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Very Low Frequency of Pathological Findings in One-year Protocol Biopsies of Uneventful Standard Risk Kidney Transplant Recipients: Results From the Nordic Protocol Biopsy Study

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Background. The clinical significance of kidney transplant protocol biopsies has been debated. We studied the frequency of borderline changes and T cell–mediated rejection (TCMR) in 1-y protocol biopsies in standard risk kidney transplant recipients. **Methods.** Consecutive non-HLA-sensitized recipients of kidney transplants between 2006 and 2017, who underwent a protocol biopsy at 1 y in 2 national transplant centers were studied retrospectively (N = 1546). Donor-specific HLA antibodies (DSAs), graft function (plasma creatinine), and proteinuria were measured at the time of 1-y protocol biopsy. The occurrence of subclinical acute TCMR (i2t2v0 or higher) or borderline changes suspicious of TCMR (i1t1v0 or higher) in the protocol biopsy was studied, together with frequency of findings causing changes in the composite score iBox. **Results.** Subclinical acute TCMR was detected in 30 of 1546 (1.9%) of the protocol biopsies, and borderline or TCMR in 179 of 1546 (12%). Among patients with no history of acute rejection, and no proteinuria or DSA, TCMR was detected in only 1 of 974 (0.1%) and borderline or TCMR in only 48 of 974 (4.9%) patients at 1 y. In the absence of proteinuria (<30 mg/g, or equivalent as measured with a negative dipstick proteinuria) or DSA, or history of acute rejection, only 50 of 974 (5.1%) biopsies showed any lesions significant for the iBox score. **Conclusions.** The likelihood of pathological findings in 1-y protocol biopsies in non-HLA-sensitized patients without previous immunological events is low. Clinical usefulness of protocol biopsies seems limited in these patients.

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Protocol biopsies have been routine practice after kidney transplantation in many transplant centers for decades because existing noninvasive markers of renal function or kidney transplant injury continue to lack sensitivity, specificity, or clinical utility to adequately detect pathological changes in the graft.[1] The most common justification for performing invasive protocol biopsies is the possible detection of subclinical inflammatory responses because early evidence has shown the clinical benefit of treating subclinical acute rejection.[2] In addition to the possibility for early treatment of inflammatory lesions, protocol biopsies are considered useful in predicting long-term outcomes. Recently, a composite score "iBox" has been developed and validated for accurately predicting graft outcome and is based on several parameters, including histopathological scoring of defined biopsy components.[3] Risk of complications associated with kidney transplant protocol biopsies is considered very low.[4]

Despite the potential benefits, most transplant centers do not perform surveillance biopsies after kidney transplantation. According to a US survey, only 17% of the respondent transplant centers performed protocol biopsies on all patients and 21% on selected cases.[5] The most common reasons for not taking protocol biopsies were low yield of pathological findings and the belief that biopsy will not change outcome. Indeed, the frequency of subclinical acute rejection in, for example, 1-y protocol biopsies seems to vary substantially with different transplant cohorts, ranging between 7% and 28%.[6-9] With a very low incidence of subclinical acute rejection, the risk–benefit ratio of protocol biopsies in relation to clinical decision-making may be questionable. Accordingly, in a randomized trial by Rush et al,[10] no clinical benefit was detected with early protocol biopsies.

The aim of the current study is to describe findings in 1-y protocol biopsies in immunologically standard risk patients. Our hypothesis was that the frequency of pathological findings among nonsensitized patients without any clinical evidence of graft injury is low, and thus, the clinical usefulness of 1-y protocol biopsies in these patients may be questionable.

MATERIALS AND METHODS

Patients

Nonsensitized recipients of ABO compatible kidney transplants between 2006 and 2017, who had a functioning graft at 1 y and underwent a protocol biopsy at 1 y, according to the local protocol in the national transplant centers of Finland (Helsinki since 2006) or Norway (Oslo since 2009), were included in this retrospective study. Donor-specific HLA antibodies (DSA), graft function (plasma creatinine), and proteinuria (dipstick proteinuria in Helsinki and the albumin–creatinine ratio in Oslo) were measured at the time of 1 y protocol biopsy. Dipstick proteinuria measurements were compared with equivalent categories of albumin–creatinine ratios, as recommended by the assay standard (HUSLAB, Helsinki University Hospital). As the purpose was to analyze the usefulness of protocol biopsies in immunologically standard risk patients, only patients who were nonsensitized (no preformed HLA antibodies, measured as complement-dependent cytotoxicity panel-reactive antibodies 0%) at the time of transplantation were included. As the complement-dependent cytotoxicity PRA is less sensitive than single-antigen bead (SAB) assays, some patients may have had HLA antibodies measured with SAB assays. However, all patients with preformed HLA DSA were excluded from the analyses. Patients with missing data in either of the parameters of interest (DSA, proteinuria, graft function, biopsy data) were excluded, as were also recipients of multiorgan transplants (pancreas-kidney, liver-kidney, heart-kidney). Clinical data were collected from electronic medical records, laboratory databases, and national transplant registries (Finnish Transplant Registry or Norwegian Renal Registry), as appropriate. Acute rejections during the first year were defined as biopsy-proven borderline changes or higher grade of T cell–mediated rejection (TCMR) or antibody-mediated rejection.[11] This study had the approval from the institutional review boards of both Helsinki and Oslo University Hospitals.

Immunosuppression in Helsinki

Baseline maintenance immunosuppression in nonsensitized patients in Helsinki consisted of calcineurin inhibitors (cyclosporine or tacrolimus), mycophenolate, and steroids. Induction with basiliximab was only used in patients with retransplantation or poor HLA match (>3 mismatches in the A, B, and DR loci). Steroids were usually withdrawn in stable patients, but only after 1–1.5 y from transplantation (after the 1-y protocol biopsy). Target trough level after kidney transplantation for tacrolimus was 7–10 μg/L during the first 3 mo, and 4–6 μg/L thereafter, whereas the trough-level target for cyclosporine was 160–200 μg/L for the first 3 mo after transplantation, with tapering doses until trough target of 80–110 μg/L until 1 y from transplantation. Conversion of cyclosporine to tacrolimus is considered in case of acute rejections. Mycophenolate mofetil was given 1000 mg bid with cyclosporine, and 500 mg bid with tacrolimus (or corresponding mycophenolate sodium doses).

Immunosuppression in Oslo

Baseline immunosuppression in nonsensitized patients in Oslo consisted of calcineurin inhibitors (cyclosporine or tacrolimus), mycophenolate, and steroids. All patients received induction with basiliximab. Steroids were tapered to 5 mg daily at 6 mo posttransplant, and never withdrawn. The target trough level after kidney transplantation for tacrolimus was 4–7 μg/L, whereas the trough-level target for cyclosporine was 200–300 μg/L for the first month after transplantation, with tapering doses until trough target of 75–125 μg/L from 6 mo after transplantation. Conversion of cyclosporine to tacrolimus is considered in case of acute rejections. Mycophenolate mofetil was given 1000 mg bid with cyclosporine, and 750 mg bid with tacrolimus (or corresponding mycophenolate sodium doses).

Protocol Biopsies

Helsinki is the only kidney transplant center in Finland, a country of 5.5 million inhabitants. Of the 21 regional hospitals responsible for the follow-up of kidney transplant recipients, 12 hospitals sent their patients for protocol biopsies to Helsinki University Hospital at 1 y after transplantation between 2006 and 2017.

Oslo is the only kidney transplant center in Norway, a country of 5.5 million inhabitants. After 1–2 mo of follow-up in Oslo, patients are referred to one of the 25 regional nephrology centers for long-term follow-up. All patients were offered a control visit at 12 mo, including a protocol biopsy.

Two cores of tissue were obtained under ultrasound guidance with an automated gun using either a 16- or 18-Gauge needle, and samples were processed for routine light microscopy. Histopathological changes were scored by experienced renal pathologists according to the respective Banff classification

during routine clinical practice.[11] Biopsies were not rescored for the purposes of this study because our aim was to analyze the usefulness of the protocol biopsies in clinical decision-making at the time of the biopsy. Individual biopsy lesion findings were categorized according to the Banff 2019 classification.[12] The occurrence of subclinical acute TCMR (i2t2v0 or higher) or borderline changes (i1t1v0) in the protocol biopsy was studied. In addition, histopathological findings included in the iBox score were studied, namely the presence of interstitial fibrosis/tubular atrophy > 1, glomerulitis + peritubular capillaritis (>2), inflammation + tubulitis > 2, or transplant glomerulopathy > 0.[3]

Donor-specific HLA Antibodies

Both in Helsinki and in Oslo, One Lambda Labscreen mixed antigen bead and SAB with Luminex were used for HLA antibody screening and identification with the use of HLA Fusion software (One Lambda Inc, Canoga Park, CA) at the time of the protocol biopsy. A normalized mean fluorescence intensity (MFI) cutoff point of 1000 was used for positivity in single-antigen analyses.

Statistical Analyses

Differences between 2 groups in categorical variables were compared with the Fisher exact test. Nonparametric statistics were chosen because all distributions were not normal. Calculations were performed using IBM SPSS Statistics (version 25, IBM Corporation, Somers, NY). Cases with missing data were excluded from the analyses because the frequency of missing data were <5% in each variable.

RESULTS

Study Cohort From Helsinki

A flowchart of selection of patients to the study from Helsinki is presented in Figure 1A. Altogether 784 kidney transplantations were performed between 2006 and 2017

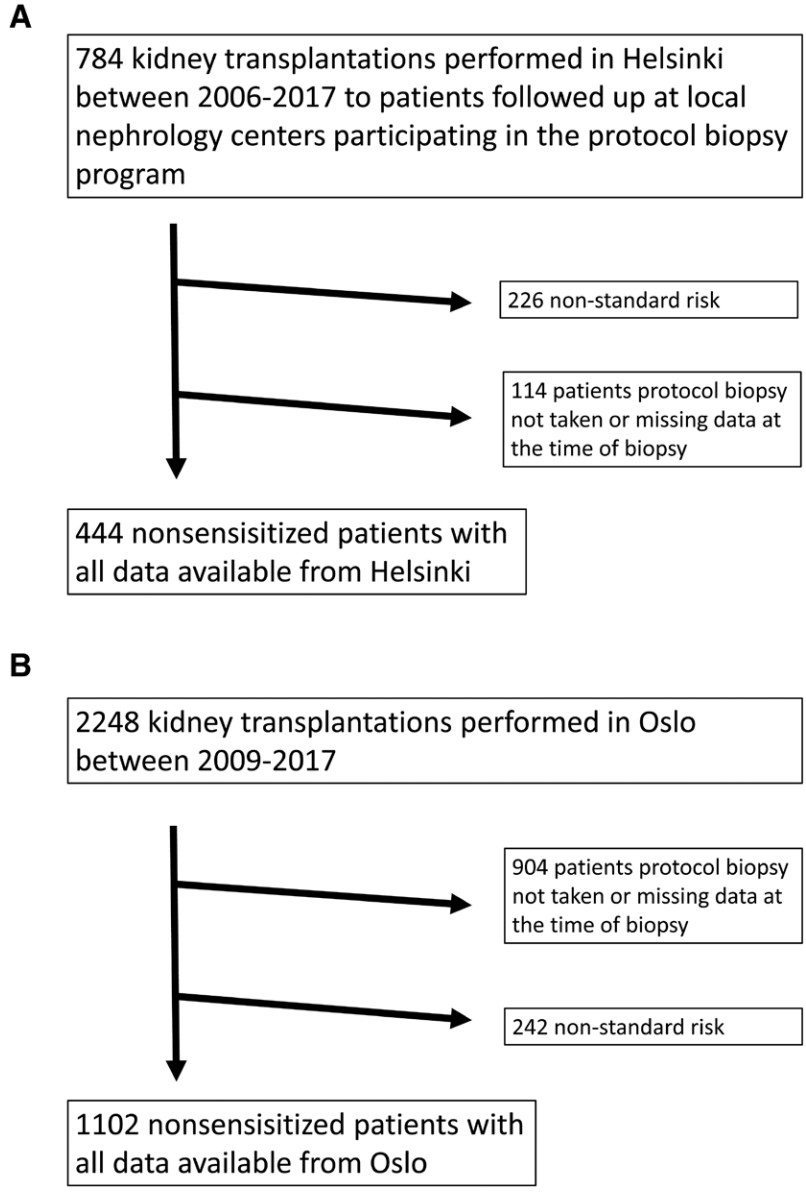

FIGURE 1. Patients included in the study. Flowchart of the selection of patients to the cohorts in (A) Helsinki (Finland) and (B) Oslo (Norway).

to patients followed up at the defined regional hospitals, which were part of the protocol biopsy program. Of these transplants, 36 were multiorgan transplants, 15 never gained function, 8 returned to dialysis during the first year, and 16 patients died within the first year. Altogether 653 transplants had a protocol biopsy taken, and 634 had also proteinuria and DSA data available from the time of the biopsy. The reason for not taking a protocol biopsy of the remaining 56 patients is not known. Those 444 patients, who were nonsensitized at transplantation, were included in this study.

Study Cohort From Oslo

A flowchart of selection of patients to the study from Oslo is presented in Figure 1B. Altogether 2248 kidney transplantations were performed between 2009 and 2017. A total of 1455 transplants had a protocol biopsy taken. Of these, 1241 were standard immunological risk at the time of transplant. Patients with other immunosuppression regimens or biopsies that were taken on clinical indications were excluded. Finally, a total of 1102 standard immunological risk patients were included for study.

This resulted in a total of 1546 patients with protocol biopsies in the final cohort, as characterized in Table 1.

Biopsy Findings: TCMR

Table 2 characterizes clinical findings at the time of 1-y protocol biopsies. Table 3 depicts the findings in the protocol biopsies, categorized by the presence of DSA, proteinuria, or history of acute rejection. Subclinical acute TCMR was detected in altogether 30 of 1546 (1.9%) of the protocol biopsies in the whole cohort, and borderline changes or TCMR in 179 of 1546 (12%). Among patients with de novo DSA detected at 1 y, subclinical TCMR was detected in 11 of 106 (10%), and borderline changes or TCMR in 35 of 106 (33%). Subclinical antibody-mediated rejection with typical light microscopy features, positive C4d, and de novo DSAs were detected in 1 biopsy in Helsinki and 2 in Oslo.

TABLE 1.

Baseline characteristics of the patients with 1-y protocol biopsy included in the study

All patients	N = 444, Helsinki	N = 1102, Oslo
Male patients (%)	316 (71%)	778 (71%)
Mean recipient age (±1 SD)	53 ± 13	55 ± 14
Deceased donor (%)	422 (95%)	790 (72%)
Mean donor age (±1 SD)	53 ± 13	50 ± 17
Mean HLA AB mismatch (±1 SD)[a]	1.8 ± 0.8	2.2 ± 0.8
Mean HLA DR mismatch (±1 SD)[b]	0.7 ± 0.5	0.8 ± 0.5
Delayed graft function (%)[c]	148 (33%)	NA
Start CNI tacrolimus (vs CyA) (%)	75 (17%)	931 (85%)
Induction with basiliximab (vs no induction)	14 (3%)	1102 (100%)
Treated acute rejection during first year	72 (16%)	263 (24%)
TCMR (including borderline)	66 (15%)	230 (21%)
Borderline changes	26 (6%)	NA
Grade 1A-1B	28 (6%)	NA
Grade 2A-2B	12 (3%)	NA
AMR	6 (1%)	33 (3%)

[a] Number of HLA mismatches in serological AB loci.
[b] Number of HLA mismatches in serological DR loci.
[c] Defined as need for dialysis during the first posttransplant week.
AMR, antibody-mediated rejection; CNI, calcineurin inhibitor; CyA, cyclosporin A; NA, not available; TCMR, T cell–mediated rejection.

TABLE 2.

Clinical findings at the time of the 1-y protocol biopsy

At 1 y after transplantation	N = 444, Helsinki	N = 1102, Oslo
De novo DSA	22 (5%)[a]	84 (8%)
Anti-HLA-A	3	NA
Anti-HLA-B	3	
Anti-HLA-DQ	14	
Anti-HLA-DR	2	
Proteinuria (dipstick or urine albumin–creatinine ratio)		
None	357 (80%)	935 (84%)
1+ or 30–100 mg/g	71 (16%)	116 (11%)
2+ or 100–300 mg/g	9 (2%)	44 (4%)
3+ or >300 mg/g	7 (2%)	7 (1%)
Plasma creatinine (±1 SD), mg/dL	1.38 ± 0.51	1.32 ± 0.44

[a] Of the patients with de novo DSAs, only 2 had dominant DSA MFI <1400, which is the cutoff used for the qualified iBox scoring system.[13]
DSAs, donor-specific HLA antibodies; NA, not available.

TABLE 3.

Findings of TCMR in 1-y protocol biopsies among the total cohort of 1546 patients

	TCMR at 1-y protocol biopsy	Borderline changes or TCMR at 1-y protocol biopsy
Whole cohort (N = 1546)	28 (1.8%)	184 (12%)
Patients with de novo DSA at 1 y (N = 106)	11 (10%)[a]	36 (34%)[a]
Patients with any proteinuria (urine protein-to-creatinine >30 mg/g or equivalent) (N = 254)	11 (4.3%)[a]	43 (17%)[a]
Patients with a history of acute rejection before the protocol biopsy (N = 335)	24 (7.2%)[a]	101 (30%)[a]
Patients with none of the abovementioned risk factors (N = 974)	1 (0.1%)	48 (4.9%)

[a] $P < 0.001$, compared with patients with none of the risk factors within the same column.
DSAs, donor-specific antibodies.

Among patients with a history of previous acute rejection within the first year (including borderline changes treated as acute rejections), TCMR was detected at 1 y in 25 of 335 (7.5%) and borderline changes or TCMR in 103 of 335 (31%). Of the patients with de novo DSA detected at 1 y, 55 of 106 (52%) had a previous acute rejection during the first year. On the contrary, among patients with no history of acute rejection, and no proteinuria (<30 mg/g, or equivalent as measured with a negative dipstick proteinuria) or DSA, TCMR was detected in only 1 of 974 (0.1%) and borderline changes or TCMR in only 48 of 974 (4.9%) patients at 1 y (table 2).

Biopsy Findings: Any Components of the iBox Score

Table 4 presents the overall findings in the protocol biopsies, and table 5 presents findings significant for the iBox score. When the presence of any lesions significant in the iBox composite score was evaluated, the likelihood of histopathological findings with additional value for the iBox remained similarly low. Among the total cohort, 196 of 1546 (13%) biopsies showed any lesions significant in the iBox score, whereas in the absence of proteinuria or DSA, or history of acute rejection, only 50 of 974 (5.1%) biopsies showed any lesions significant for the iBox score. The findings of this study are summarized in Figure 2, showing the frequency of TCMR, borderline or TCMR, or any findings significant in the iBox score among the different subgroups.

Stratification of Findings Based on Kidney Function

As a sensitivity analysis, the biopsy findings at 1 y were also stratified based on kidney function (**Table S1, SDC**, http://links.lww.com/TXD/A641). Based on an arbitrary cutoff of good graft function as estimated glomerular filtration rate 45 mL/min (with the CKD-EPI [Chronic Kidney Disease Epidemiology Collaboration] equation), no significant differences were found in the frequency of TCMR between the groups in 1 y protocol biopsies (2.9% versus 1.6%, $P = 0.19$). When borderline changes were included, the likelihood of pathological findings was significantly higher among patients with suboptimal kidney function (19% versus 11%, $P < 0.001$), similarly as also was the likelihood of finding significant lesions for the iBox composite score (30 versus 9.6%, $P < 0.001$). However, adding graft function to the variables included in Table 2 did not filter out more patients with pathological findings (data not shown).

TABLE 4.

Histological lesion scores in the 1-y protocol biopsies in the total cohort

Biopsy findings at 1 y	Helsinki, N = 444	Oslo, N = 1102
Interstitial inflammation		
0	300 (68%)	932 (85%)
1	123 (28%)	137 (12%)
2–3	21 (5%)	33 (3%)
Tubulitis		
0	405 (91%)	771 (70%)
1	29 (7%)	263 (24%)
2–3	9 (2%)	68 (6%)
i + t		
0	298 (67%)	749 (68%)
1	103 (23%)	187 (17%)
2	26 (6%)	102 (9%)
3–6	17 (4%)	64 (6%)
g+ptc		
0	443 (99.8%)	1050 (95%)
1	0	23 (2%)
2	1 (0.2%)	21 (2%)
3–6	0	8 (0.8%)
IFTA		
No IFTA	295 (66%)	170 (15%)
grI	132 (30%)	819 (74%)
grII	16 (4%)	74 (7%)
grIII	1 (0.2%)	39 (4%)
Arteritis (vs lesion)		
0	442 (99.5%)	1102 (100%)
1	2 (0.5%)	0 (0%)
iBox histopathological score >0[a]	31 (7%)	165 (15%)

[a] Lesion scores causing changes to the iBox score are: IF/TA > 1, g+ptc >2, i+t > 2, or cg > 0.
cg, transplant glomerulopathy; g+ptc, glomerulitis + peritubular capillaritis; i+t, inflammation + tubulitis; IF/TA, interstitial fibrosis/tubular atrophy.

DISCUSSION

In this study, we found that the likelihood of pathological findings in 1-y protocol biopsies after kidney transplantation remains low among nonsensitized patients. Findings of TCMR or borderline changes were rarely seen, especially among patients with no DSA or proteinuria detected, and no history of acute rejection. Only 0.1% of these low-risk patients showed subclinical TCMR, and 4.9% showed subclinical borderline changes or TCMR. This means that to be able to detect one subclinical rejection almost 1000 biopsies must be performed in these low-risk patients. Because of the low frequency of pathological findings, the usefulness of

TABLE 5.

Findings significant for the iBox score in the protocol biopsies

	Any significant lesions in the iBox score
Whole cohort (N = 1546)	197 (13%)
Patients with de novo DSA at 1 y (N = 106)	37 (35%)
Patients with any proteinuria (urine protein-to-creatinine >10 mg/dL or equivalent) (N = 254)	57 (22%)
Patients with a history of acute rejection before the protocol biopsy (N = 335)	99 (30%)
Patients with none of the abovementioned risk factors (N = 974)	50 (5.1%)

Lesion scores causing changes to the iBox score are: IF/TA > 1, g+ptc >2, i + t > 2, or cg > 0. cg, transplant glomerulopathy; DSAs, donor-specific antibodies; g+ptc, glomerulitis + peritubular capillaritis; i+t, inflammation + tubulitis; IF/TA, interstitial fibrosis/tubular atrophy.

protocol biopsies to detect subclinical rejection in this group should be questioned.

The most important justification of taking protocol biopsies is detecting subclinical rejection responses because earlier evidence shows that treating subclinical alloimmune activation may be of clinical benefit.[2] However, there are also other benefits of protocol biopsies, which must be taken into consideration. In addition to detecting subclinical rejection, protocol biopsies may allow earlier detection of recurrence of baseline kidney disease. For example, recurrence of IgA nephropathy in protocol biopsies has been shown in immunofluorescence in up to 32% patients, without any clinical manifestations.[14] How this translates to treatment interventions remains yet to be defined.

In addition, protocol biopsies can be useful for research purposes, such as for molecular analyses, but also as surrogate markers for later graft prognosis. The most recent composite predictive score is iBox, which is currently being evaluated by the Food and Drug Administration for qualification as a reasonably likely surrogate endpoint, and has recently received regulatory endorsement by the European Medicines Agency as a secondary efficacy endpoint in clinical trials.[13] The iBox composite score includes histopathological lesion data, and protocol biopsies would allow to use this score as an endpoint in clinical trials. In our current study, however, the usefulness of protocol biopsies in standard risk patients without previous immunological events remains low also regarding the iBox score; in the absence of proteinuria, de novo DSA (which are also included in the iBox score), or previous history of acute rejection, only 5% of biopsies showed any significant lesions to add to the iBox score. Our finding is well in line with recent analyses of the iBox qualification data, in which iBox score can be used also without biopsy data, with close to equal predictive performance.[13] We suggest that our findings could be used in clinical practice to guide the decision to take protocol biopsies on a more individual basis. Protocol biopsies are more likely to bring additional value to treatment decisions or evaluation of prognosis among patients with proteinuria, or the presence of DSA. Naturally one might argue whether these should be called protocol biopsies, or biopsies performed with an indication (DSA, proteinuria), but in the current study, all included biopsies were prescheduled protocol biopsies, often without knowledge of the results of the DSA testing or proteinuria at the time of scheduling the biopsy. In patients without any of these risk factors, graft prognosis probably can be equally well predicted using the iBox parameters without including histological data. However, for purposes of clinical trials, protocol biopsies may have additional benefits, such as molecular analyses of the biopsies for mechanistical

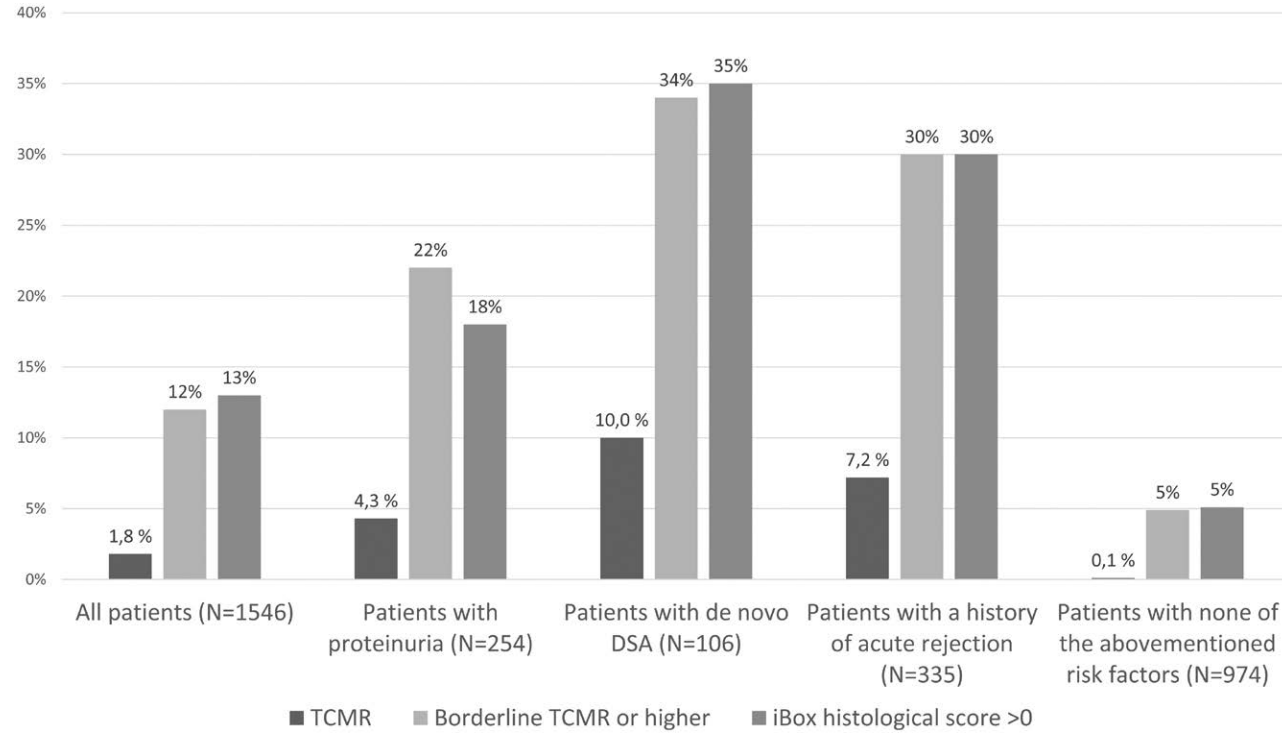

FIGURE 2. Frequency of pathological findings in different subgroups within the study cohort. Lesion scores causing changes to the iBox score are: IF/TA > 1, g+ptc >2, i + t > 2, or cg > 0. cg, transplant glomerulopathy; DSAs, donor-specific antibodies; g+ptc, glomerulitis + peritubular capillaritis; i+t, inflammation + tubulitis; IF/TA, interstitial fibrosis/tubular atrophy; TCMR, T cell–mediated rejection.

hypotheses. In higher-risk patients, or patients with any signs of graft injury, the likelihood of pathological findings remains higher arguing for continuing protocol biopsy policies in some patients. As a result of the current findings, the local protocol biopsy policy in Helsinki has already been changed toward more targeted biopsies not including all patients.

Evaluating the presence of DSA with an SAB assay, as in our study, requires an arbitrary MFI cutoff to define positivity of the detected antibodies, and because of methodological issues these results are often not entirely comparable between different laboratories. In the original description of the iBox scoring system, different MFI levels of DSAs were included in the scoring system (500–3000, 3000–6000, or >6000 MFI), but in the EMA qualifaction opinion, a cutoff of 1400 MFI was used to define the positive DSA level.[3,13] Unfortunately detailed information about the subclasses of DSAs or MFIs were available only from a subset of patients in our current study, which is clearly a limitation. Nevertheless, detection of DSA using the lower cutoff of 1000 MFI also proved useful for risk stratification for pathological findings in the biopsies.

Our study has limitations of note. As the focus of our study was on the usefulness of protocol biopsies among standard risk patients (nonsensitized at the time of transplantation), our findings cannot be applied to previously sensitized patients. In addition, although our cohort is relatively large and is from 2 national transplant centers, the selected immunosuppressive protocol might be associated with our findings. Therefore, these results cannot be directly generalized to patients receiving other immunosuppressive protocols, such as steroid-free regimens, patients receiving lymphocyte-depleting induction, or patients on noncalcineurin inhibitor–based protocols, which are underrepresented in our cohort. In addition, the exact dosing or trough levels of the immunosuppressive drugs at the time of the protocol biopsy are not captured in the registries, and were not available for the purposes of this study. However, per protocol all the patients were on CNI-based triple drug immunosuppression at the time of the 12-mo protocol biopsy. Similarly, the registries we used for the purposes of this study do not capture data regarding, for example, Banff grading of acute rejection or the treatment of acute rejection, which adds natural limitations to this retrospective registry study. Other limitations are the noncentralized reading (Helsinki or Oslo) of the protocol biopsies and inclusion of biopsies over a long time period, which may contribute to different distribution of pathological findings between the 2 centers. Interobserver correlation, especially with regard to borderline changes, has been shown to be far from optimal in assessing kidney transplant pathology,[15] and interobserver agreement could not be investigated in the current study, limiting the validity of our findings. In addition, the Banff scoring system has undergone changes during the study period. The purpose of our study was to evaluate the real-life usefulness of protocol biopsies, and therefore, these results have to be evaluated in the context of local circumstances. This may, however, create bias in the exact frequency of pathological findings, and the results may not be comparable between different centers.

On the other hand, our study has several strengths. Our cohort is from 2 large national transplant centers and includes consecutive patients without selection. The immunosuppressive protocols remained fairly stable during the study period and comparable between the centers, creating a relatively homogenous population.

In conclusion, our findings among non-HLA–sensitized kidney transplant recipients suggest that both the clinical and prognostic value of 1-y protocol biopsies in patients with no signs or history of graft injury remains very low, and the usefulness of 1-y protocol biopsies in these patients is questionable.

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