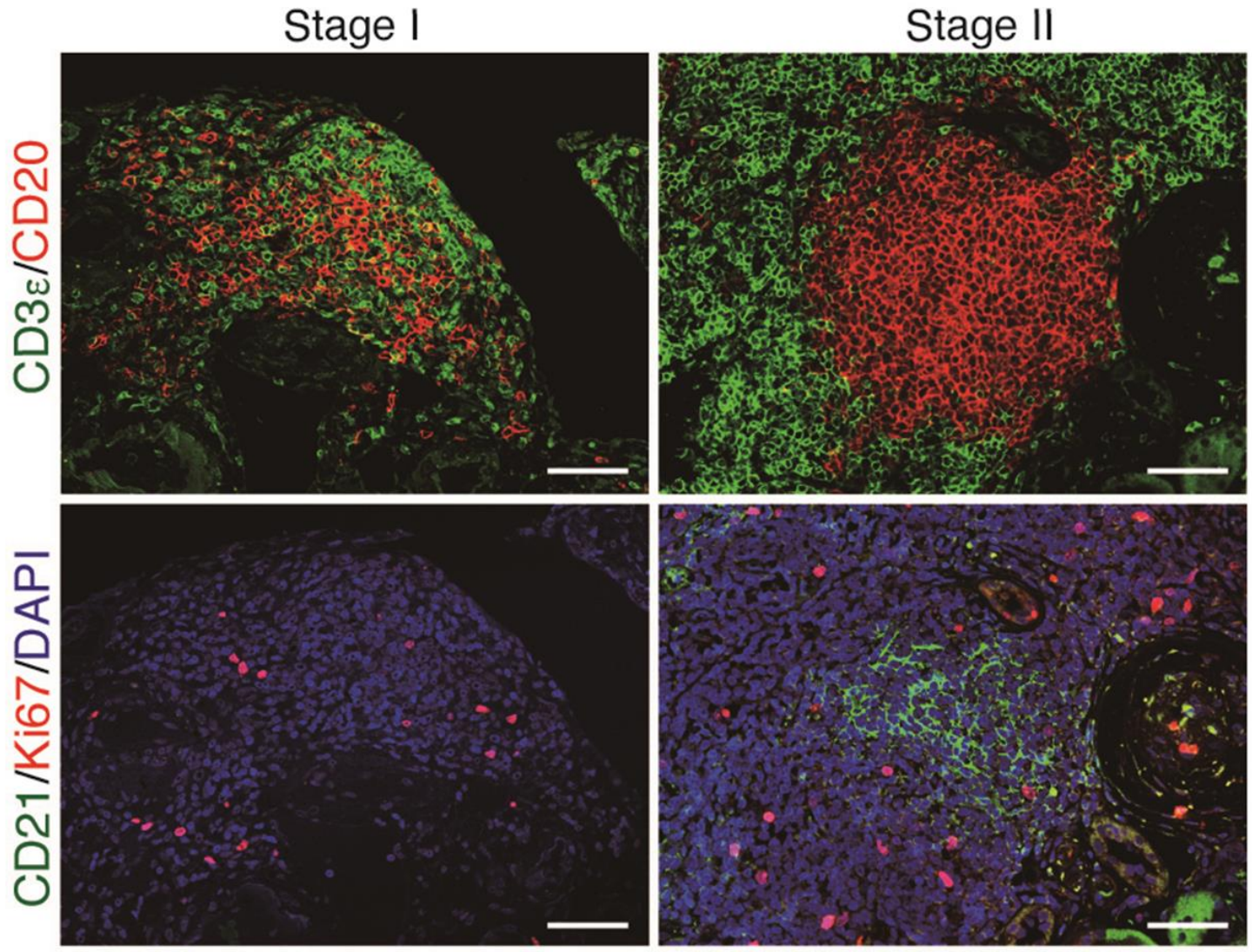
Recipient information	
ABO incompatible KT (n, %)	48 (26.5)
Pre-transplantation rituximab (n, %)	48 (26.5)
Death-censored ESRD progression (n, %)	3/170 (1.8)
Induction immunosuppressive agent (n, %)	
Basiliximab	181 (100)
Follow-up eGFR (ml/min/1.73 m^2)	
1-month	68.1 ± 20.3
1-year	65.7 ± 19.9
5-year	62.8 ± 21.9

Donor information	
Age (year)	58.3 ± 10.0
Gender (Male, %)	71 (39.2)
Pre-transplantation eGFR (ml/min/1.73 m^2)	103.0 ± 11.2

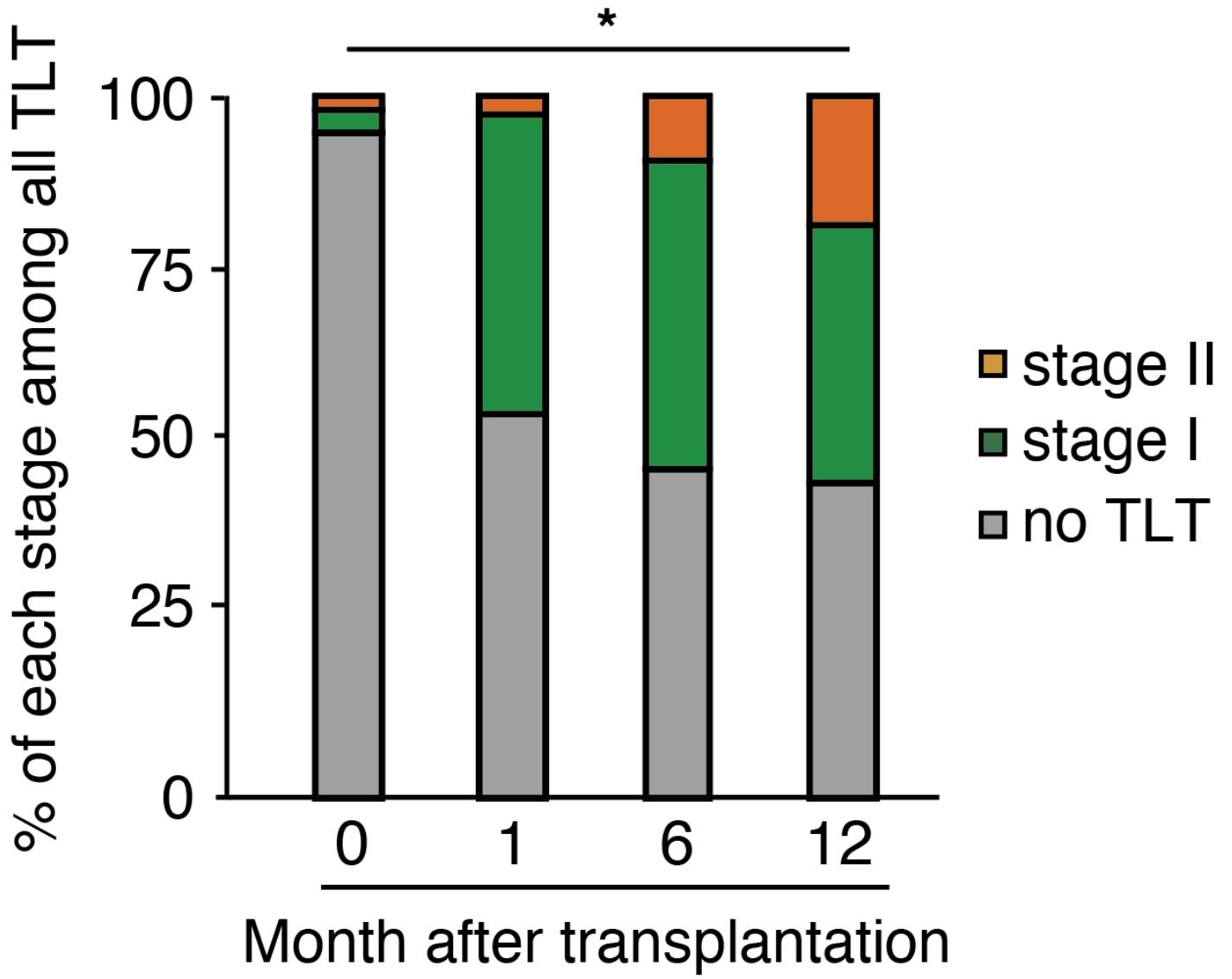
Characterization of TLTs in transplanted kidneys



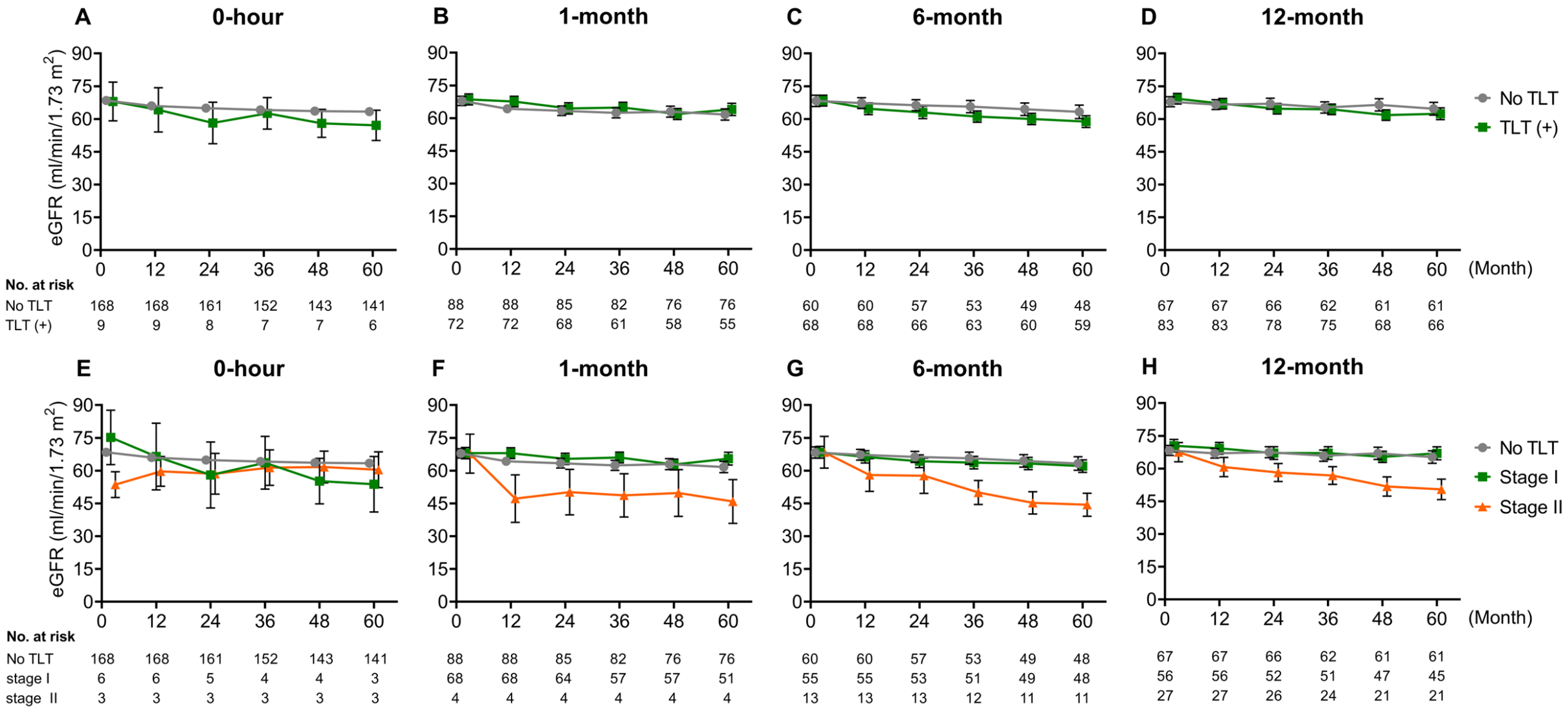
Staging of TLTs in transplanted kidney



Prevalence of TLTs in transplanted kidney



Longitudinal trends of renal allograft function according to the presence and the staging of TLTs



Longitudinal trends of renal allograft function according to the presence and the staging of TLTs

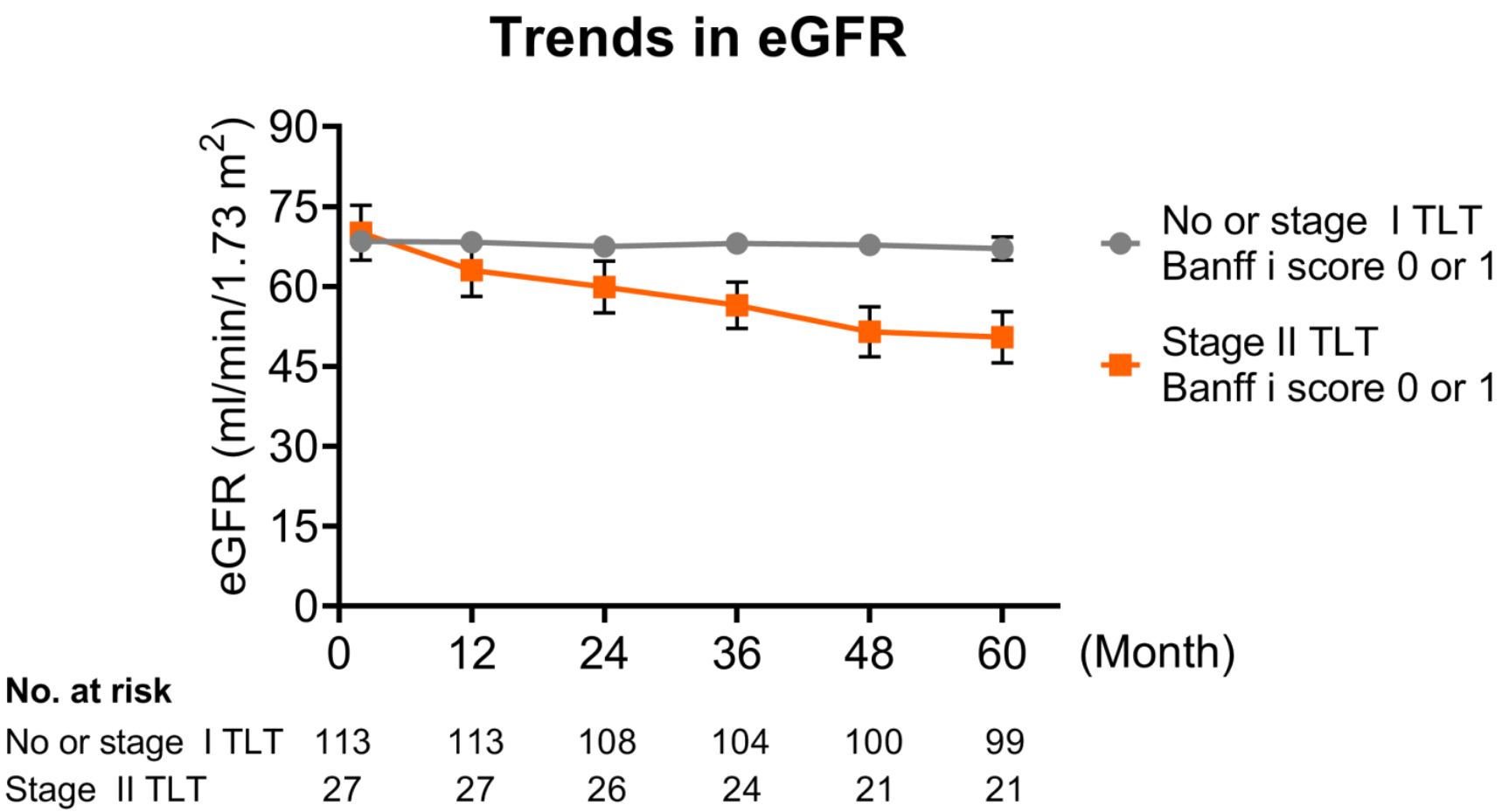
		Adjusted difference in eGFR	95% confidence interval	*p*
1-month	TLT (-)	0 (Reference)	-	-
	Stage I TLTs	3.15	-2.39 to 8.69	0.265
	Stage II TLTs	-6.21	-30.68 to 18.27	0.619
6-month	TLT (-)	0 (Reference)	-	-
	Stage I TLTs	-1.34	-7.29 to 4.61	0.658
	Stage II TLTs	**-13.31**	**-26.37 to -0.26**	**0.046**
12-month	TLT (-)	0 (Reference)	-	-
	Stage I TLTs	-0.51	-6.39 to 5.36	0.864
	Stage II TLTs	**-10.64**	**-20.92 to -0.37**	**0.042**

Association between the stages of TLTs and Banff pathologic scores at 12-month biopsy

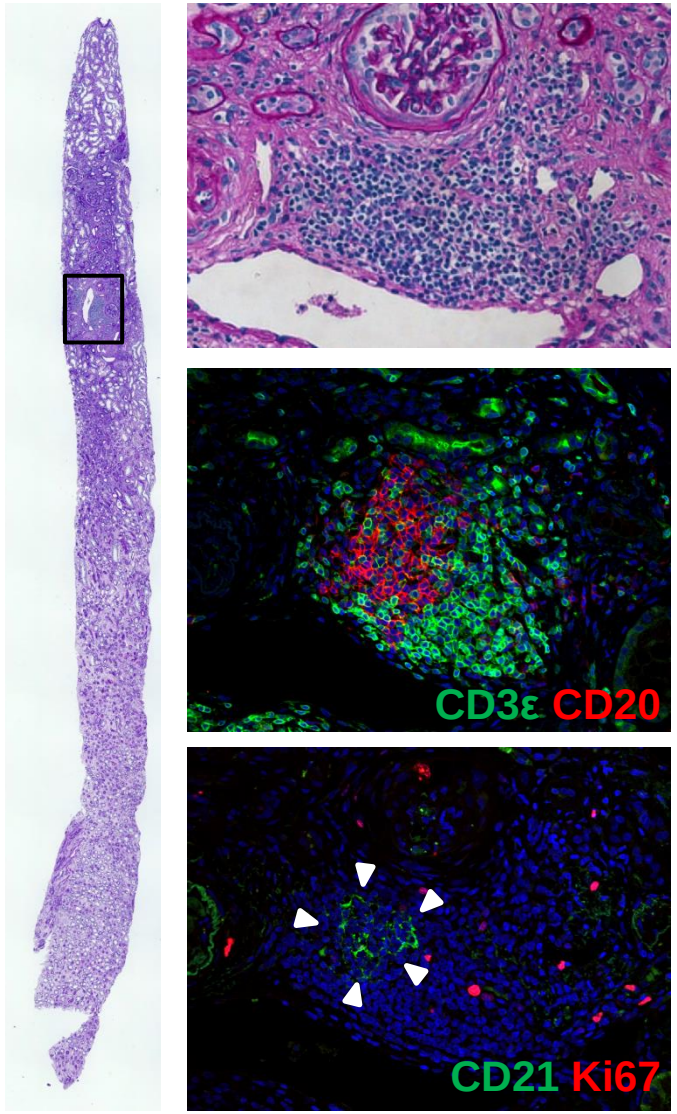
		1-month biopsy				6-month and/or 12-month biopsies			
		No TLT	Stage I TLT	Stage II TLT	*p* value	No TLT	Stage I TLT	Stage II TLT	*p* value
12-month Banff scores	i	0.60 ± 0.78	0.66 ± 0.74	0.50 ± 1.00	0.690	0.37 ± 0.61	**0.73 ± 0.81**	**0.88 ± 0.89**	**0.010[a, b]**
	t	0.30 ± 0.65	0.25 ± 0.62	0.25 ± 0.50	0.812	**0.13 ± 0.34**	**0.36 ± 0.75**	**0.55 ± 0.83**	**0.037[b]**
	v	0 ± 0	0 ± 0	0 ± 0	1.000	0 ± 0	0 ± 0	0 ± 0	1.000
	g	0.02 ± 0.13	0 ± 0	0 ± 0	0.567	0.02 ± 0.15	0 ± 0	0.03 ± 017	0.341
	ptc	0.06 ± 0.23	0.03 ± 0.18	0 ± 0	0.686	0.06 ± 0.24	0.05 ± 0.23	0.11 ± 0.32	0.416
	ct	1.02 ± 0.76	0.88 ± 0.63	1.00 ± 0	0.530	**0.78 ± 0.76**	**0.99 ± 0.72**	**1.18 ± 0.68**	**0.020[b]**
	ci	0.78 ± 0.78	0.77 ± 0.66	0.75 ± 0.50	0.982	0.63 ± 0.71	0.86 ± 0.65	0.85 ± 0.87	0.124
	cv	0 ± 0	0 ± 0	0 ± 0	1.000	0 ± 0	0 ± 0	0 ± 0	1.000
	cg	0 ± 0	0 ± 0	0 ± 0	1.000	0 ± 0	0 ± 0	0 ± 0	1.000

[a] $p < 0.05$, No TLT vs. stage I TLT group, and [b] $p < 0.01$, No TLT vs. stage II TLT group.

eGFR according to the stages of TLT among patients with mild interstitial inflammation at 12-month biopsy



Banff i score = 0, TLT stage = II



Take home message

- TLTs are **frequently detected** in any organ with chronic inflammation
  - Autoimmune disease, malignancy, transplanted organs, kidneys, etc
- **TLT staging systems** can reflect local injury and inflammation
  - CD3ε/CD20 and CD21/Ki67
- **Advanced TLTs** in kidneys are associated with **rapid renal progression**
  - Transplanted kidneys, diabetic kidney diseases