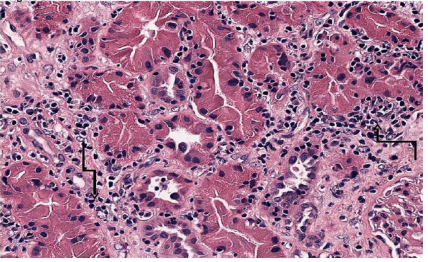
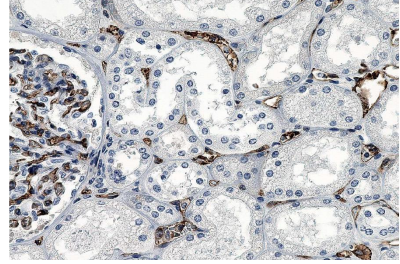
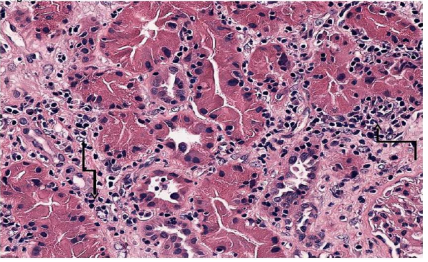




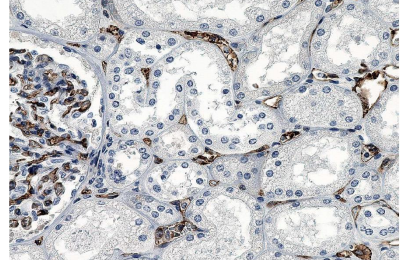
Prevalence and treatment of Acute Antibody Mediated Rejection in Renal transplantation recipients: A single center study

Esmat Abdollahpour

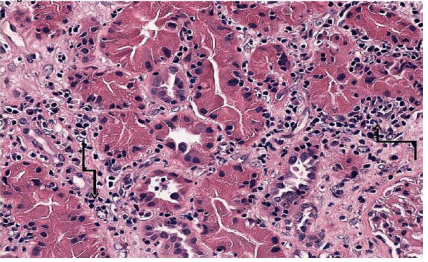
Assistant professor, department of nephrology, shariati hospital, TUMS

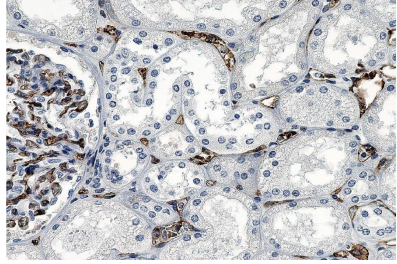


Anti body mediated rejection (AMR)



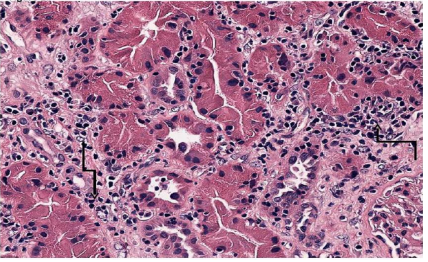
- AMR is the most common cause of allograft failure after kidney transplantation
- aAMR occurs in up to 7% of Pts
- as high as 50% of Pts with HLA-incompatible transplantation
- Kidney recipients with aAMR experience a significantly worse graft prognosis compared to those with TCMR or no rejection
- French study showed three and nine-fold increased risks of graft loss in patients with aAMR with and without a vascular component respectively, compared to those with TCMR (Lefaucheur C et al, Lancet 2013;381:313–9)
- May ccount for over half of all death-censored graft loss over time



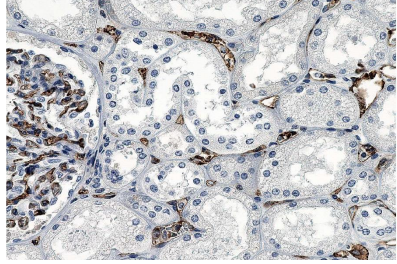


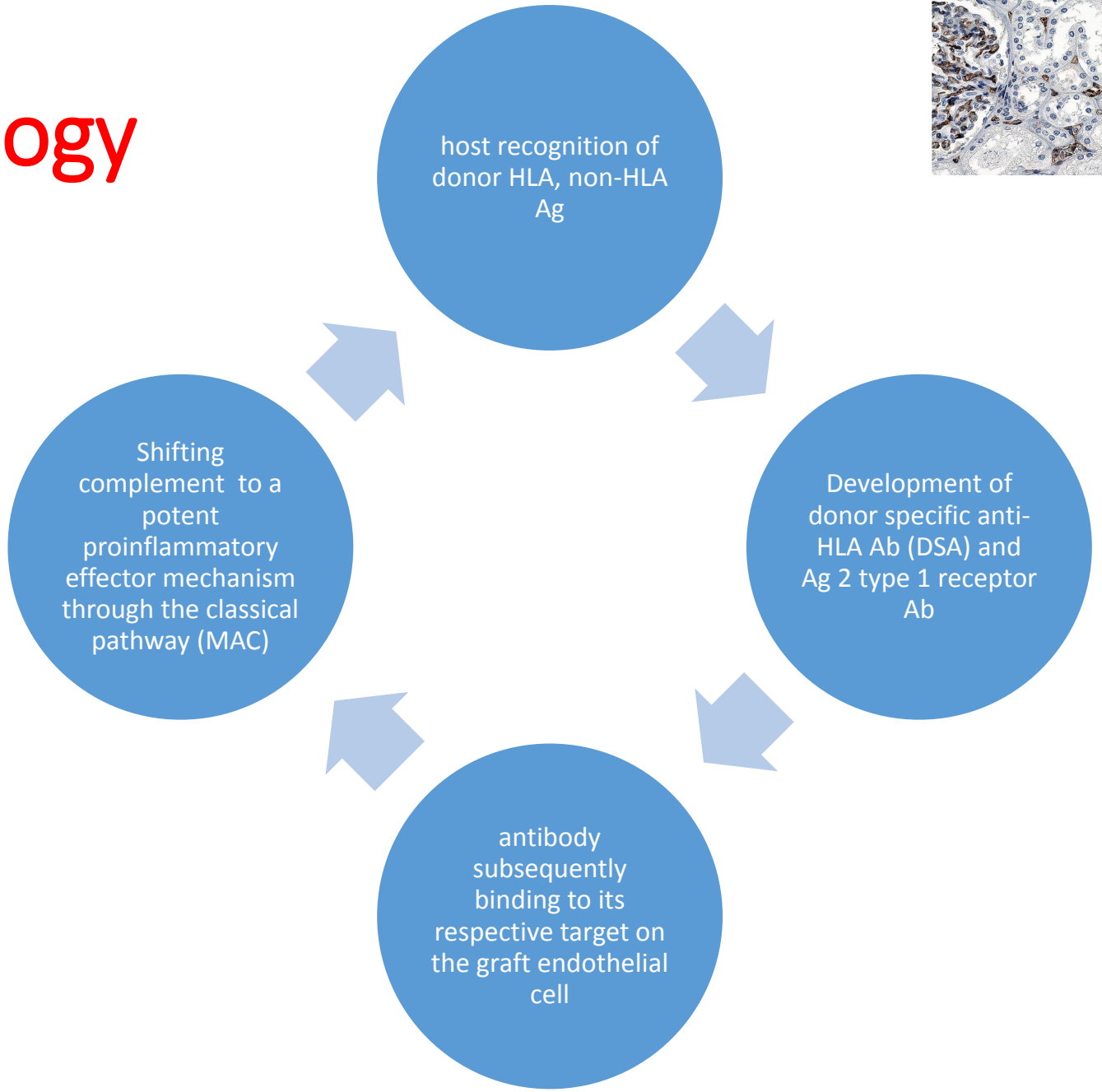
Risk factors for AMR

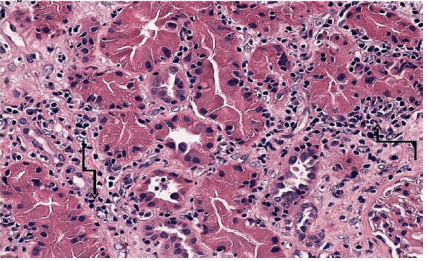
- One or more HLA mismatch
- Younger recipient and older donor age
- PRA greater than 0 percent
- Presence of DSA
- BG incompatibility
- Delayed onset of graft function
- Cold ischemia time greater than 24 hours
- Patients with a previous episode of rejection
- Those receiving a second or greater transplant

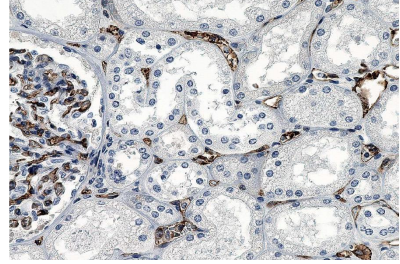


Pathophysiology

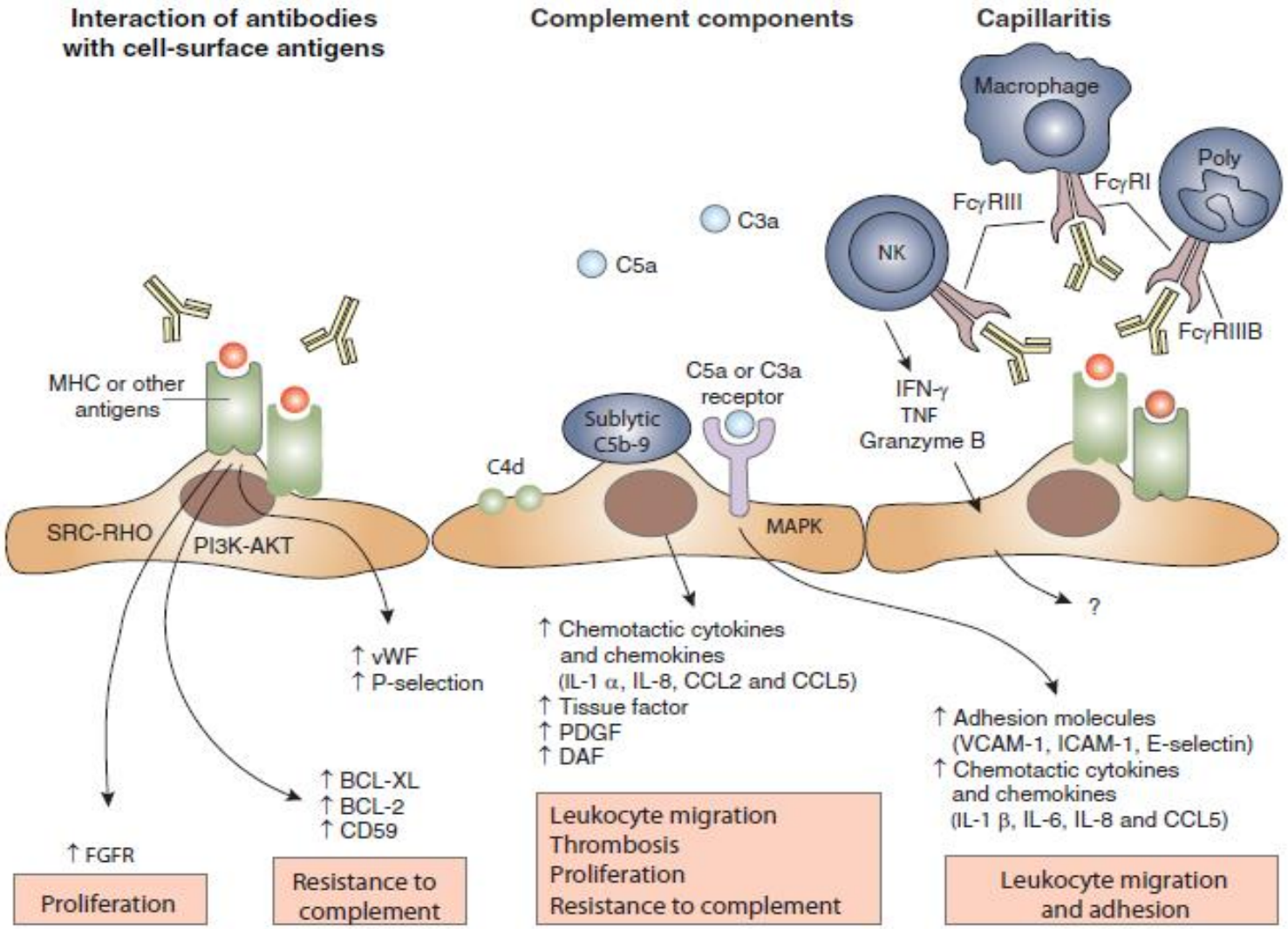


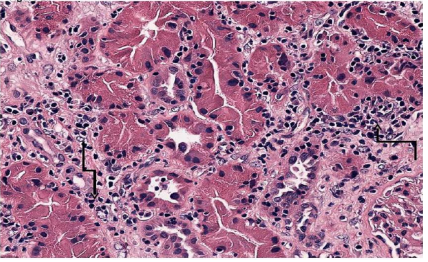


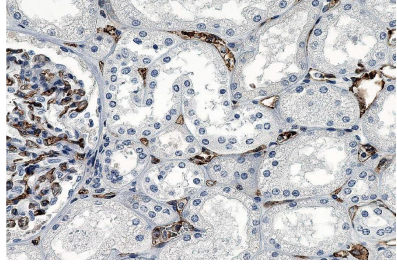




Mechanism of DSA mediated Endothelial injury in Renal Allograft







Revised (Banff 2013) classification of acute antibody-mediated rejection (all three criteria must be present)

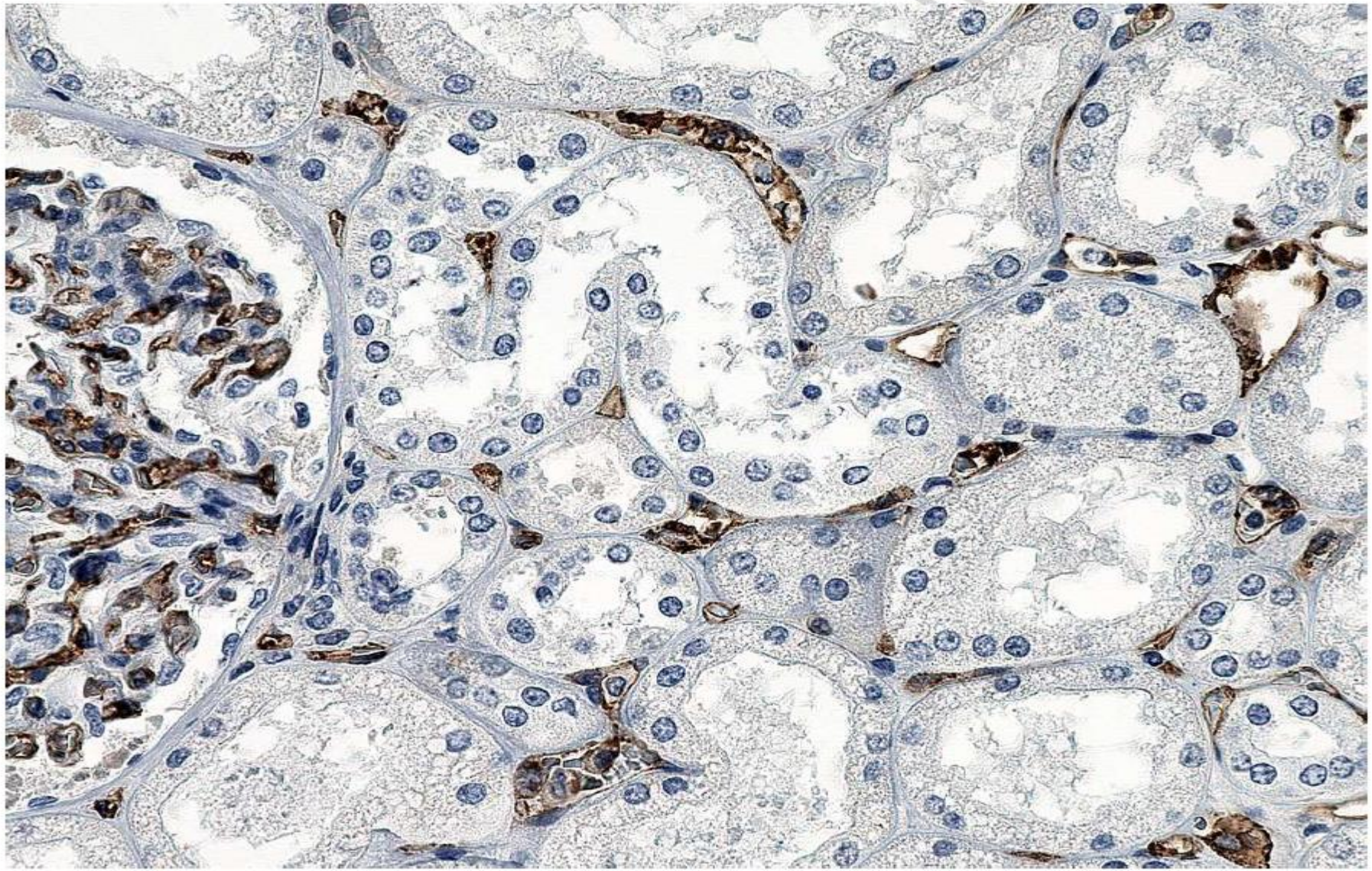
1. Presence of donor-specific antibodies, including HLA or other antibodies

2. Evidence of recent donor-specific antibodies with the vascular endothelium, evidenced by at least one of the following:

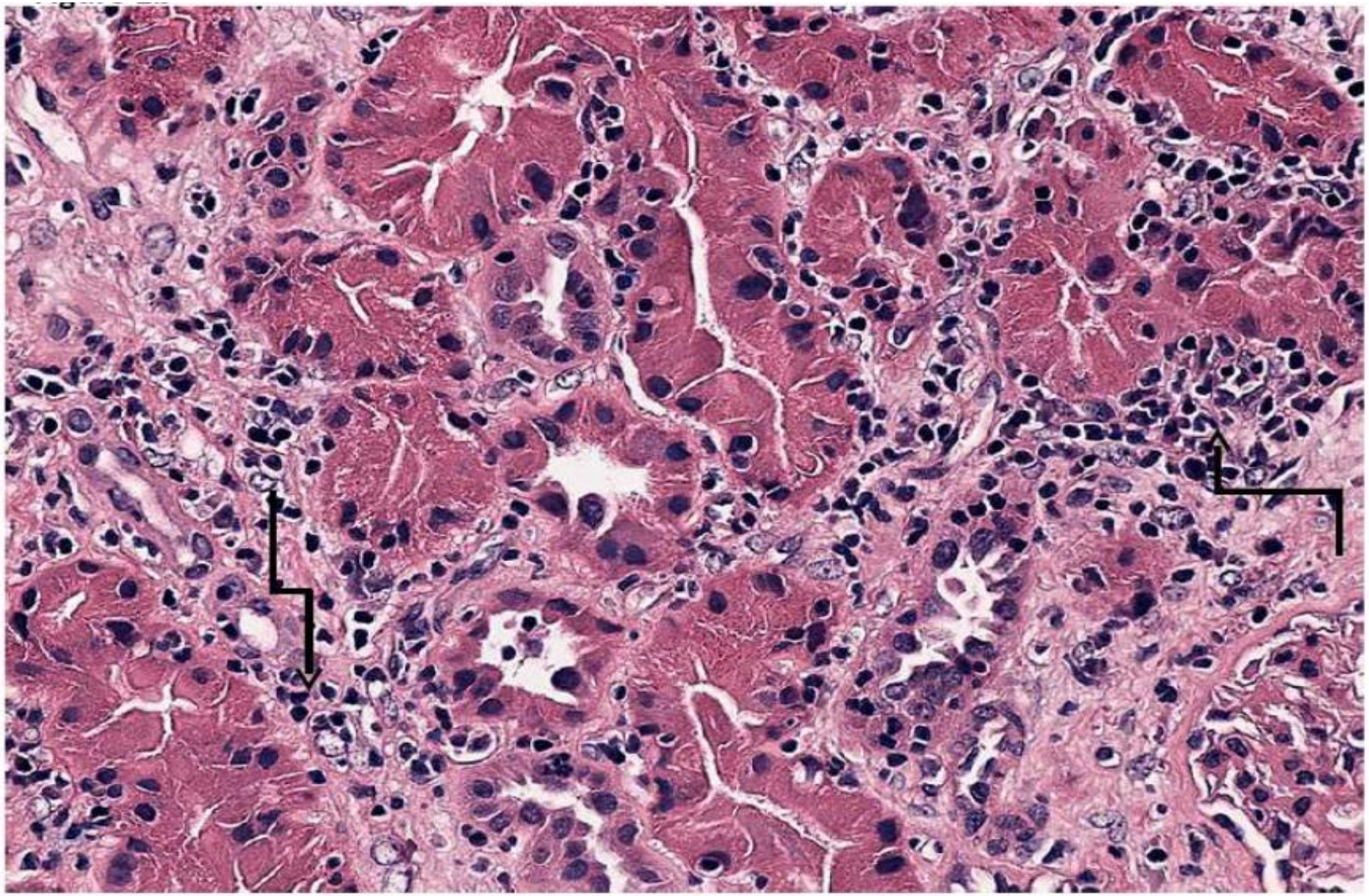
   a. Linear C4d staining in the peritubular capillaries
   b. Moderate microvascular inflammation ([g + ptc ≥2])
   c. Increased expression of gene transcripts associated with endothelial injury in biopsy tissue, if thoroughly validated

3. Histologic evidence of acute tissue injury, including one of the following:

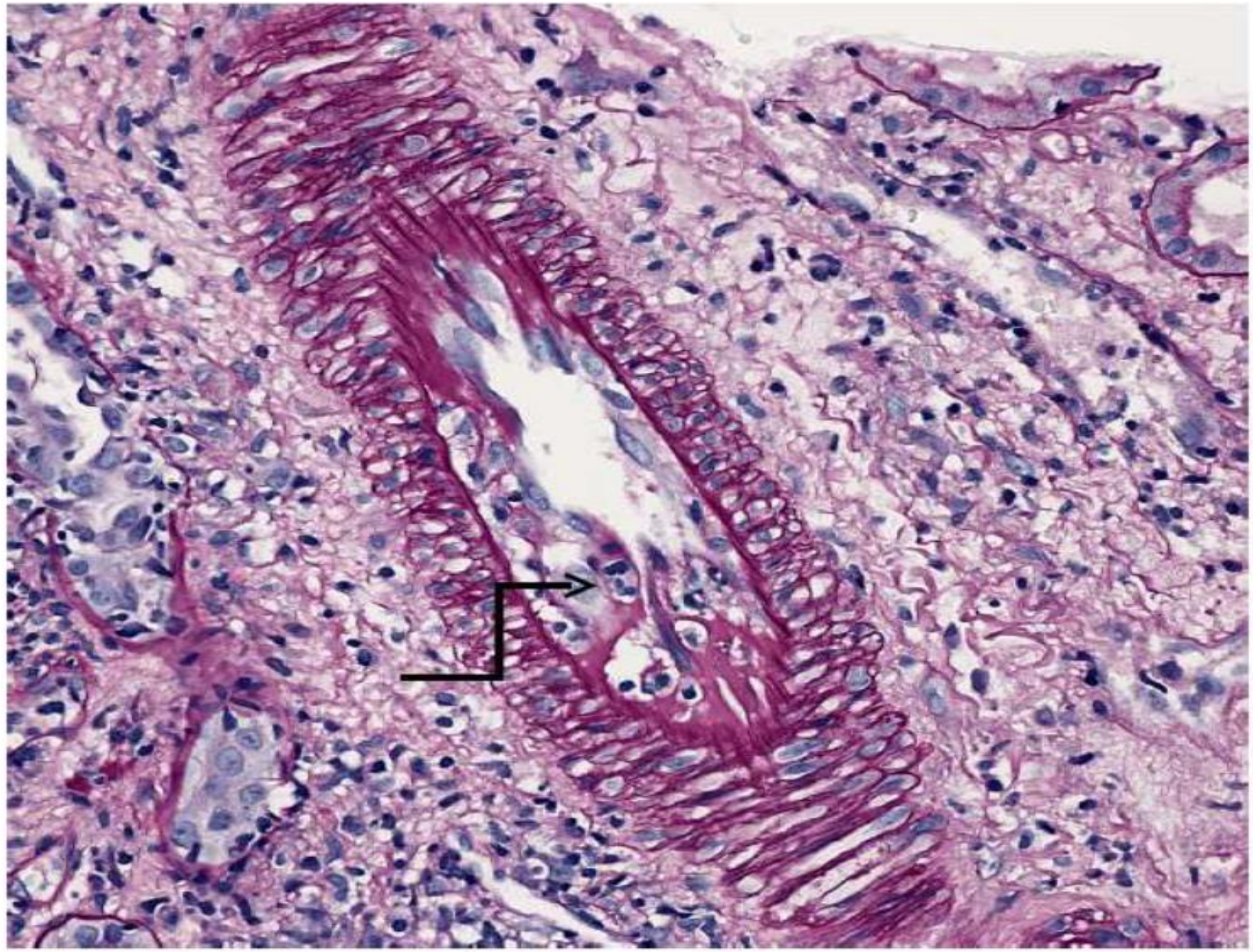
   a. Microvascular inflammation (g > 0 and/or ptc > 0)
   b. Intimal or transmural arteritis (v > 0)
   c. Acute thrombotic microangiopathy, in absence of any other cause
   d. Acute tubular injury, in the absence of any other cause



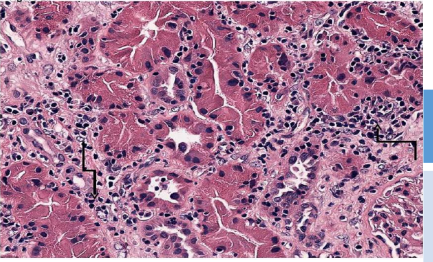
peritubular capillary C4d staining by immunohistochemistry

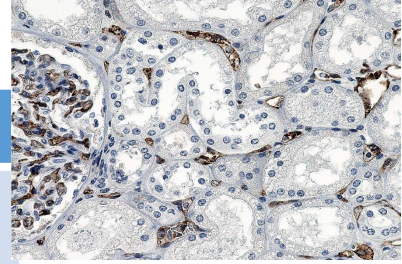


microvascular inflammation with peritubular capillaritis (arrows)



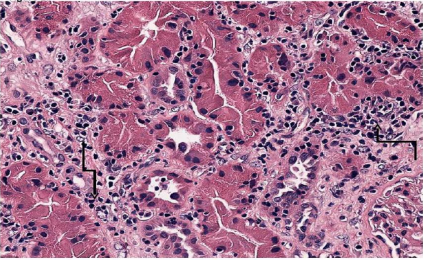
vascular endotheliitis (V-lesion, arrow)

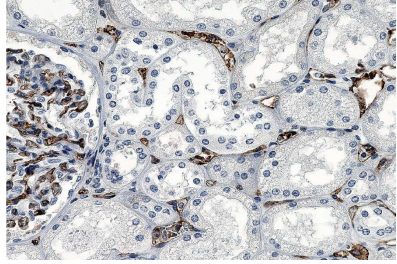




Treatment Options for Acute Antibody Mediated Rejection

Therapeutic Target	Therapy	Mechanism
Immunomodulation	**Corticosteroids**	Inhibition of cytokine transcription and production, with multiple downstream effects on lymphocyte function
	IVIG	Proposed mechanisms include inhibition of dendritic cells and macrophages, apoptosis of plasma cells, stimulation of regulatory T cells, clearance of pathogenic antibodies, and modulation of cytokines and cellular receptors
B Lymphocytes	**Splenectomy**	Removal of memory B cells
	Rituximab	Chimeric murine antibody that specifically inhibits CD20, a glycoprotein involved in B-cell activation and maturation, leading to depletion of B lymphocytes
Plasma Cells	**Bortezomib**	Proteasome inhibition causing plasma cell apoptosis
Antibodies	**Therapeutic Plasma Exchange**	Removal of pathogenic antibodies
Complement	**Eculizumab**	Anticomplement C5-antibody that inhibits the proinflammatory effects of the terminal complement components and formation of the membrane attack complex

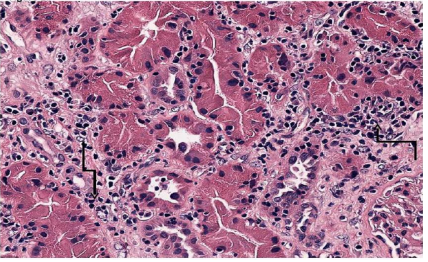




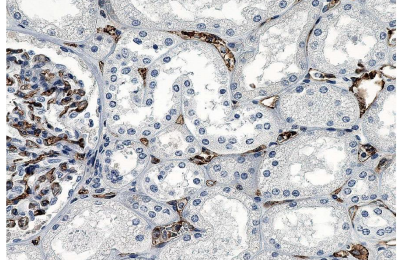
Treatment, year of publication	1972-1976	1977-1981	1982-1986	1987-1991	1992-1996	1997-2001	2002-2006	2007-2011
Plasmapheresis								
Column immunoadsorption								
IVIG								
Bortezomib								
Corticosteroids								
Antithymocyte antibodies								
Eculizumab								
Mycophenolate								
Rituximab								
Cyclophosphamide								
Deoxyspergualin								
Splenectomy								
Tacrolimus								

Transplantation 2012;94: 775-783, Darren M. Roberts (10388 citations were identified)

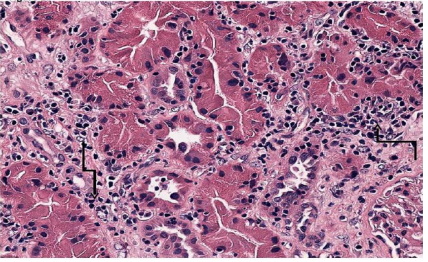
Trends in the use of treatments for AMR over time, Using a gray scale, black represents the most commonly used

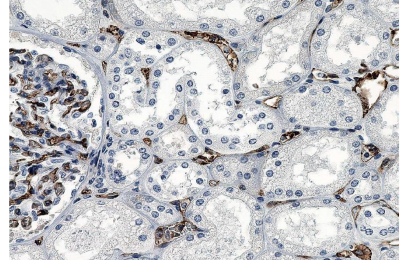


Prevalence and treatment of Acute Antibody Mediated Rejection in Renal transplantation recipients: A single center study



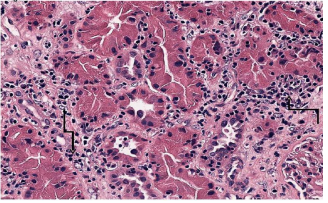
- Descriptive-comparative cross sectional study
- The study population: all patients who had received kidney transplantation in Shariati Hospital between 2014 to 2017 (374 patients)
- Prevalence of aAMR (increase more than 20% of baseline Cr, kidney biopsy)
- Risk factors for aAMR incidence
- Rate of response to treatment (in 6 months)

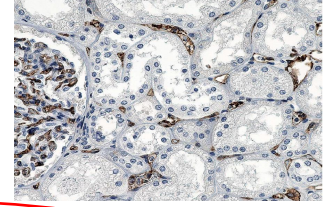


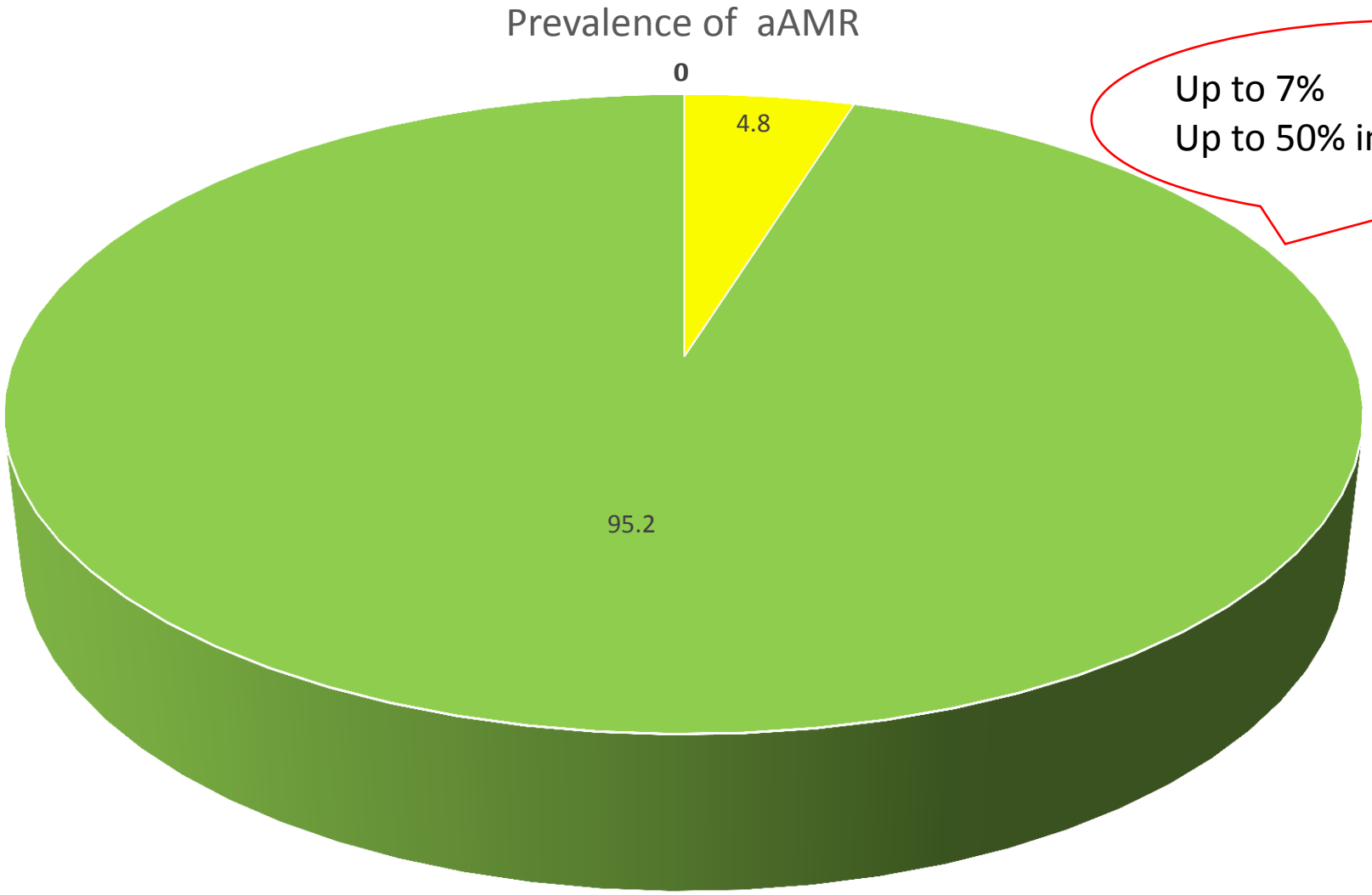


Frequency distribution of age in patients who were undergone kidney transplantation

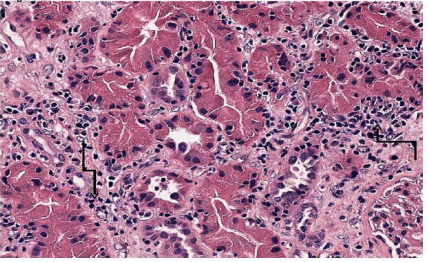
age	frequency	percent
<18	29	7.75
18-45	149	39.84
>45	196	52.41
total	374	100

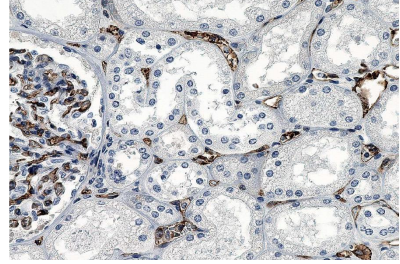




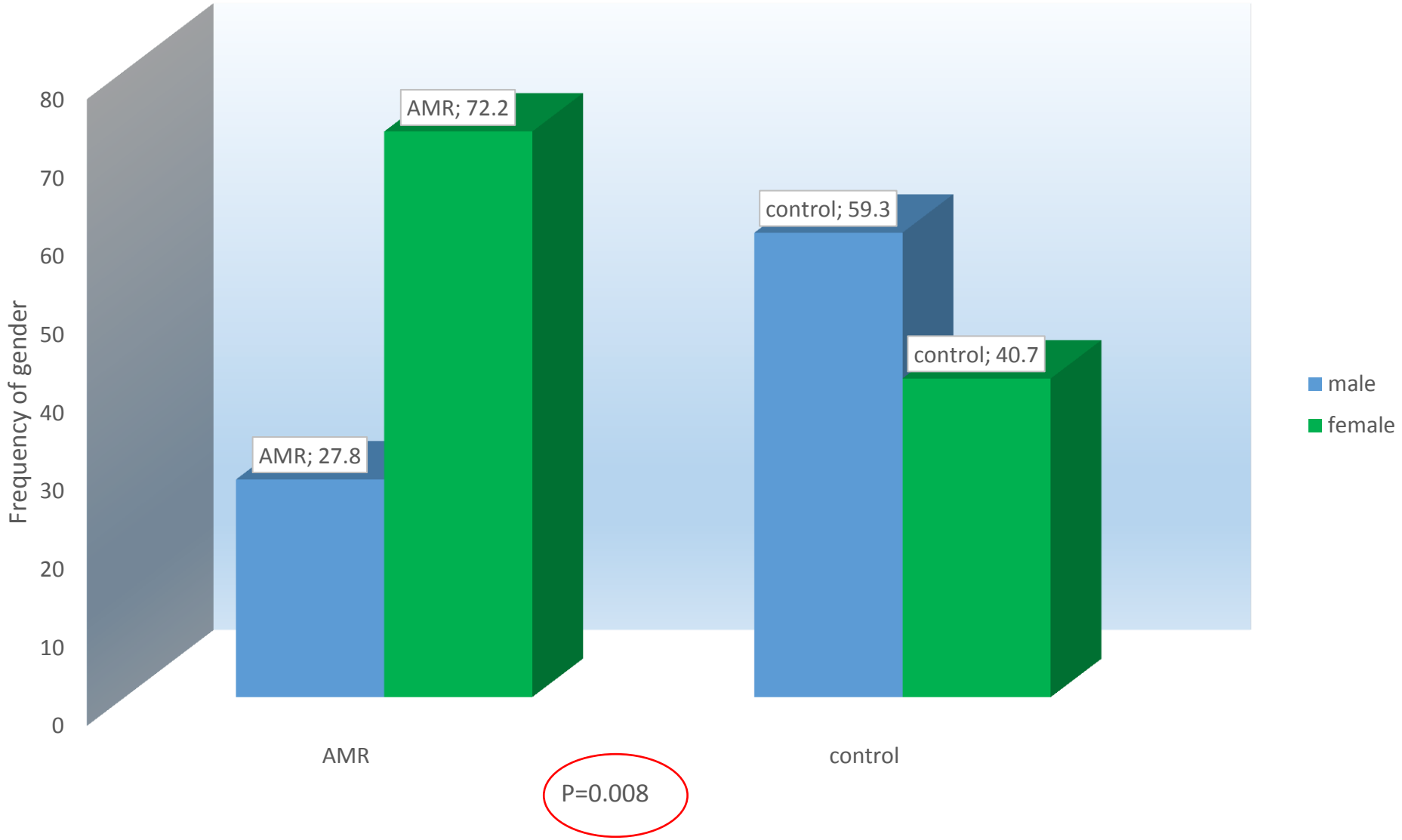


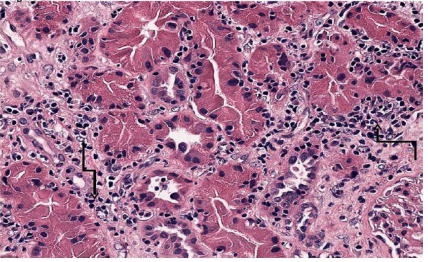
Up to 7%
Up to 50% in HLA incompatible

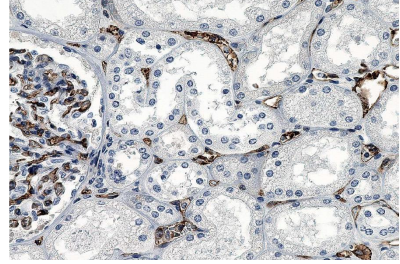




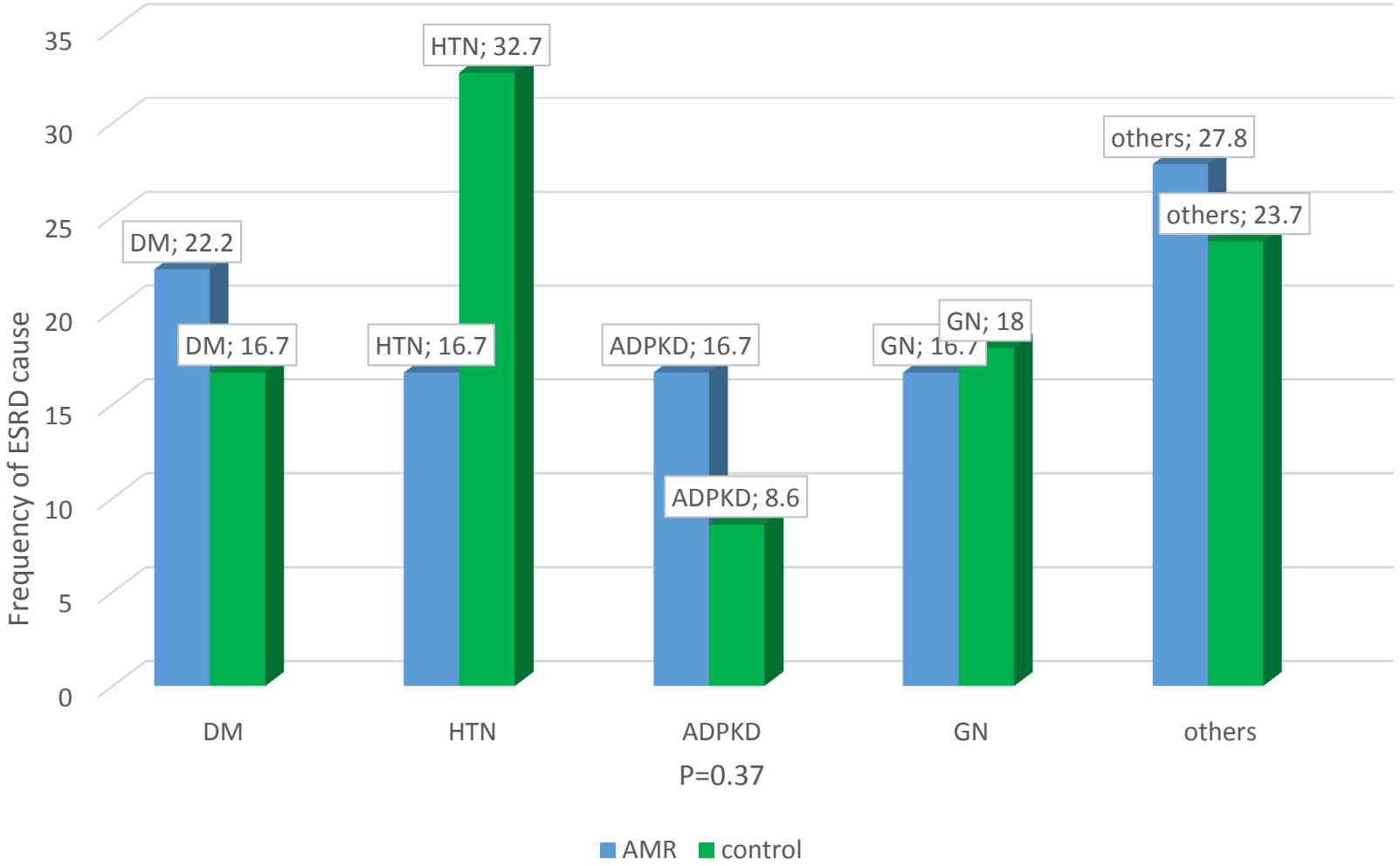
Frequency distribution of gender of kidney allograft recipients

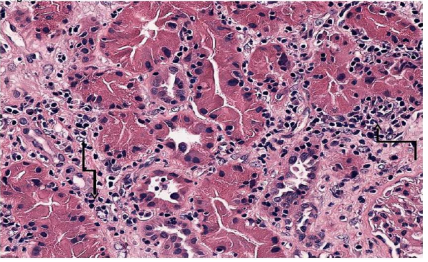


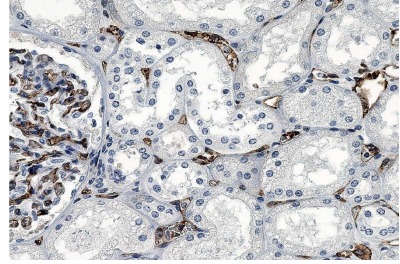




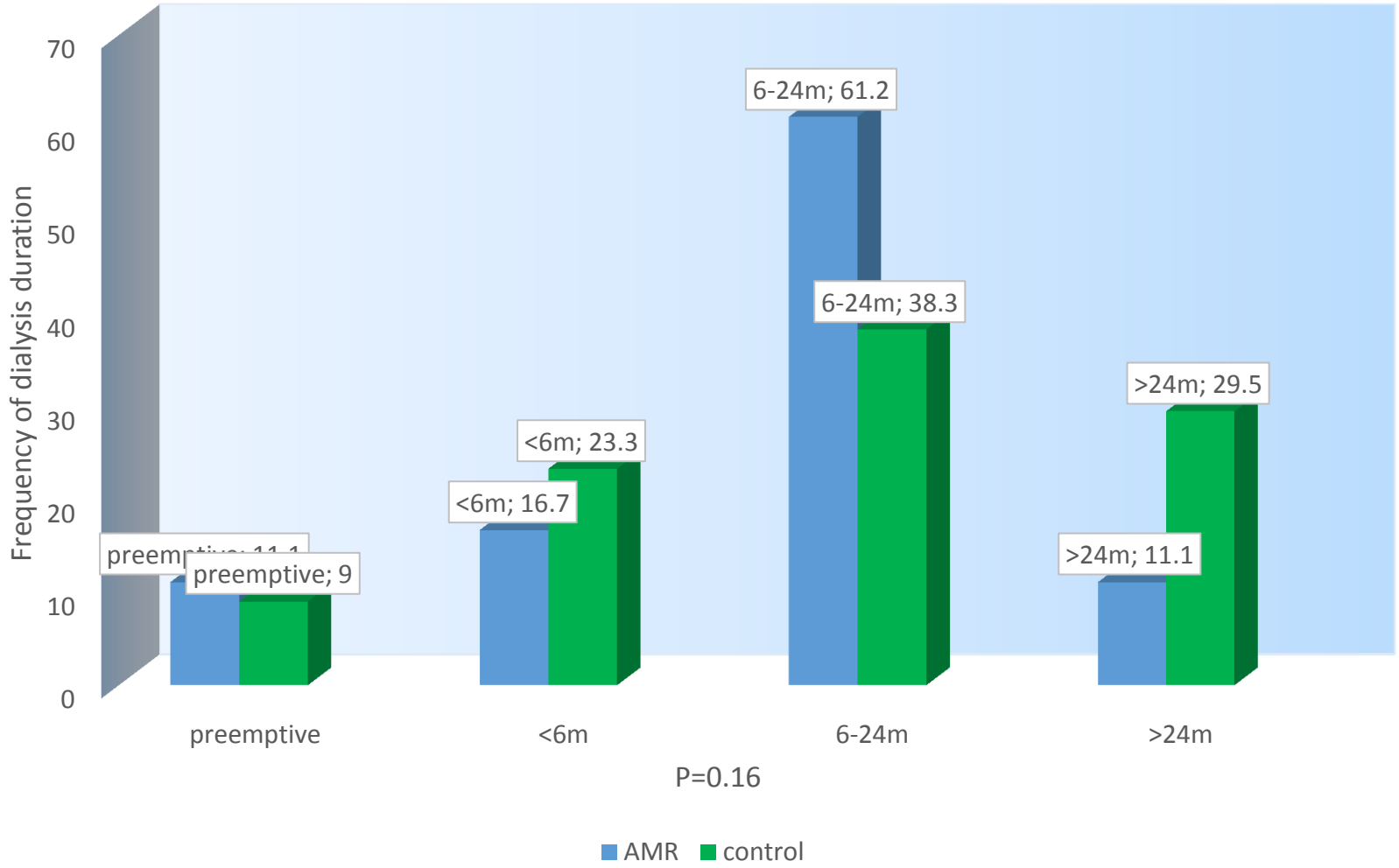
Frequency distribution of the ESRD causes

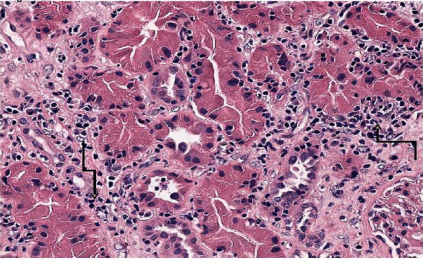


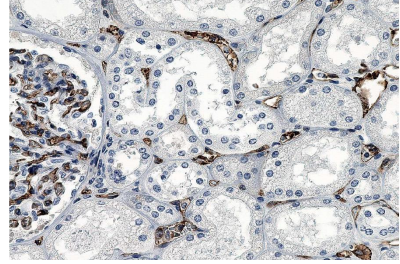


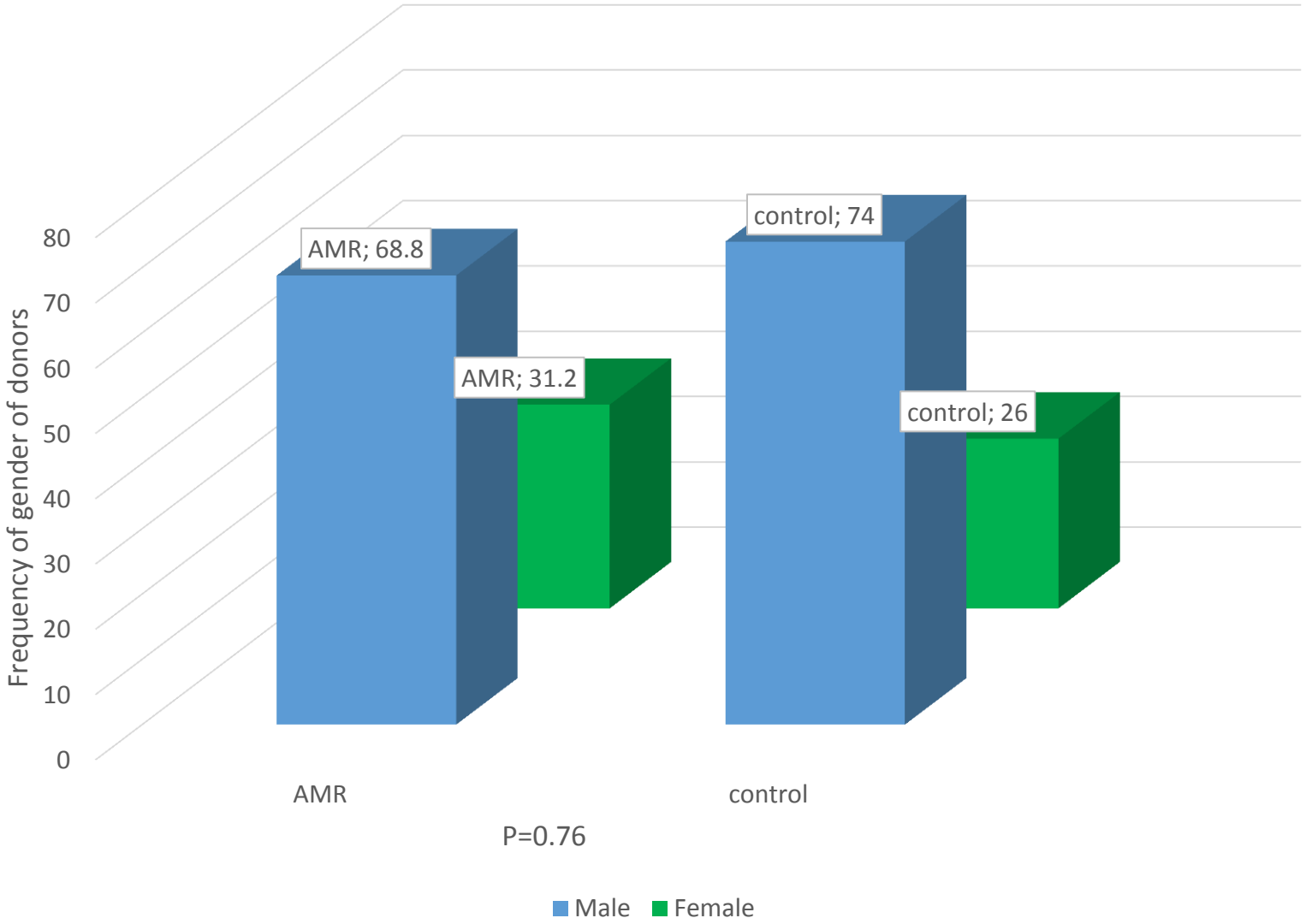


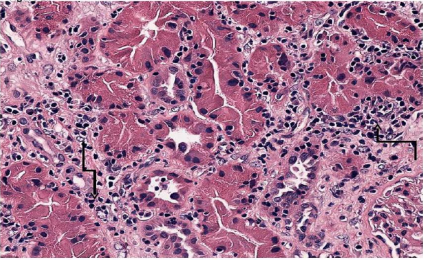
Frequency distribution of dialysis duration

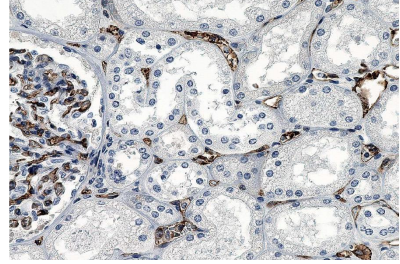


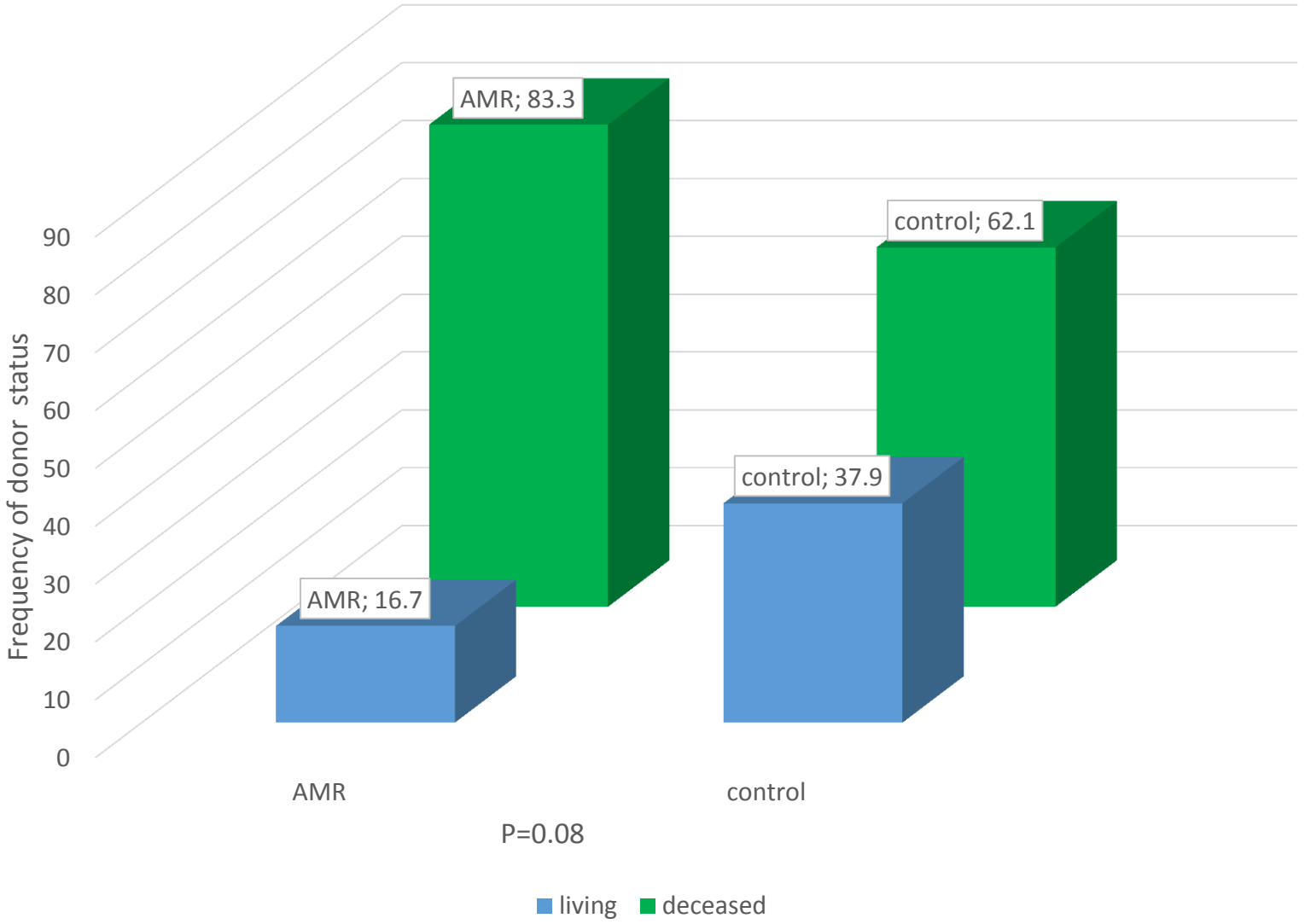


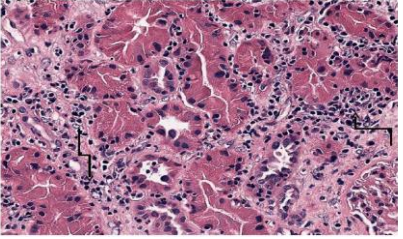


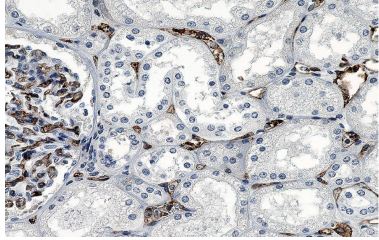

Frequency of gender of donors
80
70
60
50
40
30
20
10
0
AMR; 68.8
AMR; 31.2
control; 74
control; 26
AMR
control
P=0.76
Male
Female



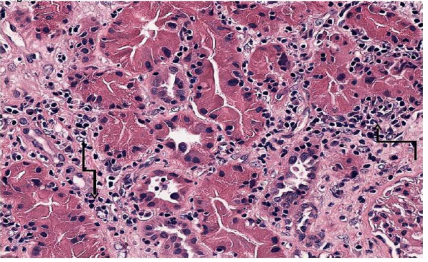


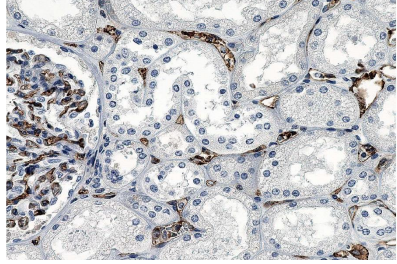

AMR; 83.3
control; 62.1
control; 37.9
AMR; 16.7
90
80
70
60
50
40
30
20
10
0
Frequency of donor status
AMR
control
P=0.08
living
deceased

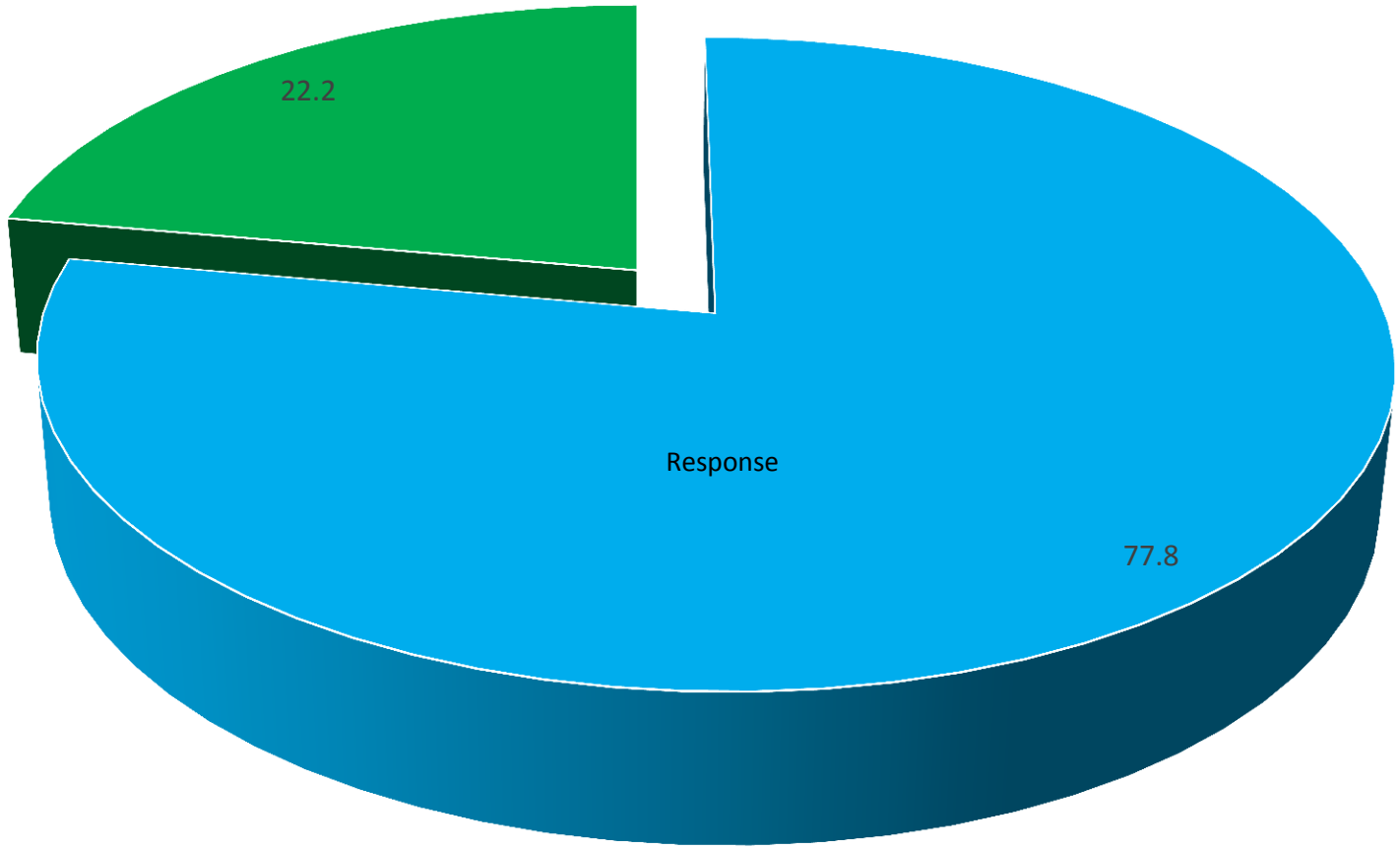




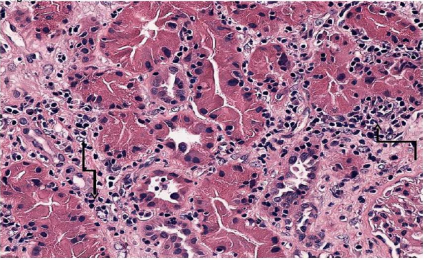
Type of treatment	Number of patients
IVIG	5
IVIG + plasma exchange	1
IVIG + plasma exchange + Rituximab	12



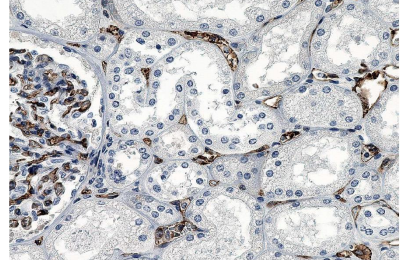




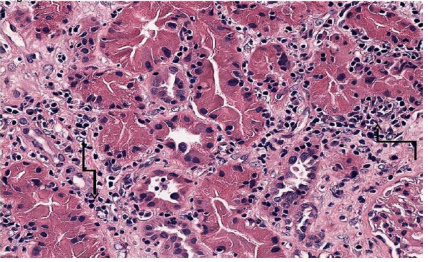
Type of treatment had no effect on response



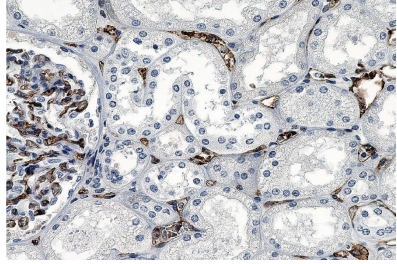
Other studies



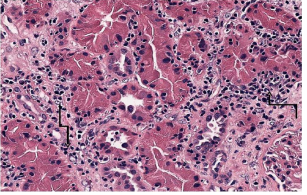
- Lefaucheur C et al reported superior outcomes in patients with aAMR treated with combination plasma exchange, IVIG, and rituximab compared to patients treated with high dose IVIG alone (Am J Transplant 2009;9:1099–107)
- These data suggest a proof of concept that IVIG monotherapy is insufficient in the treatment of aAMR.



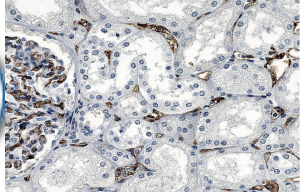
Other studies



- Sautenet et al, reported that adding rituximab to plasmapheresis, IVIg and corticosteroids did not significantly improve allograft function or survival at day 12 and at 1 year (Transplantation. 2015;100:391–399)
- Kaposztas Z, showed a better 2-year graft survival with plasmapheresis and rituximab compared with plasmapheresis alone (Clin Transplant. 2009;23:63–73)



Review



The Treatment of Antibody-Mediated Rejection in Kidney Transplantation: An Updated Systematic Review and Meta-Analysis

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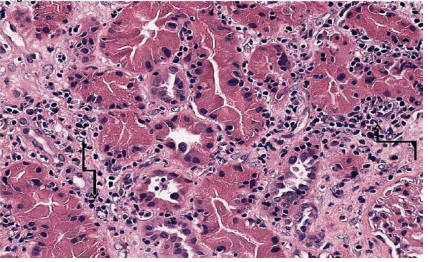
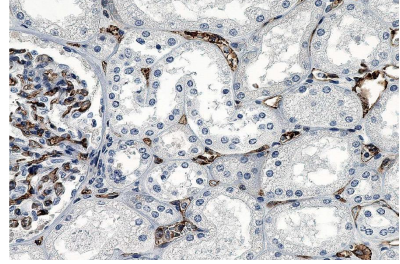
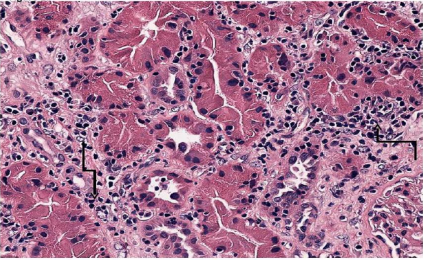
Background. Current treatments for antibody-mediated rejection (AMR) in kidney transplantation are based on low-quality data from a small number of controlled trials. Novel agents targeting B cells, plasma cells, and the complement system have featured in recent studies of AMR. **Methods.** We conducted a systematic review and meta-analysis of controlled trials in kidney transplant recipients using Medline, EMBASE, and CENTRAL from inception to February 2017. **Results.** Of 14 380 citations, we identified 21 studies, including 10 randomized controlled trials, involving 751 participants. Since the last systematic review conducted in 2011, we found nine additional studies evaluating plasmapheresis + intravenous immunoglobulin (IVIG) (two), rituximab (two), bortezomib (two), C1 inhibitor (two), and eculizumab (one). Risk of bias was serious or unclear overall and evidence quality was low for the majority of treatment strategies. Sufficient RCTs for pooled analysis were available only for antibody removal, and here there was no significant difference between groups for graft survival (HR 0.76; 95% CI 0.35-1.63; $P = 0.475$). Studies showed important heterogeneity in treatments, definition of AMR, quality, and follow-up. Plasmapheresis and IVIG were used as standard-of-care in recent studies, and to this combination, rituximab seemed to add little or no benefit. Insufficient data are available to assess the efficacy of bortezomib and complement inhibitors. **Conclusion.** Newer studies evaluating rituximab showed little or no difference to early graft survival, and the efficacy of bortezomib and complement inhibitors for the treatment of AMR remains unclear. Despite the evidence uncertainty, plasmapheresis and IVIG have become standard-of-care for the treatment of acute AMR.

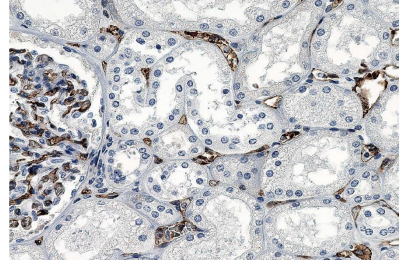
(*Transplantation* 2018;102: 557–568)



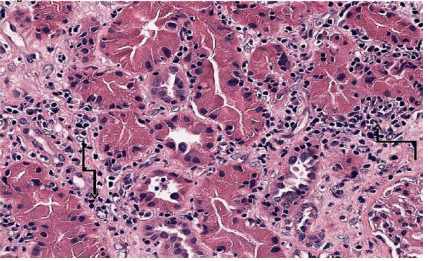


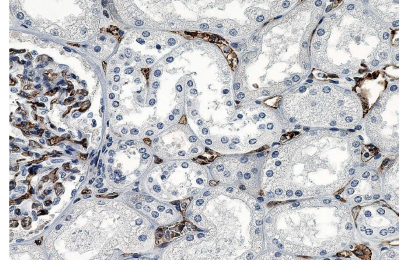
Variables		Response	No response	P-value
PRA	< 20%	78.6%	21.4%	P=0.1
	≥ 20%	75.0%	25.0%	
Recipient gender	Female	84.6%	15.4%	P=2.1
	Male	60.0%	40.0%	
Dialysis duration	preemptive	0.0%	100.0%	P=0.18
	< 6m	100.0%	0.0%	
	6-24m	81.8%	18.2%	
	> 24m	100.0%	0.0%	
Age	< 18	100.0%	0.0%	P=0.35
	18-45	75.0%	25.0%	
	> 45	77.8%	22.2%	
Donor	Living	100.0%	0.0%	P=0.12
	Deceased	73.3%	26.7%	



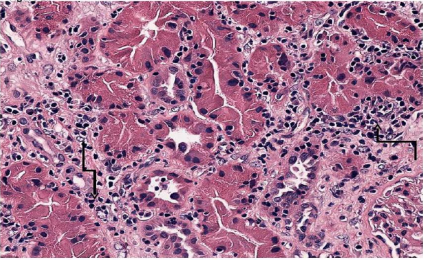


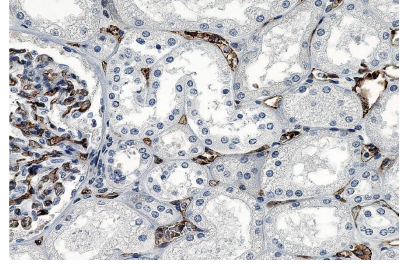
Variables		Response	No response	P-value
ESRD causes	DM	100.0%	0.0%	P=3.12
	HTN	66.7%	33.3%	
	ADPKD	100.0%	0.0%	
	GN	66.7%	33.3%	
	Others	60.0%	40.0%	
Donor gender	Female	80.0%	20.0%	P=0.58
	Male	72.7%	27.3%	
Cyclosporine	+	100.0%	0.0%	P=0.46
	-	76.5%	23.5%	
Tacrolimus	+	76.5%	23.5%	P=0.55
	-	100.0%	0.0%	
ATG	+	73.3%	26.7%	P=2.22
	-	100.0%	0.0%	





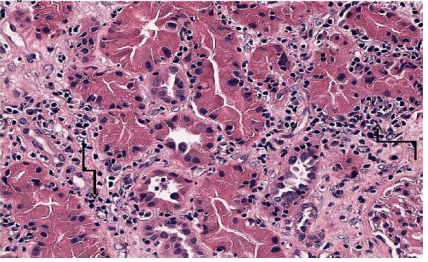
variables		Response	No response	P-value
Time of kidney transplantation	1	86.7%	13.3%	P=0.039
	2	0.0%	100.0%	
	3	100.0%	0.0%	



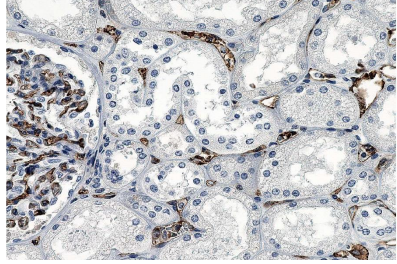


Limitations of our study

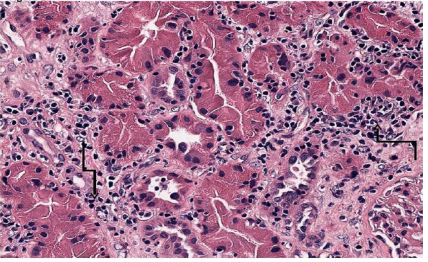
- Most important limitation of our study was the sample size, which was not large enough to draw solid and definite conclusions
- Unfortunately we didn’t have DSA

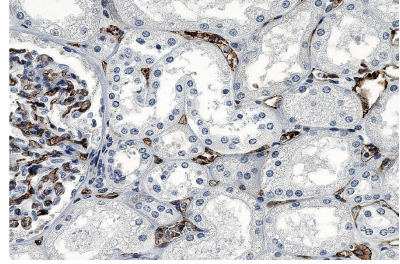


conclusion



- It is well known that if not rapidly diagnosed and properly treated, acute AMR carries a high risk of allograft loss or of residual chronic allograft dysfunction
- Early diagnosis and precise treatment would reduce morbidity, mortality, and economic costs





More clinical studies, ideally RCTs, are required to optimize the treatment of AMR and given the low incidence of AMR this is likely to require multicenter involvement