SARS-CoV-2 Antibody Point-of-Care Testing in Dialysis and Kidney Transplant Patients With COVID-19

Maria Prendecki, Candice Clarke, Tom McKinnon, Liz Lightstone, Matthew C. Pickering, David C. Thomas, Stephen P. McAdoo, and Michelle Willicombe

Rationale & Objective: A number of serologic tests for immunoglobulin G (IgG) against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are now commercially available, including multiple lateral flow immunoassays (LFIAs), which have the advantage of being inexpensive and easy to use, without the reliance on laboratory facilities. However, data on the development of humoral immunity to SARS-CoV-2 in patients with kidney disease is limited, and the utility of an LFIA to test for antibodies in these patients has not been assessed.

Study Design: Observational study.

Setting & Participants: 60 patients (40 hemodialysis and 20 kidney transplant recipients) with SARS-CoV-2 infection confirmed by viral reverse transcriptase–polymerase chain reaction (RT-PCR) testing and 88 historic negative-control samples (collected before September 2019).

Test: A commercially available LFIA to test for SARS-CoV-2 IgG in patients with infection confirmed by viral RT-PCR testing.

Outcomes: Sensitivity and specificity of the LFIA to detect SARS-CoV-2 IgG in dialysis patients and transplant recipients.

Results: 56/58 (96.6%) patients (38/39 hemodialysis and 18/19 transplant recipients) tested positive for SARS-CoV-2 IgG. 5/7 (71.4%) patients who were negative on preliminary testing had detectable IgG when retested more than 21 days postdiagnosis. Median times to first and second tests after diagnosis were 17 (interquartile range, 15-20) and 35 (interquartile range, 30-39) days, respectively. Calculation of test characteristics gave sensitivity of 96.6% (95% CI, 88.3%-99.4%) and specificity of 97.7% (95% CI, 92.0-99.6%).

Limitations: Possible exposure to other betacoronaviruses that may cross-react with the antigen used in the LFIA cannot be excluded.

Conclusions: Symptomatic dialysis patients and transplant recipients commonly develop an immune response against SARS-CoV-2 infection that can be detected using an LFIA. Used diligently, an LFIA could be used to help screen the dialysis populations or confirm exposure on a patient level, especially in facilities in which laboratory resources are limited.

Visual Abstract included

Complete author and article information provided before references.

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Patients with chronic kidney disease have been severely affected by the coronavirus disease 2019 (COVID-19) pandemic. Not only have they had to contend with the inability to effectively shield, resulting in a high risk for infection and its sequelae, but they have also had to face the anxiety associated with disruption of treatment regimens.[1-7] As a consequence, there has been a unified call to governing bodies from professional nephrological societies around the globe to ensure that patients with kidney disease are not disadvantaged in terms of access to treatment (medication or dialysis), personal protective equipment, and COVID-19 testing.[4]

The current gold-standard diagnostic test for acute infection is identifying viral RNA with reverse transcription-polymerase chain reaction (RT-PCR) of isolates from upper respiratory tract swabs, using oligonucleotides directed to nucleocapsid or viral RNA-dependent RNA polymerase genes.[8,9] Access to PCR testing around the world has not been uniform. However, even in countries in which there are no restrictions on testing, there are several potential limitations to the use of nucleic acid tests in diagnosing COVID-19. These limitations include both the need for specialized laboratory staff to perform molecular diagnostic techniques and the potential for false-negative test results, which may be linked to inadequate nasopharyngeal sampling. Hence the sensitivity and specificity of PCR from nasopharyngeal swabbing is thought to be 80% to 90% and 100%, respectively.[10] In addition to these limitations, PCR testing does not generate information on prior disease or assess the development of immunity, which requires serologic testing.

The development of serologic tests for immunoglobulin G (IgG) against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes COVID-19, has been an area of intense investigation and a number of tests are now commercially available. Due to the clinical urgency, independent validation of these tests has been occurring postmarketing, and there is a lack of data for special patient populations such as those with kidney disease. Although evidence is emerging that enzyme-linked immunosorbent assays (ELISAs) are more sensitive than lateral flow immunoassays (LFIAs) or point-of-care tests, the latter are inexpensive, are fast, and do not rely on laboratory facilities.[11,12] They may therefore be an option to enable access to rapid SARS-CoV-2 testing in patients with kidney disease, including those where laboratory resources are limited.

PLAIN-LANGUAGE SUMMARY

This study investigates the use of a point-of-care test to detect severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antibodies in 40 maintenance hemodialysis patients and 20 transplant recipients with confirmed coronavirus disease 2019 (COVID-19) infection. All patients were symptomatic at the time of diagnosis. Most patients, 38/39 (97.4%) hemodialysis patients and 18/19 (94.7%) transplant recipients, tested positive for SARS-CoV-2 immunoglobulin G antibody using the point-of-care test. 2/88 (2.3%) control samples, taken from individuals pre-pandemic, were positive. The results show that a point-of-care test can detect serologic responses in patients with end-stage kidney disease with clinically meaningful accuracy. Because these tests do not require laboratory resources, they may be used to enable equity of access to serologic testing in patients with kidney disease globally.

In this study, we assess the sensitivity and specificity of a commercially available LFIA to detect IgG against SARS-CoV-2 in patients with kidney disease with confirmed SARS-CoV-2 infection.

METHODS

Participants

All participants were prospectively recruited from Imperial College Renal and Transplant Centre, London, and provided written informed consent before participation. The study was approved by the Health Research Authority Research Ethics Committee (reference: 20/WA/0123-The Impact of COVID19 on Patients With Renal disease and Immunosuppressed Patients). A study flow diagram may be seen in Fig 1.

Samples

Sixty samples were collected from maintenance hemodialysis patients and kidney transplant recipients. Patients were identified by screening inpatient renal wards and outpatient renal clinics for individuals who were a minimum of 7 days post–positive PCR test results until 40 hemodialysis patients and 20 transplant recipients had been recruited. Twenty-five patients were recruited as outpatients, whereas 35 patients were inpatients at the time of enrollment. All patients had undergone RT-PCR testing due to symptoms. Patients who tested negative for IgG antibodies underwent repeat testing if the first test was performed on a sample taken 21 or fewer days after confirmation of infection.

Disease severity was classified according to the World Health Organisation (WHO) as severe (respiratory rate ≥ 30 breaths/min, blood oxygen saturation $\leq 93\%$, Pa_{O_2} to fraction of inspired oxygen ratio< 300 or infiltrates affecting 50% of the lung field within 24 to 48 hours) or critical (respiratory failure, septic shock, and/or multiple organ dysfunction/failure).[13] All other cases were classified as mild-moderate and we subdivided this group into mild disease (those who received outpatient care only) and moderate disease (those who required admission to the hospital).

Eighty-eight plasma samples were collected from individuals in the United Kingdom before September 2019 and were used as controls (Table S1). Cases were first identified from paired tissue bank samples for all patients with SARS-CoV-2 infection included in the study cohort. When these samples were exhausted, we identified sequentially collected samples working back from the inclusion date.

LFIA Antibody Testing

We tested a commercially available LFIA (Biomedomics Inc) according to the manufacturer's instruction. The test uses SARS-CoV-2 antigen MK201027, which is located in the receptor binding domain of the spike protein.[14] The test is validated for use with whole blood, serum, and plasma; in this study, both whole blood and plasma samples were included in the analysis (because all historic samples were plasma or serum). To ensure reproducibility of results between whole blood, plasma, and serum, a cohort of 6 people was tested using whole blood, plasma, serum, and plasma/serum that had been freeze thawed to $-80\,^{\circ}C$ (the method of storage of historic control samples). There was agreement between tests in all cases with the same intensity of positive bands. The assay was carried out strictly to the manufacturer's instructions by applying 20 μL of sample to the test, followed by 2 to 3 drops of buffer. Assays were observed to a maximum of 10 minutes, then results were assessed blindly by 2 independent observers. Tests were scored as IgG positive or negative, and any band was considered positive regardless of intensity.

Statistical Analysis

Statistical analysis was carried out using Prism, version 8 (GraphPad). For test characteristics, the Wilson-Brown method was used to compute CIs. Mann-Whitney test was used to compare nonparametric data, and t test, for normally distributed data. Data are reported as median and interquartile range. Fisher exact test or χ^2 test was used for proportional assessments. The 2-sided level of significance was set at $P < 0.05$.

RESULTS

With a median time to testing of 17 (interquartile range, 15-20) days after a positive RT-PCR result, 51/60 (85.0%) patients were IgG positive. All 9 patients who were IgG negative were tested 21 or fewer days after PCR diagnosis. Seven of these patients had further samples available for retesting at more than 21 days, and the remaining 2

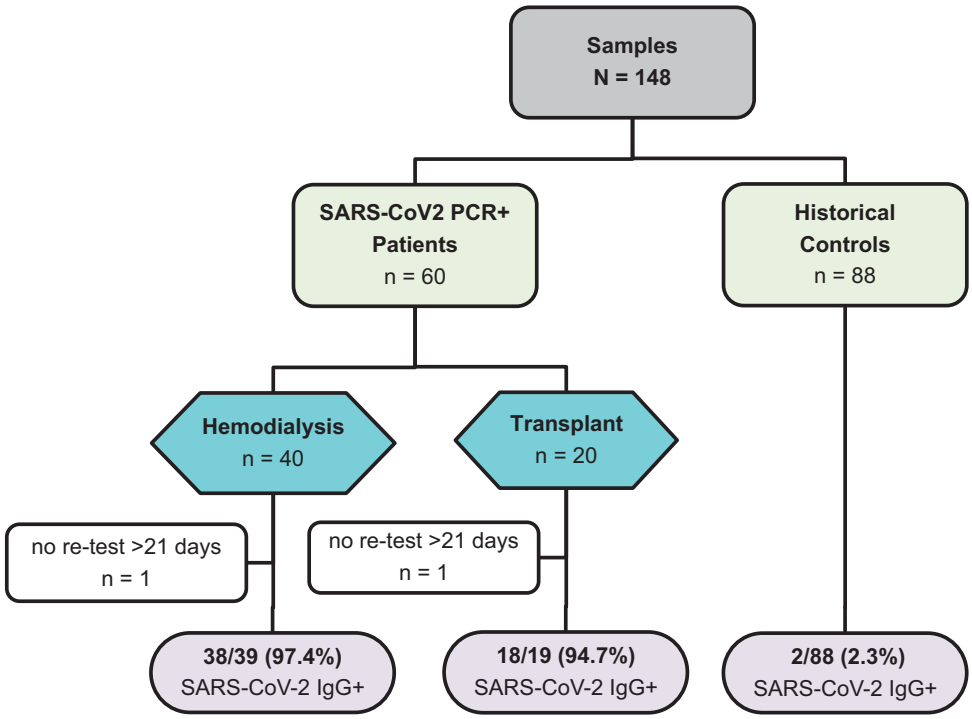

Figure 1. Study flow diagram. Abbreviations: IgG, immunoglobulin G; PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

patients were excluded from subsequent analysis. Five of 7 (71.4%) patients who were retested at more than 21 days had IgG antibodies on their second test. Median time from diagnosis to the second test was 35 (interquartile range, 30-39) days. SARS-CoV-2 IgG antibodies were therefore detected in 56/58 (96.6%) patients after 21 days after confirmation of SARS-CoV-2 infection.

Of the 2 patients who failed to develop IgG antibodies, 1 was a transplant recipient who had received a kidney transplant with alemtuzumab induction within 6 weeks of acquiring SARS-CoV-2 infection. This patient had a mild COVID-19 course by WHO criteria. The second patient was a maintenance hemodialysis patient who was not currently receiving immunosuppression treatment, although had previously been treated with chemotherapy for breast cancer more than 5 years previously. This second patient had critical disease severity by WHO criteria.

Clinical characteristics of study participants together with the clinical manifestations of their corresponding SARS-CoV-2 infection are shown in Table 1. Although there was no difference in the proportion of hemodialysis patients and transplant recipients who developed antibodies, 38/39 (97.4%) and 18/19 (94.7%), respectively, $P = 0.54$, there were several baseline differences between the 2 patient cohorts. Hemodialysis patients were older, $P = 0.004$, and more likely to have end-stage kidney disease secondary to diabetic nephropathy than transplant recipients, $P = 0.02$, as shown in Table 1. Intuitively, transplant recipients were more likely to be receiving immunosuppression. However, 5/39 (12.8%)

Table 1. Clinical Characteristics of Study Patients Assessed by LFIA

Variable	HD Patients (N = 39)	Transplant Recipients (N = 19)	P
Time of IgG+ test post PCR diagnosis, d	17 [13-26]	18 [14-23]	0.43
Age, y	64 [58-76]	55 [47-62]	0.004[a]
Men	24 (61.5%)	12 (63.2%)	0.91
Ethnicity			
White	9 (23.7%)	3 (16.7%)	0.52
BAME	30 (76.9%)	16 (84.2%)	
Cause of ESKD			
APKD	1 (2.6%)	2 (10.5%)	0.02[a]
Diabetes mellitus[b]	19 (48.7%)	3 (15.8%)	
Glomerulonephritis	5 (12.8%)	3 (15.8%)	
Unknown	8 (20.5%)	8 (42.1%)	
Other	6 (15.4%)	3 (15.8%)	
Baseline immunosuppression			
No[b]	35 (89.7%)	0 (0%)	<0.001[a]
Prednisolone	1 (2.6%)	—	
FK only	1 (2.6%)	3 (16.7%)	
Predisolone, FK	1 (2.6%)	—	
Prednisolone, FK, MMF	1 (2.6%)	6 (33.3%)	
FK, MMF	—	7 (38.9%)	
Sirolimus, prednisolone, MMF	—	2 (11.1%)	

(Continued)

Table 1 (Cont'd). Clinical Characteristics of Study Patients Assessed by LFIA

Variable	HD Patients (N = 39)	Transplant Recipients (N = 19)	P
Historic cytotoxic, B- or T-cell monoclonal antibody use			
No[b]	34 (89.7%)	0 (0%)	<0.001[a]
CyP	1 (2.6%)	—	
CyP/Ritux	1 (2.6%)	—	
Alemtuzumab	2 (5.1%)	16 (84.2%)	
IL-2R blocker	—	1 (5.3%)	
CyP/bortezomib	1 (2.6%)	—	
Alemtuzumab/Ritux	—	1 (5.3%)	
Unknown	—	1 (5.3%)	
Disease severity			
Mild[b]	6 (15.4%)	12 (63.2%)	<0.001[a]
Moderate	19 (48.7%)	6 (31.6%)	
Severe	11 (28.2%)	1 (5.3%)	
Critical	3 (7.7%)	—	
Care level			
Outpatient[b]	5 (12.8%)	15 (78.9%)	<0.001[a]
Inpatient ward	31 (79.5%)	3 (15.8%)	
Intensive care unit	3 (7.7%)	1 (5.3%)	
Current patient status			
Alive	36 (92.3%)	19 (100%)	0.22
Died	3 (7.7%)	—	

Note: Values expressed as median [interquartile range] or number (percent).
Abbreviations: APKD, adult polycystic kidney disease; BAME, Black, Asian, and minority ethnic; CyP, cyclophosphamide; FK, tacrolimus; HD, hemodialysis; IgG, immunoglobulin G; IL-2R, interleukin 2 receptor; LFIA, lateral flow immunoassay; MMF, mycophenolate mofetil; PCR, polymerase chain reaction; Ritux, rituximab.
[a]Statistically significant.
[b]Comparator.

hemodialysis patients were also receiving immunosuppression therapy at the time of SARS-CoV-2 infection; the indications for which were the presence of an in situ kidney transplant (3 patients) or to treat an underlying multisystemic autoimmune condition (2 patients). Seventeen of 18 (89.5%) kidney transplant recipients had received alemtuzumab induction, 5 of whom had undergone transplantation less than 1 year before having SARS-CoV-2 infection diagnosed. Compared with transplant recipients, the hemodialysis population was less likely to have mild disease, with 12 (63.2%) and 6/39 (15.4%) patients, respectively, having mild disease as classified by WHO, $P < 0.001$.

As a negative-control cohort, we used 88 saved plasma samples collected before September 2019. Two of 88 (2.3%) of these samples gave a false-positive IgG reading. Twenty-five of the 88 (28.4%) samples were historic samples stored from the current study patients with confirmed SARS-CoV-2 infection, all 25 of these samples tested negative for IgG. The false-positive samples were taken from patients who were receiving immunosuppression at the time of sampling, 1 for treatment of anti-neutrophil cytoplasmic antibody–associated vasculitis and the other from a hemodialysis patient with a failed transplant in situ.

Results from the study cohort and historic controls were used to calculate test characteristics for IgG detection at more than 21 days after confirmation of SARS-CoV-2 infection by PCR (Tables 2 and 3), giving sensitivity of 96.6% (95% CI, 88.3%-99.4%) and specificity of 97.7% (95% CI, 92.0-99.6%).

DISCUSSION

In this study we describe performance characteristics of an LFIA to detect SARS-CoV-2 IgG in a cohort of hemodialysis patients and kidney transplant recipients with SARS-CoV-2 infection confirmed by RT-PCR.

There has been a massive surge in the development of serologic tests for IgM and IgG against SARS-CoV-2. Numerous different assays are now available in addition to the LFIA point-of-care test; including ELISAs, chemiluminescence enzyme immunoassays, fluorescence immunoassays, and pseudovirus neutralization assays.[12,14,15] As assays are refined and developed, it is likely that the accuracy will improve, and the optimal serologic test has not yet been established.

The 96.6% sensitivity and 97.7% specificity of the LFIA we tested falls within the published ranges of other LFIA validation studies in the general population.[11,12] Although these test characteristics are insufficient to meet Public Health England approval status in the United Kingdom, which stipulate a requirement of 98.0% sensitivity and specificity, they provide findings that should be of interest to the nephrology community.[12] Given that these tests are simple to use, are inexpensive to manufacture, and give

Table 2. Antibody Results for SARS-CoV-2 IgG More Than 21 Days After PCR Test

	RT-PCR+ Cases	Historic Controls	Total
Antibody result			
Positive	56	2	58
Negative	2	86	88
Total	58	88	146

Abbreviations: IgG, immunoglobulin G; RT-PCR, reverse transcriptase–polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Table 3. Test Characteristics for SARS-CoV-2 IgG More Than 21 Days After PCR Test

Statistic	Value (95% CI)
Sensitivity	96.6% (88.3%-99.4%)
Specificity	97.7% (92.0%-99.6%)
Positive predictive value	96.6% (88.3%-99.4%)
Negative predictive value	97.7% (92.1%-99.6%)
Accuracy	97.3% (93.1%-99.2%)

Abbreviations: IgG, immunoglobulin G; RT-PCR, reverse transcriptase–polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

rapid results, they could play a role in population-level screening in high-risk cohorts, such as in-center hemodialysis patients.[16] One potential use would be to estimate prevalence across different dialysis facilities to allow planning for further outbreaks. Although it is important to highlight that while this study has investigated the use of an LFIA to detect antibodies in patients with symptomatic SARS-CoV-2 infection, its validity in patients with asymptomatic disease has not been established. LFIA antibody testing could also potentially be used to aid diagnosis.[17] Given the false-negative rates seen with RT-PCR secondary to sampling error, if clinically the pretest probability of SARS-CoV-2 infection is high, antibody testing may be used to help confirm or refute a diagnosis.[17,18] In dialysis facilities with no access to RT-PCR testing, interpretation of LFIA results in conjunction with clinical symptoms may enable a confirmatory diagnosis.

The use of IgM serologic testing would be preferable to IgG to help with the diagnosis of acute infection. We excluded the interpretation of IgM in this study because SARS-CoV-2 IgG assays are recognized to be more specific than IgM.[12,19] Five of 88 (5.7%) historic controls had false-positive IgM antibodies. Conversely, of the 2 IgG-negative patients who were unavailable to retest at more than 21 days, both had IgM antibodies that we were able to determine as new because both patients had historic samples in the control group that were IgM negative. It is therefore likely that the IgM detected in these 2 particular patients was in response to the acute SARS-CoV-2 infection, which would be useful information clinically if the test was accurate. However, incorporating IgM antibody data to calculate the LFIA test characteristics would have resulted in a significant reduction of the test performance, with sensitivity of 96.7% (95% CI, 88.5%-99.6%) and specificity of 84.1% (95% CI, 74.8%-91.0%), confirming an unacceptable IgM false-positive rate.

At the time of writing, this is the first report of the use of a SARS-CoV-2 LFIA in an immunosuppressed population. Patients with kidney disease are commonly considered to be immunosuppressed, either iatrogenically through the prescription of immunosuppressive medications or functionally from the effects of uremia.[20] Humoral responses to viruses may be impaired in these patients and it is well described that antibody responses to viral vaccines such as hepatitis B and influenza are impaired in both kidney transplant recipients and those with chronic kidney disease.[21-23] Although the serologic response to SARS-CoV-2 infection tested by ELISAs in patients receiving dialysis has been reported in 2 small studies, to our knowledge, no previous study has reported the immune response against SARS-CoV-2 in a cohort of kidney transplant recipients.[24,25] Although it is not yet known whether patients who have developed antibody responses to SARS-CoV-2 are protected from reinfection, proof of an immune response is reassuring and demonstration that this immune response may be detected by an LFIA is a novel finding.

This study has several limitations, including sample size and lack of serial testing to estimate the optimal time for antibody detection. In addition, we do not know if the study population (cases and controls) had prior exposure to other beta-coronaviruses that may have the potential to cross-react with the antigen used in this LFIA. Studies have shown, using micro-array, that there is only low-level cross-reactivity with the spike protein antigen. However, it is possible that the false-positive IgG results in our historic samples were due to prior exposure to another beta-coronavirus.[26] On a final note, LFIAs are nonquantitative tests so it was not possible to determine the effect of kidney disease or immunosuppression on antibody levels, which would be of interest and warrants further investigation.

In conclusion, we have shown that an LFIA can detect SARS-CoV-2 IgG antibody in venous blood of symptomatic hemodialysis patients and transplant recipients with clinically meaningful sensitivity and specificity. Used diligently, an LFIA could be used to help screen dialysis populations or aid diagnosis on a patient level, especially in facilities in which laboratory resources are limited. LFIAs could therefore enable equity of access to SARS-CoV-2 serology testing for patients with kidney disease across the globe.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Table S1: Clinical characteristics of historic controls.

ARTICLE INFORMATION

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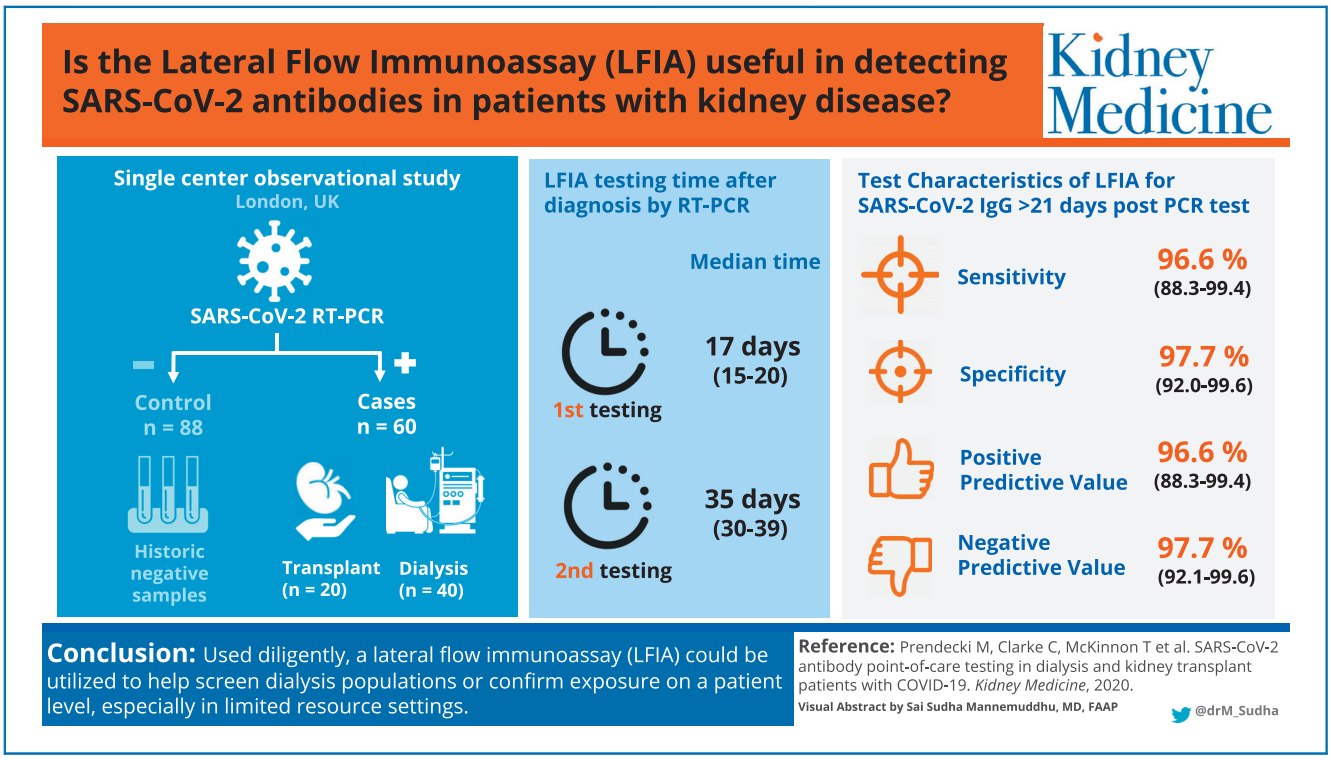
Is the Lateral Flow Immunoassay (LFIA) useful in detecting SARS-CoV-2 antibodies in patients with kidney disease?
Kidney Medicine
Single center observational study
London, UK
SARS-CoV-2 RT-PCR
Control
n = 88
Cases
n = 60
Historic negative samples
Transplant
(n = 20)
Dialysis
(n = 40)
LFIA testing time after diagnosis by RT-PCR
Median time
1st testing
17 days
(15-20)
2nd testing
35 days
(30-39)
Test Characteristics of LFIA for SARS-CoV-2 IgG >21 days post PCR test
Sensitivity
96.6 %
(88.3-99.4)
Specificity
97.7 %
(92.0-99.6)
Positive Predictive Value
96.6 %
(88.3-99.4)
Negative Predictive Value
97.7 %
(92.1-99.6)
Conclusion: Used diligently, a lateral flow immunoassay (LFIA) could be utilized to help screen dialysis populations or confirm exposure on a patient level, especially in limited resource settings.
Reference: Prendecki M, Clarke C, McKinnon T et al. SARS-CoV-2 antibody point-of-care testing in dialysis and kidney transplant patients with COVID-19. Kidney Medicine, 2020.
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