

# Results of Questionnaire Survey of Current Immune Monitoring Practice of Transplant Clinicians and Clinical Pathologists in Korea: Basis for Establishment of Harmonized Immune Monitoring Guidelines

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Detection of significant alloimmune response, which affects graft function and survival by effective immune monitoring, is critical for treatment decision making. However, there is no consensus regarding immune monitoring (IM) for kidney transplantation (flow KT) in Korea. The IM protocol may be affected by the level of immunological risk, the methods of desensitization and the availabilities of resources such as laboratory support and cost of tests. Questionnaire surveys designed to identify the current practices regarding immune monitoring of KT among transplant clinicians and clinical pathologists in Korea and eventually provide a basis for the establishment of harmonized immune monitoring guidelines in KT were administered as part of a Korean Society for Transplantation Sponsored Research Project. The survey results revealed significant variations in IM protocols and interpretation of tests affecting treatment decisions between institutes. Moreover, the results revealed a need to expand the histocompatibility tests into high resolution HLA typing in multiple loci and non-HLA antibody tests that facilitate the epitope analysis and eventually virtual crossmatching. The results of the questionnaire survey from clinical pathologists are addressing the urgent need for the standardization of interpretation and harmonization of results reporting in single antigen bead based HLA antibody identification. Finally, communication between clinicians and clinical pathologists to meet the clinical expectations regarding various immune monitoring tests is needed.

**Key Words:** Kidney transplantation, Immunologic monitoring, Questionnaire survey

**중심 단어:** 신장이식, 면역감시, 설문조사

## INTRODUCTION

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With the advancement of immunosuppression, control of alloimmune response has been increasingly effective, although the incidence of acute rejection remains approximately 8% in most institutes according to Organ Procurement and Transplantation Network/The Scientific Registry of Transplant Recipients (OPTN/SRTR) annual report(1). Determination of unacceptable human leukocyte antigen (HLA) antigen mismatches, risk assessment by assessing the HLA antibodies, combination of desensitization and careful monitoring of posttransplant immunologic events contributed to

improve allograft and patient survival(2-4). For the histocompatibility tests, in addition to conventional complement-dependent lymphocytotoxicity (CDC) crossmatching test (XM) and low resolution HLA typing, technical developments in XM using flow cytometry and HLA antibody detection methods using luminex microbead array have helped to further understand and identify the immunological components involved in alloimmune response(5-11). With regards that the detection of HLA and non-HLA antibodies specific to donor (DSA) is critical finding to predict alloimmune response to kidney allograft, particularly antibody mediated rejection (AMR)(12-14), understanding the significance of various aspects of each test and utilization of tests in different stages of kidney transplantation (flow KT) would have significant importance.

Until now, the immunological monitoring of alloimmune responses are focused on the detection of rejection events in practice than detection of adverse immune activity which might be preceded clinically or pathologically evident rejection signs. It might be rather because there were no reliable and well validated laboratory methods to be applicable. However, luminex bead technologies used for the detection of antibodies in antigen, allele or epitope levels for HLA(7-9) and non-HLA systems(15), and molecular technologies to detect transcript signatures of diverse immunologic changes are broadening our choice of tests(16-18). And it is continuously reflected on diagnostic criteria such as Banff criteria(19,20). However, the diagnostic criteria does not specify the practical way of immune monitoring in real world, so, there is no standardized guidelines and is rather institute- or clinician- based protocols. Risk stratification based on pretransplant sensitization history and presence of donor-specific antibody (DSA) is generally accepted. Therefore, in pretransplant period, determination of clinically relevant alloantibodies in sensitized patients and monitoring of antibody level during desensitization treatment would be needed. But in posttransplant period, although there are significant amount of evidences for the causal effect of DSA in graft rejection, the uniform consensus or guidelines for immune monitoring is hard to be set up partly because the lack of validated therapy once DSA are detected in a clinically and pathologically stable patient and *vice versa*(21-24) and partly because the lack

of data whether low level of DSA or anti-allelic DSA cause graft dysfunction(25,26). The Transplantation Society has published consensus guidelines on testing and clinical management issues associated with HLA and non-HLA antibodies in transplantation including KT and other solid organ transplantations in 2013(27). The consensus guidelines suggested by a group of clinical and laboratory experts in the field of transplantation are largely covering the technical issues related with current HLA antibody tests and the monitoring strategies in patients with different level of risk in pre- and post- transplantation. It also had proposed some clinical research issues which would clarify the unanswered aspects at that time and actually, lasting until this moment.

In Korea, about 59 institutes have performed 2,147 KT in 2016 (2017 KONOS Annual Data Report)(28). About 50 and 22 laboratories are performing HLA XM and antibody identification test, respectively, according to 40th HLA External Proficiency Test Program (HLA-EPT) organized by Korean Society of Laboratory Medicine (KSLM). Significant efforts on standardization of histocompatibility tests have been done. The interlaboratory variability of HLA antibody identification tests (phenotyping) using same kit seemed to be reasonably low(29). The questionnaires survey and wet workshop for HLA CDC and FCM XM contributed the protocol harmonization of tests(30). However, adoption of single antigen bead-based (SAB) antibody identification, DQ (B1/A1) locus typing and introduction of complement binding assay continuously challenge not only the clinical pathologists but also the clinicians to understand and to interpret data. Moreover, there has been no consensus on immune monitoring in Kidney transplantation among clinicians including nephrologists, surgeons and clinical pathologists in Korea. Why would it be important or necessary? It may be gained from how different ideas the clinicians have and how different practices affect the clinical outcome.

This study aimed to identify the current practice on immune monitoring of KT among transplant physicians and clinical pathologists in Korea and eventually to provide a basis for the establishment of harmonized immune monitoring guidelines in KT.

The study was performed by questionnaire surveys through emailing. The questionnaires were developed in two

parts for transplant physicians and clinical pathologists by four clinical pathologists and one nephrologist participating in this study. The questionnaires for transplant physicians focused on utilization of laboratory tests for immune monitoring and deciding therapeutic strategies during pre- and post- KT periods in both recipients and donors. And for clinical pathologists, it covered the laboratory practices of various histocompatibility tests in methods, interpretation and result reporting. The common questionnaires for both parties include deficiencies in current practice and suggestions for further improvement.

CURRENT PRACTICE AND VIEWS ON IMMUNE MONITORING OF KIDNEY TRANSPLANTATION AMONG TRANSPLANT CLINICIANS

Questionnaire survey had been distributed to clinicians in 33 institutes where performing KT. Thirty two clinicians including 23 nephrologists and 9 surgeons from 25 institutes (76%) replied to questionnaire survey which conducted in twice (Fig. 1). The responded institutes had varied number of KT performed per year based on 2016 KONOS data (Fig. 2). The median number of KT per year in low volume institute performing <30 was 20 (range 7~29), in medium

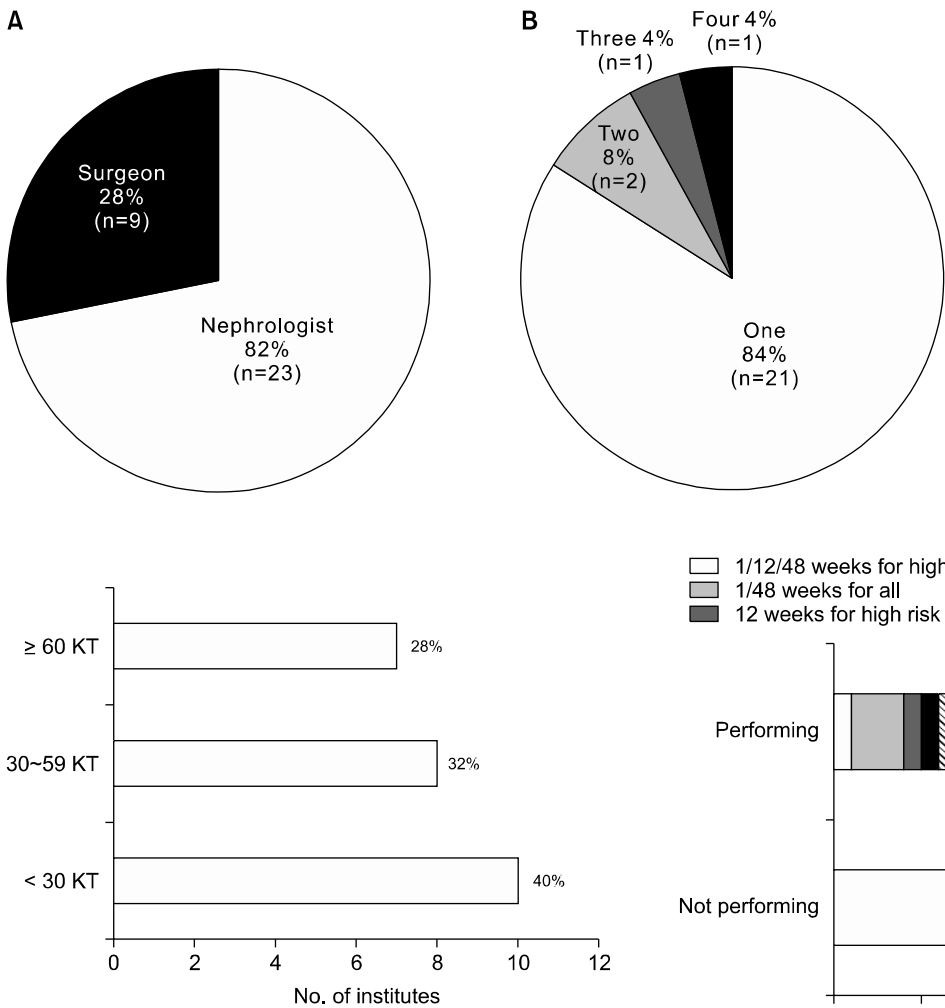


Fig. 1. Proportions of transplant clinicians responded in questionnaire surveys according to (A) specialties and (B) number of clinicians per single institute.

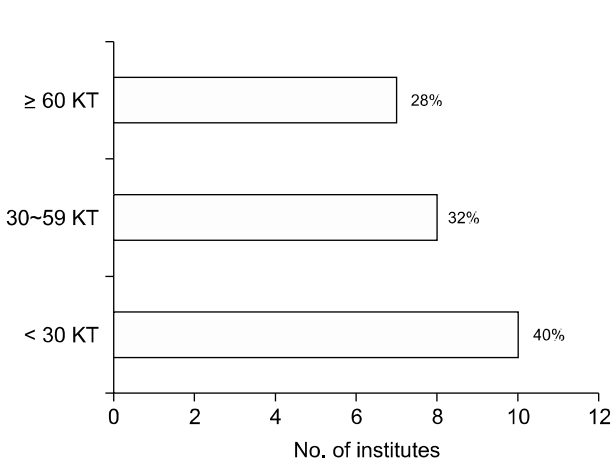


Fig. 2. The number of kidney transplantation performed per year in institutes where the transplant clinicians responded to questionnaire survey. Abbreviation: KT, kidney transplantation.

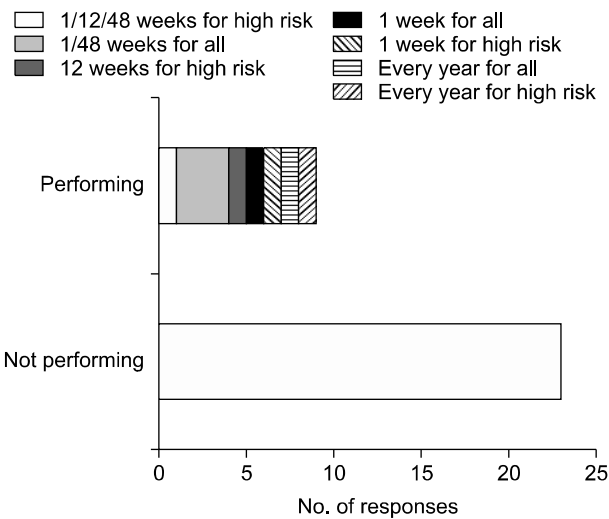
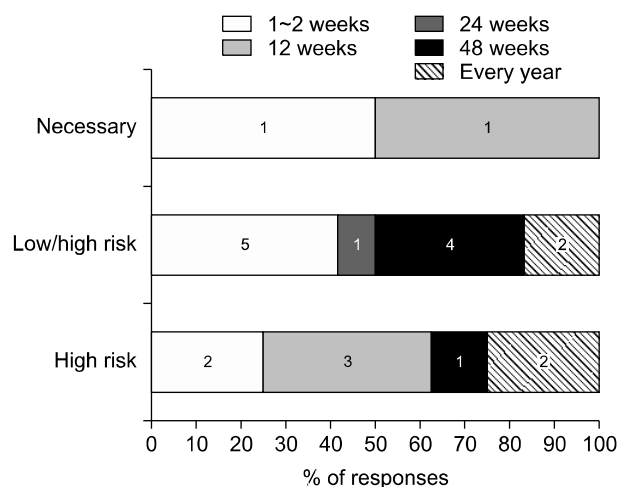


Fig. 3. Status of performing protocol biopsies after kidney transplantation. Responses of 32 clinicians from 25 institutes.

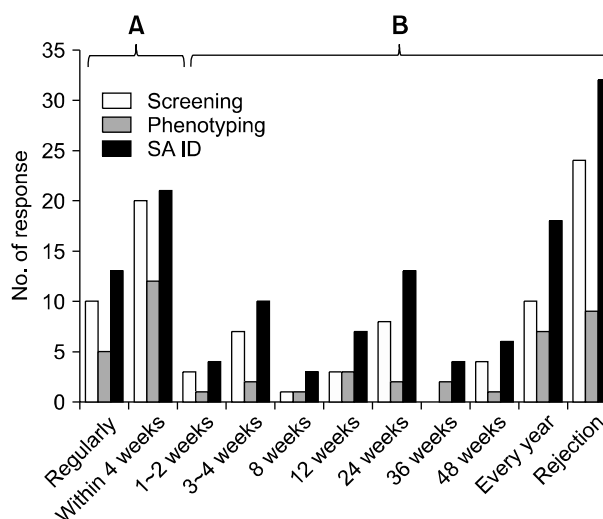


**Fig. 4.** Status of performing protocol biopsies depending on the level of immunological risk after kidney transplantation. The protocol biopsies are being performed in recipients with high immunological risk or regardless of immunological risk in different time points. Two clinicians responded that protocol biopsies are necessary on 1~2 week and 12 week posttransplant. Responses of 32 clinicians from 25 institutes.

volume institute performing 30~59 was 45 (range 32~56) and in high volume institute performing over 60 was 157 (range 63~363). The questionnaires comprised of questions about the current status of immune monitoring protocols including protocol biopsy, the indications of HLA antibody tests, the impact and threshold of HLA typing and antibody tests and the need of further immune monitoring modalities.

### 1. Immune monitoring protocols

About 28% (9/32) of clinicians from 6 institutes (6/25, 24%) are performing protocol biopsies at various time points and the number of biopsy depending on the level of immunological risks (Fig. 3). When higher the risk, more frequent biopsies are being performed within posttransplant 12 weeks (Fig. 4). Clinicians are applying different combinations of HLA antibody tests in different time points and also depending on the level of immunological risks. Antibody monitoring is being performed frequently at posttransplant 3~4 weeks, 24 weeks and yearly (Fig. 5). Antibody screening test is used for low risk patients, however for high risk patients, HLA antibody phenotyping or SAB identification tests are used more frequently (Fig. 6). The suggested time points of HLA antibody monitoring test in patients waiting for kidney transplantation was questioned regardless of cur-



**Fig. 5.** Status of performing HLA antibody tests in (A) pre- and (B) post- kidney transplantation. Responses of 32 clinicians from 25 institutes.

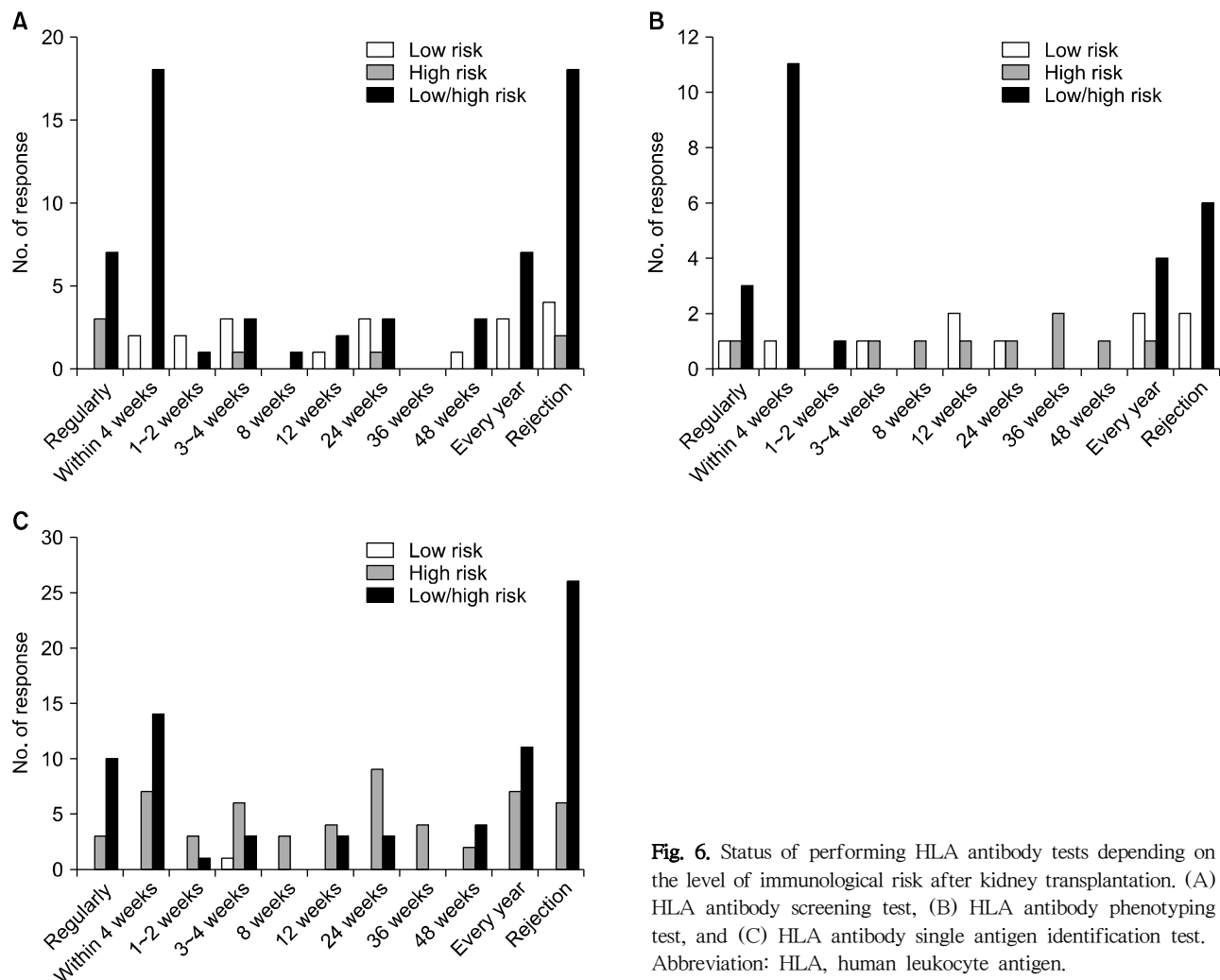
Abbreviation: SA ID, single antigen identification.

rent protocols (Fig. 7). Twenty-four out of 26 (92%) respondents answered that the presence of HLA antibody needed to be checked at registration in KONOS regardless of immunological risk levels, and for living donor kidney transplant (LDKT) candidates, it is suggested to do within pre-transplant 4 weeks. Twelve (46%) respondents replied that the monitoring of HLA antibody is necessary if the patients had recent transfusion or pregnancy episodes.

As on-demand test when the rejection is suspected clinically, 70% (22/32) of respondents answered proceeding to HLA antibody test but 15% (5/32) answered to do HLA antibody test when the pathologic finding of AMR in biopsy identified (Fig. 8).

### 2. The impact of immune monitoring tests on deciding treatment strategies

When we asked the opinions of clinician whether various immune monitoring results influence on deciding treatment strategies, presence of DSA, positive T and B cell CDC XM, positive T cell FCM XM and biopsy findings had affected above 90% of respondents (Table 1). However, only 67% of respondents for the presence of DQ DSA alone and 56% of respondents for the presence of complement binding antibodies replied that their decision making in treatment was affected by those results. The interpretation of these re-



**Fig. 6.** Status of performing HLA antibody tests depending on the level of immunological risk after kidney transplantation. (A) HLA antibody screening test, (B) HLA antibody phenotyping test, and (C) HLA antibody single antigen identification test. Abbreviation: HLA, human leukocyte antigen.

sponses needs to be cautious because it may be rather because not all the institutes are performing or having enough own experiences for those two occasions and the clinical significance are still controversial in current publications.

The threshold of % PRA or % cPRA to define high immunological risk other than the presence of DSA was variable from 20% to 80% although 50% was the most frequent (Fig. 9). And the threshold of DSA MFI to define high immunological risk was quite different in different institute but not in each locus (Table 2).

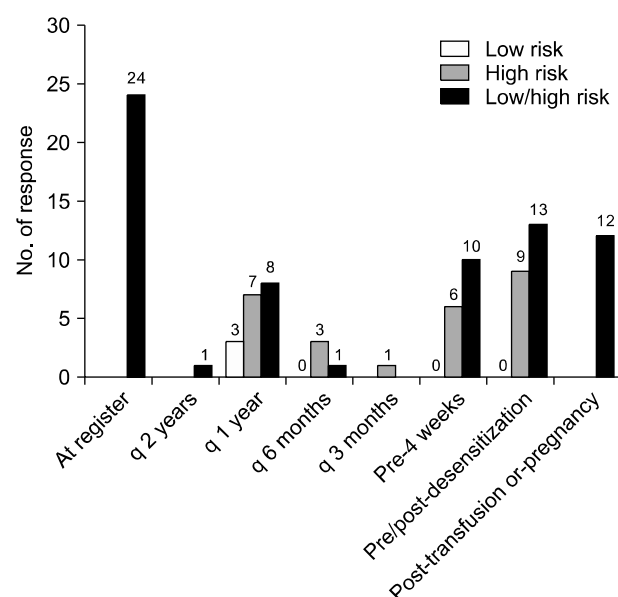
### 3. The need of further immune monitoring tests

The current HLA antibody tests based on luminex bead technologies made it possible to identify antibodies to HLA-C, HLA-DQA, HLA-DQB, HLA-DPA and HLA-DPB

loci and epitope-specific antibodies which was not previously possible in most diagnostic routine laboratories. And the significance of such antibodies in KT allograft rejection is increasingly recognized(31-34). HLA-DQ types are being performed or considered to be needed by all respondents but HLA-C or HLA-DP typing is performed or needed much less currently. In line with the need of epitope analysis and virtual crossmatch, 85% (22/26) of respondents answered that high resolution HLA typing is necessary in KT (Fig. 10). In Banff diagnostic criteria, the extent of DSA includes not only to HLA but also to non-HLA antigens(19,20). And the need for non-HLA antibody test is significant among clinicians because 65% (17/26) of respondents answered that they were doing the anti-MICA antibody or Angiotensin II type 1-receptor antibody test as a supplementary test

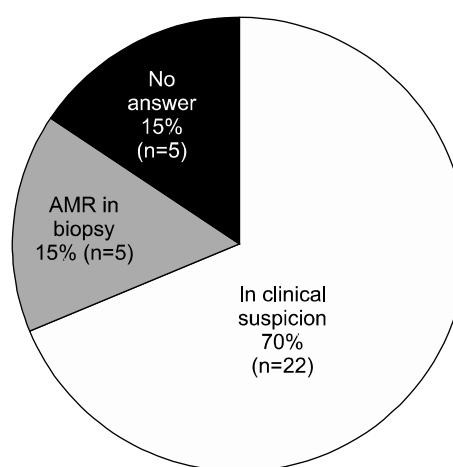
(24%, 4/17) with grant or agreed that the non-HLA antibody test was necessary in clinical practice (77%, 13/17) (Fig. 10). However, in real practice, usage of antibody tests to non-HLA antigens are still limited by uncertainty in selection of etiologic targets, underdeveloped multiplex technique to cover various targets, lack of IVD approved test kit in the market and insurance reimbursement issue.

Other than histocompatibility tests and biopsy, there are



**Fig. 7.** Suggested time points of HLA antibody monitoring test in patients waiting for kidney transplantation.  
Abbreviation: HLA, human leukocyte antigen.

tests for diagnosing or stratifying risks of infection or degree of immunosuppression based immunological or molecular technology (Fig. 11). Interferon-gamma releasing assay (IGRA) for *Mycobacterium tuberculosis* (TB) enabled the diagnosis of latent TB infection or recent TB exposure(35). There are active clinical trials for investigating the clinical utility of IGRA for cytomegalovirus (CMV) infection which measuring CMV-specific immunity in host(36). The assays to estimate the degree of adverse immunosuppression or immune activation potentially against allograft have been

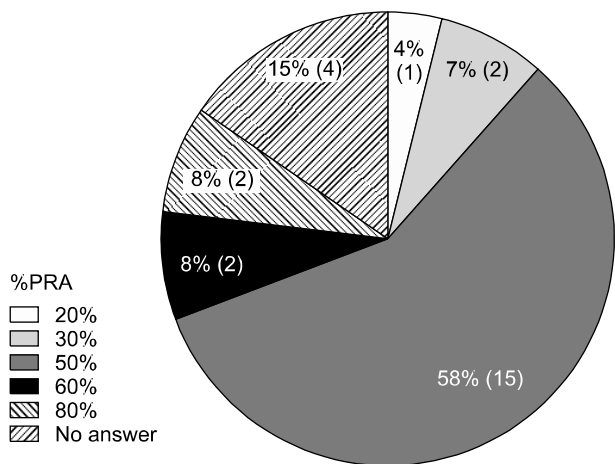


**Fig. 8.** Indications of HLA antibody tests after kidney transplantation.  
Abbreviations: HLA, human leukocyte antigen; AMR, antibody mediated rejection.

**Table 1.** Clinicians opinions about the impact of immune monitoring tests on deciding treatment strategies regardless of current practices

Immune monitoring tests	Total	Effect	No effect	Not performing	No answer
HLA type matching	32	19 (59)	12 (38)	0 (0)	1 (3)
DSA(−) but high PRA	32	26 (81)	5 (16)	0 (0)	1 (3)
DSA (+)	32	31 (97)	0 (0)	0 (0)	1 (3)
DQ DSA alone	27	18 (67)	9 (33)	0 (0)	0 (0)
C or DP DSA alone	27	7 (26)	19 (70)	1 (3)	0 (0)
Complement binding antibody (+)	32	18 (56)	11 (34)	2 (6)	1 (3)
CDC crossmatching, T cell (+)	32	31 (97)	0 (0)	0 (0)	1 (3)
CDC crossmatching, B cell (+)	32	29 (91)	2 (6)	0 (0)	1 (3)
FCM crossmatching, T cell (+)	32	30 (94)	0 (0)	1 (3)	1 (3)
FCM crossmatching, B cell (+)	32	27 (84)	0 (0)	2 (6)	1 (3)
Biopsy finding	32	31 (97)	0 (0)	0 (0)	1 (3)
MIC antibody (+)	32	5 (16)	24 (75)	2 (6)	1 (3)
Lymphocyte subset analysis	32	4 (13)	27 (84)	0 (0)	1 (3)

Abbreviations: DSA, donor specific antibody; PRA, percent reactive antibody; CDC, complement dependent cytotoxicity; FCM, flow cytometry; MIC, MHC class I chain-related protein.



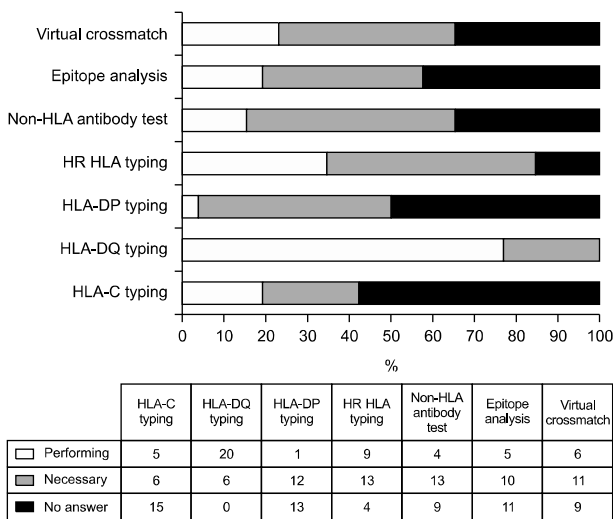
**Fig. 9.** The threshold of %PRA to define high immunological risk in patients responded from 26 clinicians of 20 institutes. Abbreviation: PRA, percent reactive antibodies.

**Table 2.** The threshold of DSA MFI in each locus to define high immunological risk in patients responded from 32 clinicians of 25 institutes

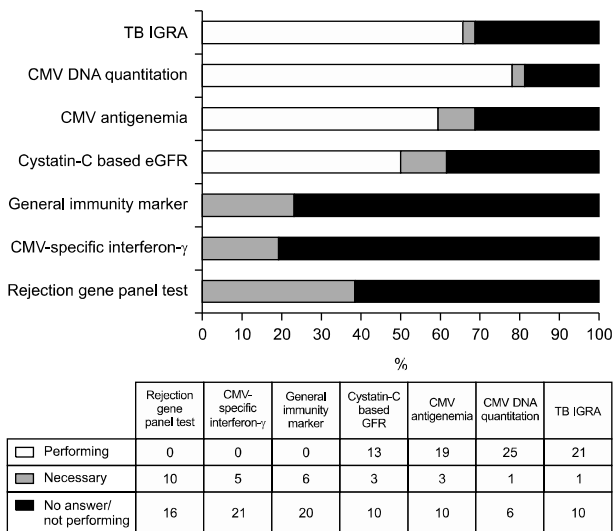
Threshold of DSA MFI	AB (n=26)	DR (n=26)	DQ (n=22)
1,000	6	7	6
2,000~3,000	8	7	7
4,000	1	1	1
5,000	9	9	7
10,000	2	2	1

Abbreviations: DSA, donor specific antibody; MFI, mean fluorescence intensity.

developed (ImmuKnow from Cylex, Columbia, MD, USA and QuanFERON Monitor from Qiagen, USA, etc), although the evidence for the clinical utility needs to be validated more extensively(37,38). Not as much as TB IGRA (85%, 22/26), CMV IGRA and general immunity markers were answered to be needed by a portion of respondents (19%, 5/26 and 23%, 6/26, respectively). Significant proportion of respondents (39%, 10/26) answered that the rejection gene panels in tissue, blood or urine was necessary. Increased expression of gene transcripts in the biopsy tissue has been included as a criteria of ABMR from 2013 Banff criteria(39), however there is no consensus on which transcripts are diagnostic or on the criteria for positivity although a set of gene list has been suggested(20). Furthermore, standards for platforms, methods and performance criteria have not yet been set. In practical aspect, specimen



**Fig. 10.** Clinicians opinions about the need of further tests on histocompatibility. Abbreviation: HLA, human leukocyte antigen.



**Fig. 11.** Clinicians opinions about the need of further immune monitoring tests. Abbreviations: IGRA, interferon gamma releasing assay; CMV, cytomegalovirus; eGFR, estimated glomerular filtration rate.

for gene test may be important. Actually, blood was the most preferred specimen (80%, 8/10) followed by tissue (70%, 7/10) and urine (50%, 5/10) among respondents.

#### 4. Areas which needs to be improved

Lastly, questions were about the current shortcoming of immune monitoring tests and areas which needs to be improved. As shown in Fig. 12, standardization of report

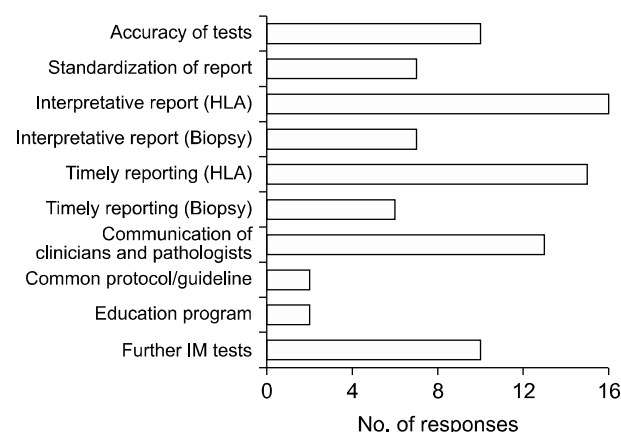
with interpretative format, particularly for HLA tests are most needed among questions. And this was reflected on need of communications between clinicians and pathologists to expedite understanding of tests.

## CURRENT PRACTICE AND VIEWS ON IMMUNE MONITORING OF KIDNEY TRANSPLANTATION AMONG CLINICAL PATHOLOGISTS

Questionnaire survey had been distributed to clinical pathologists in 69 institutes participating in 2017 HLA-EPT organized by KSLM. Forty institutes including three reference laboratories and one institute not performing any organ transplantation (58%) replied to questionnaire survey. The response from 39 institutes has included for the analysis. The questionnaires comprised of questions about the current methods of HLA typing and antibody identification, reporting time, interpretation and reporting contents of each test.

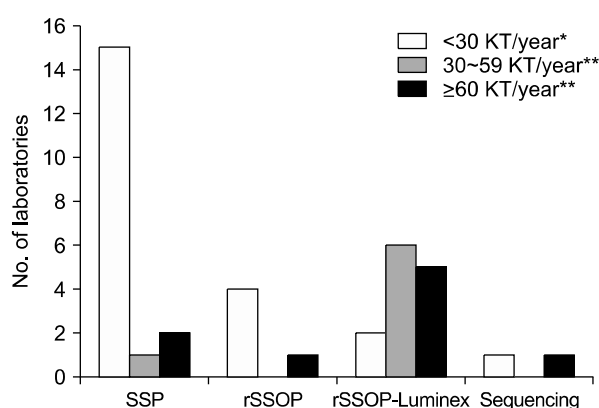
### 1. HLA typing

Sequence-specific polymerase chain reaction (SSP) are the most common method of HLA typing in KT and particularly, in institute performing low volume of KT (< 30 per year). Also reverse sequence-specific oligonucleotide probe hybridization (rSSOP) not using luminex bead technology are also common in institute performing low volume of KT.

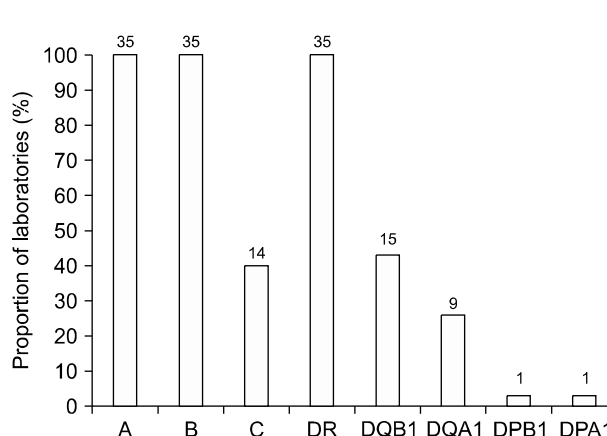


**Fig. 12.** Clinicians opinions in areas which needs to be improved. Abbreviations: HLA, human leukocyte antigen; IM, immune monitoring.

Otherwise rSSOP-luminex was the commonly used method. Two institutes are performing high resolution sequence-based typing (SBT) in KT. Two institutes answered as performing SSP and rSSOP-luminex depending on situation (routine or emergency) (Fig. 13). All the 35 laboratories (100%, 35/35) where the HLA typing set up are examining for HLA-A, -B and -DR loci and 15 labs (43%, 15/35) for HLA-DQB1, 14 labs (40%, 14/35) for HLA-C and 9 labs (26%, 9/35) for HLA-DQA1. One lab (3%, 1/35) is typing HLA-DP locus but not reporting routinely (Fig. 14). For



**Fig. 13.** The principles of methods for HLA typing for kidney transplantation in responded laboratories according to the number of kidney transplantation performed per year in institutes. The data of three institutes referring HLA typing to outside labs are not included (\*) and the data of one institute of each performing HLA typing using two different methods are included (\*\*). Abbreviations: SSP, sequence-specific polymerase chain reaction; rSSOP, reverse sequence-specific oligonucleotide probe hybridization.



**Fig. 14.** HLA loci tested for kidney transplantation in responding laboratories. Abbreviation: HLA, human leukocyte antigen.



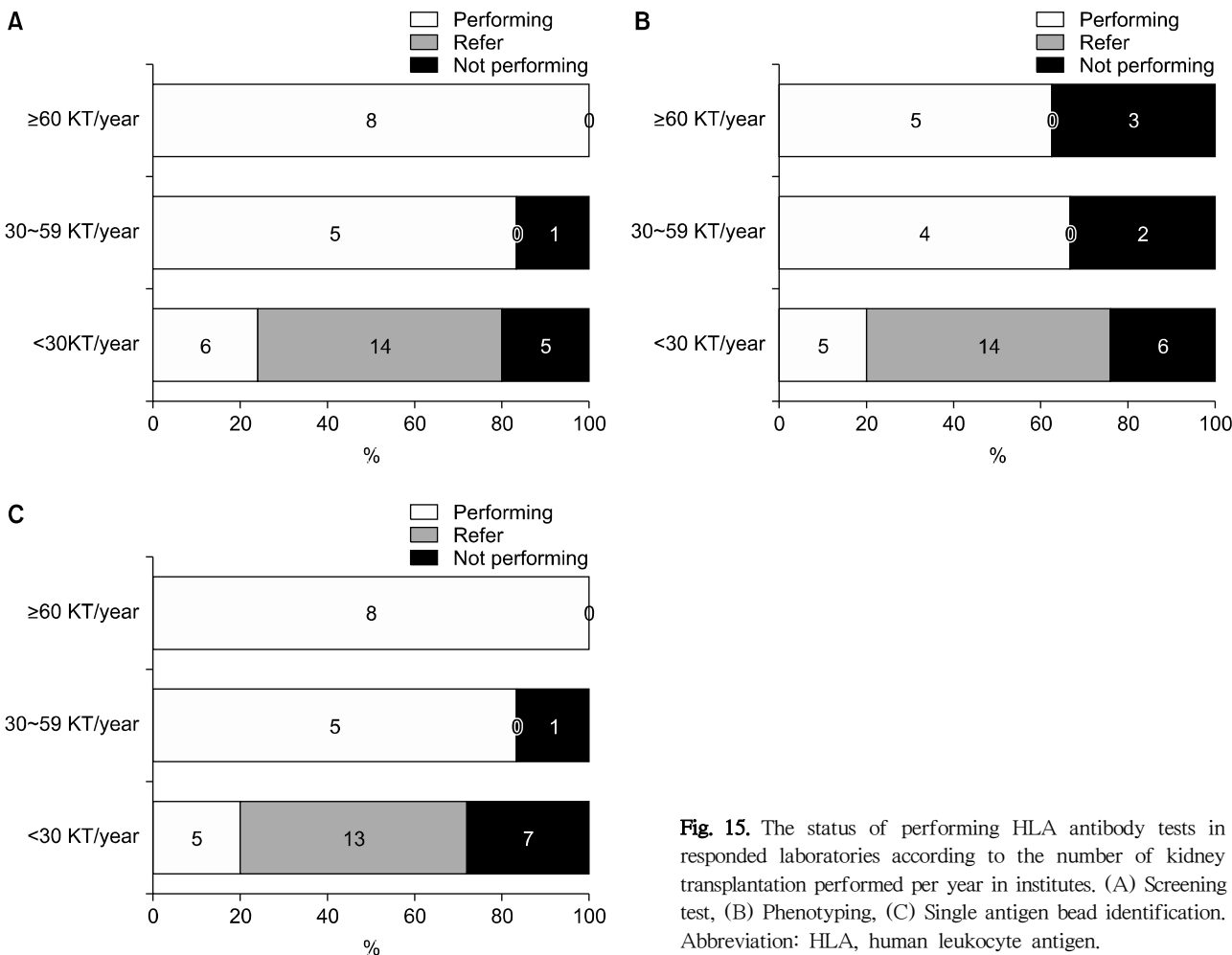
the reporting of HLA types, 25 labs (72%, 25/35) are describing both in generic type and serological equivalent according to WHO nomenclature(40) but five of each labs replied that they are reporting only in generic type (14%, 5/35) or in serological equivalent (14%, 5/35), respectively.

2. HLA antibody screening and identification

All laboratories in institutes performing over 60 KT per year (100%, 8/8) and most in institutes performing 30~59 KT per year (83%, 5/6) are conducting SAB identification test in addition to screening test while phenotyping is being tested in part of laboratories (63%, 5/8 and 37%, 4/6, respectively). Clinical pathologists in institutes performing less than 30 KT per year are referring the tests to the outside laboratories (14/25, 56%) rather than conducting at their own laboratories, probably because of inefficiency from

dealing low volume tests or lacking laboratory resources (Fig. 15). The reporting times for screening, phenotyping and SAB identification were widely varied from 2 to 14 days (median 8 days) after requested.

The format and content of reporting would be the most important part of complex antibody identification test to facilitate the understanding of significance of test results. The reply from 18 laboratories showed the variations in reporting content of SAB identification (Table 3) Since the SAB identification provides the antibody specificities to target antigen in generic and allelic levels, 61% (11/18) of labs are reporting generic and/or allelic types. To differentiate the generic types which have same two digit genotype but different serological equivalent, description of both types has to be mandatory. All 18 labs responded are reporting anti-DQB1 antibodies. Although several labs are reporting



**Fig. 15.** The status of performing HLA antibody tests in responded laboratories according to the number of kidney transplantation performed per year in institutes. (A) Screening test, (B) Phenotyping, (C) Single antigen bead identification. Abbreviation: HLA, human leukocyte antigen.

anti-DQA1, -DPB1, or DPA1 antibodies, the clinical utility of that information is limited yet because most labs are not performing or not reaching the enough resolution in HLA-DQA1, -DPB1, or DPA1 typing. Some labs are including the MFI interval and some labs are including the MFIs of each antibody identified in their test report. Although the MFI does not represent the exact amount (titer) or affinity (strength) of antibodies but the degree of saturation on the beads included in test kit, it has been attempted to be used predicting FCM or CDC XM results(41). We know that so called prozone effect mostly from the interference by IgM or C1 can cause underestimation of antibody level(42-44). However, the semiquantitative value of MFI may not be disregarded in current situation because any quantitative measure for the level of DSA would help for further test or treatment decision. The complement binding assay such as C1q or C3d assay may or may not provide further information of antibodies identified because of its ability to detect complement fixing cytotoxic antibodies but not enough sensitivity at the moment(45,46). Only four clinical pathologists has answered that they are conducting C1q as-

**Table 3.** The format and content of single antigen bead based HLA antibody identification result reporting in different HLA laboratories (n=18)

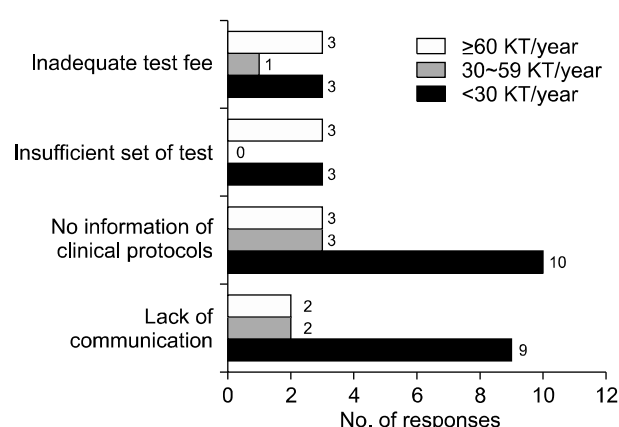
Contents of SAB identification	No. of laboratories (%)
Resolution	
Serological equivalent	7 (39)
Generic/allelic type	6 (33)
Both	5 (28)
Reporting of antibodies	
Anti-DQB1	18 (100)
Anti-DPB1	11 (61)
Anti-DQA1 or -DPA1	9 (50)
Reporting of MFI values	
MFI interval	7 (39)
Each MFI	9 (50)
MFI max	1 (6)
Not reporting	1 (6)
Reporting of % PRA	
% cPRA	13 (72)
% cPRA including DQ antibodies	11 (61)
Each Class I and II	8 (44)
Combined Class I and II	2 (11)
Both	2 (11)

Abbreviations: SAB, single antigen bead; MFI, mean fluorescence intensity; % cPRA, % calculated percent reactive antibodies.

say in their own laboratories, which is the only available KFDA approved kit in Korea at the moment. The Korean calculator to estimate % calculated percent reactive antibodies (% cPRA) based on HLA frequencies of Korean has been developed by KSLM and freely available to clinical laboratories (<http://www.pra-calculator.kr/form/form.html>). However, the size of database is not big enough and does not include all the loci yet. As shown in Table 3, each laboratory is generating % cPRA in different ways. So the values of % cPRA from different institutes even generated from same calculator may be not the same.

### 3. HLA crossmatching

As in Table 1 and nationwide HLA-EPT data, not all the institutes are conducting all phases of CDC XM including direct warm/NIH/long phases and augmented AHG phase or FCM XM for T and/or B cells. According to 40th nationwide HLA-EPT result performed in October 2017, three labs (6%, 3/50) are conducting T-CDC-AHG phase and T-FCM XM but not T-direct CDC, two labs (4%, 2/50) are conducting T-direct CDC phase and T-FCM XM but not T-CDC-AHG and 12 labs (24%, 12/50) are conducting only B-FCM XM but not B-CDC XM. This shows that CDC XM which has been considered as standard prerequisite test before KT are going to be replaced by more sensitive and informative assays such as FCM XM and SAB identification without or with complement binding assay.



**Fig. 16.** Clinical pathologist opinions on current shortcomings in laboratory practices.

#### 4. Area which needs to be improved

Like as to clinicians, when questioned about the current shortcoming in laboratory practices to clinical pathologists, lack of communications and not being shared the clinical protocols by transplant clinicians were the most common responses. The other issues were the insufficient set of tests and the inadequate cost of tests, which were related with policies of governmental sectors such as Ministry of Food and Drug Safety (MFDS) and Health Insurance Review and Assessment (HIRA) (Fig. 16).

The results of questionnaire survey from clinical pathologists have addressed the urgent need for the standardization of interpretation and the harmonization of result reporting particularly in SAB identification. And the communication between transplant clinicians and clinical pathologists to meet the clinical expectations on various immune monitoring tests seems to be paramount.

### CONCLUSION

This is the first nationwide survey for immune monitoring status in KT. The results show substantial variation in clinical and laboratory practices and address the issues and areas which need to be considered for establishment of harmonized immune monitoring guidelines in near future. The key things which need to be considered for the establishment of harmonized immune monitoring guidelines in Korea are; 1) the consensus criteria to define the risk level of AMR as low, intermediate and high, 2) the practical use of monitoring tools and frequencies to perform, 3) the standardization of test interpretation, 4) the harmonization of result reporting, and 5) importantly, the governmental policy which enabling the adoption of new tests in practice for the proof of concept. Lastly, with the collaboration of transplant experts, having the nationwide KT registry including recipient and donor demography, laboratory results, treatments and outcomes may contribute to draw the questions and answers which are supposed to be shared and reflected to the harmonization of clinical practices.

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