# A clinical signature surrogate of histological lesions to avoid unnecessary one year surveillance biopsy after renal transplantation

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## Introduction

In renal transplantation, **early surveillance biopsies** are becoming a current tool for the detection of histological lesions without associated clinical abnormality[1] but possible consequences on long-term prognostic. Despite the lack of specific recommendations, 3-months and/or 12-months surveillance biopsies are nowadays widely practiced by physicians in charge of kidney transplanted patients.

**Nevertheless**, surveillance biopsy remains debated after renal transplantation[2] since:

- ✓ Biopsy is an invasive chirurgical act exposing patients to risks of bleeding, bruise, infection, graft loss, etc.[3]
- ✓ Whatever the type of discovery on the surveillance biopsies (particularly at one year of follow-up), either normal or abnormal features, the histological diagnosis does not lead to clear therapeutic and consensual recommendations[4,5].
- ✓ Biopsy are "costly" for the patient since it generates a specific stress and for the society since it needs specific hospitalization.

**Hypothesis:** To practice a surveillance biopsy could sometimes be unnecessary since, among normal histology or low lesions of specific IFTA grade 1, benefit/risk balance is controversial (no evidence for a benefit of a therapeutic intervention but a risk for the kidney and the patient and a cost for the society).

## Objectives

- ✓ To identify and validate a **clinical diagnostic signature** of histological lesions from surveillance biopsy at one year after renal transplantation
- ✓ In order to not propose surveillance biopsy **to patients for whom it may be useless**

## Study population

Patients were selected from the 3 centers of the French prospective DIVAT cohort of transplanted patients who practice routinely the one year surveillance biopsy (Nantes, Lyon and Necker) (www.divat.fr)

Inclusion criteria :

- ✓ Adult recipients,
- ✓ Of Kidney or combined Kidney-Pancreas transplantation,
- ✓ Transplanted between 2006 and 2012,
- ✓ For the first or second times,
- ✓ From deceased donor,
- ✓ Alive with a functioning graft at one year post-transplantation
- ✓ With a complete Banff classification for the one year post-transplantation systematic biopsy,
- ✓ Without BKV infection in the first post-transplantation year

## Definition of histological group of interest

All 12–months surveillance biopsies were retrospectively reclassified according to the predominant anatomo-pathologic diagnosis based on Banff 2013 criteria.

The main judgment criteria is the histological group of interest defined according the possibility for a physician to take a medical decision:

- ✓ ***Interventional group:*** Patients displaying abnormal biopsies including isolated IFTA (grade 2 or 3), borderline changes, acute or chronic T-cell mediated rejection (TCMR), and acute or chronic antibody-mediated rejection (ABMR), recurrent or de novo glomerulopathy
- ✓ ***Non-interventional group:*** Patients with normal histology or IFTA grade 1

## Statistical analysis

Modeling strategy was divided in 2 steps :

1) **Learning step on a learning patient sample**

✓ Identification of diagnostic score by using

- a penalized logistic regression (to study the probability for a patient to be considered in the interventional group)
- with a ROC 0,632+ bootstrap (in order to select regression covariates constituting the score directly on their diagnostic capacities[6])

✓ Identification of discriminating threshold according to the objective to avoid unnecessary biopsy

- i.e. the discriminating threshold $c$ defined for a minimal Negative Predictive Value (NPV) of 75 %

2) **Validation step on a independent patient sample**

✓ Validation of global diagnostic score capacities from ROC curve estimated and the associated AUC

✓ Validation of the discriminating threshold with the corresponding obtained NPV

## Learning results

### Learning sample description (N=567)

| | Interventional group N=264 (46.6%) | Non-interventional group N=303 (53.4%) | p |
|---|---|---|---|
| *Quantitative variables (mean)* | | | |
| Recipient age (years) | 47.78 | 47.00 | 0.4486 |
| HLA incompatibilities ABDR | 3.30 | 3.32 | 0.8279 |
| Recipient BMI (kg/m²) | 23.66 | 23.3 | 0.2865 |
| Recipient serum creatinine at 3 months (µmol/l) | 140.15 | 118.55 | <0.0001 |
| Recipient serum creatinine at 6 months (µmol/l) | 139.46 | 117.51 | <0.0001 |
| Recipient serum creatinine at 12 months (µmol/l) | 139.25 | 118.47 | <0.0001 |
| Donor age (years) | 48.89 | 44.72 | 0.0026 |
| Donor serum creatinine (µmol/l) | 92.20 | 96.17 | 0.4818 |
| Cold ischemia time (hours) | 19.36 | 18.93 | 0.4743 |
| *Qualitative variables (%)* | | | |
| Recipient men | 56.44 | 64.69 | 0.0486 |
| Recurrent initial disease | 16.29 | 17.82 | 0.7411 |
| Daily anticlass I >0 | 24.62 | 17.16 | 0.0183 |
| Daily anticlass II >0 | 28.41 | 17.82 | 0.0011 |
| History of hypertension | 82.20 | 86.47 | 0.1988 |
| History of cardiovascular diseases | 17.05 | 21.12 | 0.2619 |
| History of type I diabetes | 20.08 | 22.44 | 0.5597 |
| History of type II diabetes | 5.68 | 5.61 | 0.9999 |
| History of dyslipidaemia | 28.41 | 28.38 | 0.9999 |
| History of obesity | 10.23 | 11.55 | 0.7121 |
| Cerebro-vascular donor death | 52.65 | 47.85 | 0.2878 |
| Donor men | 63.64 | 60.73 | 0.5315 |
| Pancreas-Kidney | 13.26 | 21.45 | 0.0146 |
| 2nd transplantation | 19.32 | 11.88 | 0.0196 |
| DGF | 28.79 | 27.06 | 0.7347 |
| Dialysis technique before transplantation | | | 0.0004 |
| DP | 5.68 | 7.59 | |
| Haemodialysis | 85.61 | 72.28 | |
| CMV infection | 14.02 | 8.25 | 0.0395 |
| Graft infection | 15.53 | 6.93 | 0.0017 |
| Urinary infection | 36.36 | 31.68 | 0.2776 |
| Acute rejection | | | 0.0037 |
| Cellular | 15.53 | 7.26 | |
| Humoral | 2.27 | 1.32 | |

### Clinical diagnostic score $X$

- ✓ Constituted of 8 covariates (no relevant clinical interaction were retained) including
  - Recipient serum creatinine at 3-months, 6-months, and 12-months,
  - Recipient and donor gender,
  - Daily anticlass II immunization,
  - Dialysis technique before transplantation (extra-renal filtration vs. pre-emptive graft)
  - Graft type (Pancreas-Kidney vs. Kidney)
- ✓ AUC of ROC curve = 0,69
- ✓ For NPV=75%, discriminating threshold $c = -0{,}31$ leads to PPV=51%, Sensitivity=93%, Specificity=25%

## Validation results

- ✓ Among 150 independent patients for whom the diagnostic score $X$ can be calculated,
  - 61 patients (41%) had abnormal biopsies
  - 89 patients (59%) had normal histology or IFTA grade 1
- ✓ AUC of ROC curve = 0,64 (95%CI:[0,55-0,73] )

➔ **Diagnostic capacities of the clinical score are reasonable and validated**

### Medical decision making

| | High risk to be considered in Interventional group ($X \geq -0{,}31$) | High risk to be considered in Non-interventional group ($X < -0{,}31$) | Total |
|---|---|---|---|
| Interventional group | 59 | 2 | 61 |
| Non-interventional group | 69 | 20 | 89 |
| Total | 128 | 22 | 150 |

➔ **NPV = 20/22 = 90%** and PPV = 59/128 = 46%
With Sensitivity = 59/61 = 97% and Specificity = 20/89 = 22%

- ✓ 15% patients (=22/150) were classified in the non-interventional group
- ✓ Among them, 90% realized biopsies reveal normal histology or IFTA grade 1, leading to consider realized biopsies as useless
- ✓ The minimal level of NPV is confirmed validating the discriminating threshold $c$=−0,31

➔ **Medical decision rules validated**

## Conclusions

In this study, we built a **clinical score** that may allow:

- ✓ To diagnose patients at high risk of normal histology or IFTA grade 1 lesions without inflammation (i.e. Non-interventional group) with a very low risk of error (NPV=90%)
- ✓ To avoid useless biopsies in 15% of patients in whom probably no therapeutic change will follow as a consequence of this invasive intervention

## References

[1] Kasiske BL, Vazquez MA, Harmon WE, Brown RS, Danovitch GM, Gaston RS, et al. (2000). Recommendations for the Outpatient Surveillance of Renal Transplant Recipients. J Am Soc Nephrol. 11(suppl 1):S1-86.

[2] Wilkinson A (2006). Protocol Transplant Biopsies: Are They Really Needed? Clin J Am Soc Nephrol. 1(1):130-7.

[3] Whittier WL, Korbet SM (2004). Timing of Complications in Percutaneous Renal Biopsy. J Am Soc Nephrol. 15(1):142-7.

[4] Rush D, Arlen D, Boucher A, Busque S, Cockfield SM, Girardin C, et al. (2007). Lack of Benefit of Early Protocol Biopsies in Renal Transplant Patients Receiving TAC and MMF: A Randomized Study. Am J Transplant. 7(11):2538-45.

[5] Kurtkoti J, Sakhuja V, Sud K, Minz M, Nada R, Kohli HS, et al. (2008). The Utility of 1- and 3-Month Protocol Biopsies on Renal Allograft Function: A Randomized Controlled Study. Am J Transplant. 8(2):317-23.

[6] Danger R, Foucher Y (2012). Time dependent ROC curves for the estimation of true prognostic capacity of microarray data. *Stat Appl Genet Mol Biol*. 11(6):1544-6115.

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