Study Protocol

Collaborative Transplant Study Pre- and Post-Transplant Covid-19 Serum Studies

"Antibody Formation against the Transplant after SARS-CoV-2 Infection"

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Contents

1. Summary

Currently, we are in the mid of the second peak of the Covid-19 pandemic. Many patients with end-stage renal or liver failure and a SARS-CoV-2 infection in their history will receive an organ transplant in the near future and a growing number of previously transplanted patients will be hospitalized for SARS-CoV-2 virus infection. In two serum studies we want to investigate prospectively whether patients with SARS-CoV-2 infection before or after organ transplantation will develop – depending on the severity of Covid-19 disease – graft-damaging donor-specific de novo HLA antibodies (dnDSA) more frequently than matched control patients and whether the formation of dnDSA will affect graft function and survival. Furthermore, in parallel to the dnDSA development, we also want to investigate in transplant recipients the development of the subgroups of SARS-CoV-2 antibodies over time and their relation to progression of Covid-19 disease.

We hypothesize that a severe SARS-CoV-2 infection in transplanted patients may lead to formation of graft-damaging de novo DSA and associated inferior outcomes in many patients. We would like to test this hypothesis in the "Post-Transplant Covid-19 Serum Study". In the "Pre-Transplant Covid-19 Serum Study" we will investigate whether transplantation of patients with a previous SARS-CoV-2 infection, as currently assumed, is indeed safe. Induction with antibodies is avoided in many patients and SARS-CoV-2-mediated activation of the immune system may also support the formation of transplant-damaging dnDSA. If the study results show that this is not the case, patients with a SARS-CoV-2 infection in their history can be transplanted in the future without concern.

Other aspects we intend to analyze include the influence of blood group and HLA phenotype on the incidence and severity of the Covid-19 disease and the decrease of SARS-CoV-2 antibody levels on the severity of Covid-19 disease. In collaboration with Prof. Dr. Schnitzler from the Department of Virology in Heidelberg we also want to investigate whether certain subgroups of SARS-CoV-2 antibodies correlate with a more effective neutralization of the virus.

Studies on these issues in transplanted patients have either not been conducted at all or were underpowered. The international Collaborative Transplant Study, which is coordinated since 1982 in Heidelberg, Germany and in which more than 150 liver and kidney transplant centers from all over the world are currently participating, offers the unique opportunity to collect reliable information on the effects of SARS-CoV-2 infection on the outcome of organ transplant recipients in a relatively short time, even if only a small number of the centers should participate in the study. Large transplant centers with high incidence of SARS-CoV-2 have already confirmed their participation.

2. Scientific basis

a. Background

More than 60% of organ failures in the late phase of a kidney transplantation are attributed to antibody-related rejection reactions, which are usually accompanied by de novo formation of so-called donor-specific antibodies against the HLA antigens of the organ donor (dnDSA) (Sellarés et al. 2012; Wiebe et al. 2012; Morath et al. 2014; Süsal et al. 2019). The main causes of dnDSA development are considered to be changes in the immune status, either during periods of under-immunosuppression, or triggered by infections or malignancies. Thus, infection and detection of BK viruses in the graft (BK nephropathy) also appear to independently promote the formation of dnDSA and increase the risk for antibody-mediated rejection (Cheungpasitporn et al. 2018). Under-immunosuppression is considered to be the main cause of dnDSA formation either be due to the non-adherence of the patient to immunosuppressive medication or intentionally by the treating physician, e.g. in the context of a severe BK virus infection or cancer development. Higher alloreactivity of the patient due to pre-sensitization and presence of higher number of HLA mismatches between recipient and donor can also contribute to the development of dnDSA. Whether a SARS-CoV2 infection could lead to the formation of dnDSA has not been investigated.

Because of its genetic similarity, research on SARS-CoV-2 has rather been seeking to establish parallels with Middle East Respiratory Syndrome Coronavirus (MERS-CoV) and Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) infections to gain insights into the consequences of SARS-CoV-2 infection (Zhu et al. 2020). In a case report of two kidney transplant patients with a MERS-CoV infection, one patient had a respiratory infection but a stable course with a speedy recovery and good graft function whereas the other patient had a severe course of the disease with multiple organ failure (including graft failure) and died from the infection (AlGhamdi et al. 2015). Another kidney transplant patient with severe MERS-CoV infection died as a result of acute graft failure (Mailles et al. 2013). In a case report of SARS-CoV infection a kidney transplant patient was reported to die after a short stay in intensive care (Chiu 2003). The question of how SARS-CoV-2 infection progresses in transplant recipients and what impact, if any, SARS-CoV-2 infection has on graft survival is what we aim to address in the post-transplant Covid-19 Serum Study.

To date, there are no published studies that have investigated the development of dnDSA in kidney transplant patients with proven SARS-CoV-2 infection. The reported data are so far from small-size monocentric observational studies with 7 and 20 kidney transplant patients, respectively, focusing on clinical course (Banerjee et al. 2020; Alberici et al. 2020). Cravedi et al. published the first multicenter data from 12 transplant centers with a 9-week follow-up. In renal transplant recipients, the risk of acute renal failure (52% of cases) and all-cause mortality (32%) was dramatically increased compared to not transplanted patients with SARS-CoV-2 infection (Cravedi et al. 2020). Long-term consequences of an infection with SARS-CoV-2, especially with regard to the development of dnDSA, have not yet been analyzed. In transplant recipients, it has also not been investigated in detail how the strength of the different subgroups of SARS-CoV-2 antibodies changes under immunosuppression and whether these changes have an influence on the severity of Covid-19 disease. These are questions we will address in the Post-Transplant Covid-19 Serum Study.

Reports on transplantation of patients with a previous SARS-CoV-2 infection history are also limited. Most of the data stem from individual case reports and there is an urgent need for larger, multi-center studies in order to be able to make a valid statement on the safety of organ transplantation in

these patients (Coates et al. 2020). Varotti et al. published the first case report of a patient who received a kidney transplant two months after she had been infected with SARS-CoV-2 (Varotti et al. 2020). Long-term observations are lacking. This is where we would like to start our **Pre-Transplant Covid-19 Serum Study** and investigate whether the timely transplantation of patients with a history of SARS-CoV-2 infection, as currently assumed, is indeed safe. It is conceivable that the activation of the immune system triggered by SARS-CoV-2 infection promotes the formation of dnDSA in the early phase after transplantation. If the study shows that the incidence of dnDSA after transplantation is not higher in patients with a history of SARS-CoV-2 than in matched controls, these patients can be transplanted in the future without major concerns.

Serum level of soluble CD30 is a good indicator of higher alloreactivity in renal transplant patients and a predictor of poor graft survival in connection with the presence of DSA before and after transplantation (Pelzl et al. 2002; Velásquez et al. 2012; Süsal and Opelz 2012; Schaefer et al. 2016). We would like to investigate whether patients who have undergone SARS-CoV-2 infection have higher sCD30 serum levels and whether this constellation has an influence on DSA development after transplantation.

In addition, it has not yet been conclusively clarified whether a reactivation of the SARS-CoV-2 virus could occur after transplantation. Lancman et al. recently published a case of a patient who received rituximab for treatment of her acute B-cell leukemia and experienced reactivation of the SARS-CoV-2, from which she had recovered two months ago (Lancman et al. 2020). In this case report, the already formed SARS-CoV-2 antibodies disappeared and the PCR detection became again positive.

In addition, the incidence of Covid-19 disease was reported to be higher in patients with blood type A and lower in patients with blood type 0 (Wu et al. 2020; Zhao et al. 2020). Furthermore, it is possible that certain phenotypes of HLA alleles that are responsible for presentation of viral antigens to the recipient's immune system are associated with the severity of Covid-19 disease. If we recruit a high number of patients, we will try to answer this question, at least approximately.

A longer follow-up of the Covid-19 serum studies will be possible in the Collaborative Transplant Study, which has been in place since 1982 and collects information on graft survival yearly and graft function and other clinical parameters at years 1, 2, 3, 5, 10 post-transplant, and in 5 year intervals thereafter (Opelz et al. 2013). Therefore, an analysis of the short as well as long-term effects on post-transplant outcomes of a SARS-CoV-2 infection before (Pre-Transplant Covid-19 Serum Study) and after transplantation (Post-Transplant Covid-19 Serum Study) will also be possible.

b. Conclusions

The data published so far on kidney transplant patients who become infected with SARS-CoV-2 are mostly individual case reports. Multi-center data are sparse. There are first attempts to collect multi-center data (Cravedi et al. 2020); however, they are limited to a clinical evaluation and the adjustment of immunosuppressive medication in the early phase after transplantation. It remains unclear to what extent the SARS-CoV-2 infection itself could have an effect on the development of dnDSA and what influence this in turn has on transplant survival (Post-Transplant Covid-19 Serum Study).

In addition, the question arises whether transplantation is actually safe in patients who have undergone Covid-19 disease (Pre-Transplant Covid-19 Serum Study). Whether a SARS-CoV-2

activated immune system may lead to an earlier formation of dnDSA against the transplant or even to reactivation or re-infection with the SARS-CoV-2 virus has not yet been conclusively clarified.

c. Practical relevance and questions

The present prospective multicenter study will provide new insights into potential complications (e.g. development of dnDSA) of kidney and liver transplanted patients with SARS-CoV-2 infection. Furthermore, we hope to obtain results regarding the safety of transplantation after a previous SARS-CoV-2 infection.

In the Pre-Transplant Covid-19 Serum Study we would like to answer the following questions:

- What is the incidence of dnDSA formation at the end of the first year after transplantation in kidney and liver transplanted patients who have experienced a SARS-CoV-2 infection prior to transplantation? Is the incidence higher than in matched controls? Does the higher incidence depend on pre-sensitization and presence of DSA prior to transplantation or presumed higher alloreactivity with elevated sCD30 levels?
- Does the SARS-CoV-2 infection prior to transplantation and the dnDSA development after one year have an impact on the outcome parameters death-censored graft survival, mortality, rejection treatments, infections and organ function after 1, 2, 3, and 5 and after 2, 3, 5 years, respectively? Is the impact greater than in matched controls?
- How does the strength of SARS-CoV-2 antibody subgroups change within one year after transplantation? Is re-infection with SARS-CoV-2 possible? Are re-infections dependent on the strength and subtypes of antibodies at the time of transplantation?
- Do patients with a history of SARS-CoV-2 infection have higher levels of the immune activation marker sCD30 in their serum than matched control patients? Do patients with a SARS-CoV-2 infection and high serum sCD30 level before transplantation develop dnDSA more often than patients with a SARS-CoV-2 infection and low serum sCD30 level or control patients without SARS-CoV-2 infection and high or low serum sCD30 level?

In the Post-Transplant Covid-19 Serum Study, from which we expect important insights, we would like to answer the following questions:

- What is the incidence of dnDSA formation in kidney and liver transplant patients at day 60–90 and at year one after hospitalization? Is the incidence higher than in matched controls? Does the higher incidence of dnDSA depend on the level of serum sCD30 levels?
- Do hospitalization for SARS-CoV-2 infection and dnDSA development one year after hospitalization have an impact on the outcome parameters death-censored graft survival, mortality, rejection treatments, infections, and organ function 1, 2, and 3 years after hospitalization? Is the influence greater than in matched controls?
- How does the strength of SARS-Cov-2 antibody subgroups change on days 60–90 and within one year after hospitalization for SARS-CoV-2 infection?

3. Objectives of the study

The objectives of this prospective multicenter study of kidney and liver transplanted patients are:

a. Primary objectives of the Pre-Transplant Covid-19 Serum Study

- Do organ transplant recipients who had experienced SARS-CoV-2 infection prior to transplantation have a higher incidence of de novo formation of graft-damaging donor-specific HLA antibodies (dnDSA) 1 year after transplantation compared to matched control patients?
- Does dnDSA formation at the end of the first year after transplantation have an impact on death-censored graft survival, mortality, organ function, rejection reactions, and infections 2, 3, and 5 years after transplantation?

b. Secondary Objectives of the Pre-Transplant Covid-19 Serum Study

- Does the pre-transplant SARS-CoV-2 infection, independent of dnDSA formation, have an impact on the outcome parameters death-censored graft survival, mortality, organ function, infections, and rejection reactions 1, 2, 3, and 5 years after transplantation?
- Is there a decrease in antibodies against SARS-CoV-2 after transplantation or a re-activation in spite of a full recovery from infection?

c. Primary Objectives of the Post-Transplant Covid-19 Serum Study

- Do transplant recipients hospitalized for SARS-CoV-2 infection have poorer death-censored graft and patient survival, poorer organ function, and higher incidence of rejection reactions and infections 1, 2, and 3 years after hospitalization compared to the control group?
- Does SARS-CoV-2 infection in transplanted patients lead to an increased incidence of graft-damaging dnDSA on days 60–90 and at the end of the first year after hospitalization?
- Does dnDSA formation after 60–90 days or one year after hospitalization have an impact on death-censored graft survival, mortality, organ function, rejection reactions and infections 1, 2, and 3 years after hospitalization?

d. Secondary Objectives of the Post-Transplant Covid-19 Serum Study

- Do organ transplant recipients who are hospitalized for SARS-CoV-2 infection possess preferentially a certain blood group or HLA phenotype?
- How does the strength of SARS-Cov-2 antibody subgroups change within 60–90 days or one year after hospitalization?

4. Procedure to be tested

a. Description

1. In the **Pre-Transplant Covid-19 Serum Study**, the new formation of transplant-damaging DSA and SARS-CoV-2 antibody progression in the first year after transplantation will be investigated in kidney or liver transplanted patients who were already infected with SARS-CoV-2 prior to transplantation. The next two transplanted patients at the center who are matched by organ donor type (living or deceased) and, if possible, also by the age category and gender (possible only in only large centers) will serve as control patients with regard to DSA formation.

One serum sample before transplantation and one serum sample after transplantation will be drawn from all participating patients including the controls. For a reliable determination of DSA, an additional blood sample for isolation of DNA from the recipient and donor will also be taken, frozen and sent to the Institute of Immunology in Heidelberg at certain intervals. Also required are a

recruitment form and a pre-transplant SARS-CoV-2-specific questionnaire filled out by the responsible official. Further clinical data will be obtained from the regular CTS study forms published on the CTS website (https://www.ctstransplant.org/public/download.shtml).

2. In the **Post-Transplant Covid-19 Serum Study** dnDSA formation and SARS-CoV-2 antibody response in previously kidney or liver transplanted patients hospitalized for SARS-CoV-2 infection will be compared at the time of hospitalization and 60–90 days and one year after hospitalization. Two patients without SARS-CoV-2 infection from the follow-up outpatient clinic, matched for time after transplantation, organ donor type (living or deceased donation), age category, and gender will serve as controls for the development of DSA.

At least 3 serum samples are required: 1) the first from the day of admission to the clinic, 2) the second 60–90 days later (not necessary for control patients) and 3) the third one year after hospitalization. For an accurate assessment of the new formation of dnDSA, if available, a serum sample before infection and a serum sample before transplantation and DNA from the recipient and donor are also required. If a DNA sample from the donor is not available, the information on 2-field HLA typing of the donor for 11 HLA gene loci (HLA-A,-B,-C,-DRB1/3/4/5,-DQA1 and -DQB1) is required for antibody-positive patients. 60–90 days after hospitalization, the treating physician will receive a SARS-CoV-2-specific questionnaire to fill out (see 9c Conduct of the study). Further information will be deducted from regular CTS study forms (https://www.ctstransplant.org/public/download.shtml).

b. Therapeutic effects

The ex-vivo tests carried out in the patients' samples serve to determine purely diagnostic parameters. For this reason, no therapeutic effect is expected in participating study patients.

c. Undesirable effects, other risks, stress for the study participant

As described above, collection of blood samples is linked to routine transplant follow-up so that no additional venipunctures of the patient are required. The additional time required from patients who agree to participate in the study will be minimal. The additional tubes for the evaluation of the formation of dnDSA as well as for the evaluation of the antibody courses after infection with SARS-CoV-2 will be drawn during the routine blood collection after transplantation. Based on experience, collection of the additional blood tubes results in an additional time expenditure of less than 1 minute and informing patients about the study and discussing participation and informed consent is expected to take 15 minutes on the part of the patient or his/her legal representative, depending on information needs. Participants of the Pre-Transplant Serum Study will have blood drawn at two defined time points in addition to routine blood collection, namely on the day of transplant and at year one post-transplant. The SARS-CoV-2 specific questionnaire, which mainly includes questions about the health status of the patient to be transplanted after the SARS-CoV-2 disease, will be filled out by the medical staff, the patient will only have an additional effort here in case the questions cannot be answered based on the available information and queries would arise. Post-Transplant Serum Study participants will have blood drawn at three defined time points in addition to routine blood collection, namely on the day of hospitalization due to SARS-CoV-2 infection, on day 60–90 post-hospitalization due to SARS-CoV-2 infection, and one year post-hospitalization. Control patients for both the Pre- and Post-Transplant Serum Studies will have blood drawn at only two defined time points, at time point 1 and one year thereafter.

However, additional biological material for antibody testing is necessary to conduct the study, so that approximately 10–20 ml more blood than usual will be collected at each defined time point. The routine blood collection is associated with the general risks of a venous puncture. By linking study-related blood collection with the routine aftercare, no further burden in the form of additional travel or costs is to be expected for the patient.

5. Study design

The presented study is a prospective, multicenter, international, controlled, and open study.

6. Randomization procedure

There is no randomization.

7. Inclusion criteria

The following inclusion criteria apply to both Pre- and Post-Transplant Covid-19 Serum Studies:

- Deceased or living donor kidney and deceased donor "full-size" liver transplant recipient (de-novo or re-transplanted)
- Consent of the patient or his/her legal representative
- Written declaration of consent of the patient or his/her legal representative
- Recipient age 18–75 years
- A clinically diagnosed SARS-CoV-2 infection (before or after transplantation)
- We decided to include non-consenting patients in the study because hospitalized patients with SARS-CoV-2 infection may experience relatively rapid disease progression with possible intensive care hospitalization and loss of consenting capacity. Particularly in these severe courses, we expect increased formation of graft-damaging antibodies and/or impaired graft function. Following points 28 and 30 of the Declaration of Helsinki, we think that in this group in particular we can gain additional information about the course of disease in the overall group (transplanted patients with SARS-CoV-2 infection) and also information to promote the health of the overall group (e.g., prevention of rejection by timely detection of newly formed transplant-damaging antibodies). We interpret the benefit we may generate from an increased number of cases and especially from the information gain of follow-up of severe SARS-CoV-2 infections as justifiable compared with the additional burden of collecting approximately 10-20 ml of blood in addition to routine blood collection. We draw attention to the fact that we would only want to include non-consenting patients in such a case if they are patients who require intensive care due to their SARS-CoV-2 infection and are therefore incapable of giving consent. According to points 28–30 of the Declaration of Helsinki, we commit ourselves to inform patients, if they regain their capacity to consent, about the measures performed so far and to obtain consent for further participation.

Specific inclusion criteria for the Pre-Transplant Covid-19 Serum Study

- Transplantation between December 1, 2020 and December 15, 2021
- A clinically diagnosed SARS-Cov-2 infection before transplantation
- 2 sera available (one serum before and on the day of transplantation and one serum 1 year after transplantation)
- DNA or complete 2-field, 11-locus HLA typing from recipient and donor available

- Completed SARS CoV-2 specific questionnaire from day 0 of transplant

Inclusion criteria for control patients in the Pre-Transplant Covid-19 Serum Study: The next two transplanted control patients without clinically diagnosed SARS-CoV-2 infection prior to transplantation matched by the type of donor (living or deceased) and, if possible also, by the age category and gender.

Specific inclusion criteria for the Post-Transplant Covid-19 Serum Study:

- Hospitalization for SARS-Cov-2 infection after transplantation between December 1, 2020 and December 15, 2021
- 3 sera available (day of hospitalization for SARS-CoV-2, 60–90 days after hospitalization and 1 year after hospitalization)
- DNA or complete 2-field, 11-locus HLA typing from recipient and donor available

Inclusion criteria for control patients in the Post-Transplant Covid-19 Serum Study: Two previously transplanted control patients from the outpatient clinic without SARS-Cov-2 infection after transplantation matched by the time period after transplantation, type of donor (living or deceased), age category, and gender.

8. Exclusion criteria

The following criteria are defined as exclusion criteria for both studies:

- Multi organ transplant recipient
- Refusal to participate in the study
- Failure to meet the above inclusion criteria

9. Course of the study

a. Participating institutes

This is a multicenter study, which is coordinated by the above mentioned study directors, Professor Süsal from the Institute of Immunology and Professor Morath from the Kidney Center Heidelberg. Currently, more than 150 liver and kidney transplant centers from all over the world are actively participating in the Collaborative Transplant Study (CTS), which was initiated in 1982. Even if only a small number of centers should participate in the Covid-19 Serum Studies, CTS offers the unique opportunity to collect reliable information on the effects of SARS-CoV-2 infection on organ transplantation in a relatively short time. Large transplant centers have agreed to participate.

In Heidelberg itself, the study is being conducted as part of the routine transplant follow-up at the Heidelberg Transplantation Center of the Heidelberg University Hospital. The determination of SARS-CoV-2 antibodies will be performed under the direction of Prof. Dr. Paul Schnitzler in the Department of Virology. The determination of DSA and HLA phenotype, as well as a further part of the SARS-CoV-2 antibody subgroup determinations will be conducted using the recently introduced Luminex method at the Institute of Immunology under the direction of Prof. Dr. med. Caner Süsal. The statistical analysis will be performed with the help of a statistician.

b. Patient collective and patient recruitment

An exact number of patients to be recruited cannot be accurately predicted due to the multicenter and international nature of the studies and the unpredictable development of the pandemic. In the

planned recruitment period of one year, we expect to recruit 300–600 SARS-CoV-2 patients and 600–800 control patients in both studies. If these numbers are not reached in one year, we would like to extend the recruitment period to 2 years. Patients will be cared for before and after transplantation by the transplant centers participating in the CTS study. The respective inclusion and exclusion criteria for participation in the study have already been explained in the preceding sections. Due to the international nature of the studies, the individual centers must meet their own local ethical requirements using the study protocol and its translations submitted.

During an informative talk, the possibility of participating in the study is discussed together with the patient and the patient is informed in detail about the background, contents and objectives of the study. In addition, all study participants receive the information leaflets attached to this article. If the subject is not able to make autonomous decisions during hospitalization SARS-CoV-2 or intensive care, a legal representative or other decision-maker will be informed about the possibility of participating in the study. If a **legal representative has been appointed and is available** (or a health care proxy / guardian), he/she can make decisions on his/her own responsibility on behalf of the patient. The information and consent procedure is now carried out with the representative in the same way as it would otherwise be with the patient. There is a separate information leaflet and a separate consent form for this. If the person concerned is only partially able to follow a clarification discussion, this will be taken into account, for example by providing information at the patient's bedside. If transplanted patients who were hospitalized with SARS-CoV-2 and initially lacked autonomous decision-making capacity regain their decision-making capacity, they will be informed about the interventions performed to date and asked for their autonomous consent to participate.

The participating centers abroad will receive translated information leaflets and consent forms (English, Spanish, Portuguese, French). By signing the participation form, the participating centers undertake to provide sufficient information (by means of the information leaflet) to the patients and to have obtained the patient's consent to participate in the study (by means of a signed consent form). The signed consent forms remain at the respective transplant center.

c. Study schedules for blood and data collection

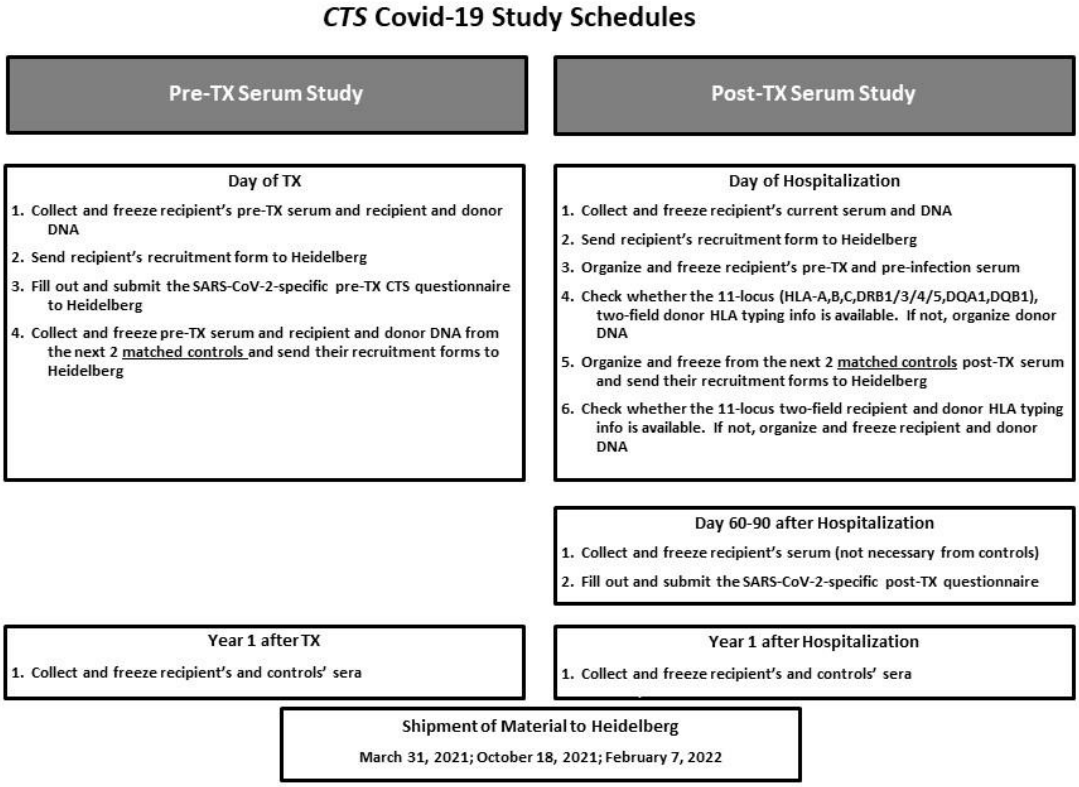

Figure 1: Schedule of Pre-Transplant (pre-TX) and Post-Transplant (post-TX) Covid-19 Serum Studies

Collection of relevant patient and transplantation associated data at the time of transplantation (standard of the Collaborative Transplant Study, NOT PART OF THIS STUDY PROTOCOL)

Patient data is collected once at the time of transplantation and corrected or supplemented as necessary during the post-transplant follow-up phase at regular intervals. The collection of the data takes place via regular CTS study forms (https://www.ctstransplant.org/public/download.shtml) and SARS-CoV-2 specific Pre- and Post-TX study questionnaires (see Appendix and (https://www.ctstransplant.org/public/download.shtml). The participating centers report only those transplantations to the CTS study where patients have agreed to have their data reported to the CTS study.

Kidney Transplantation:

The following information is requested: **Recipient** Name, age, sex, race (depending on country), smoker's history, current antidiabetic therapy, current antihypertensive therapy, blood group, EBV/CMV status, CMV prophylaxis, HLA phenotype, preformed panel reactive antibodies (PRA in %), CDC crossmatch, occurrence of donor-specific antibodies (Luminex Single Antigen Assay, positive beads in%/highest MFI), induction therapy before transplantation (+method), start of dialysis, type of dialysis therapy before transplantation (hemodialysis, peritoneal dialysis, both, none), underlying renal disease (chronic GN, pyelonephritis, nephrosclerosis, polycystic kidney disease, diabetes type 1, diabetes type 2, others), clinical general condition before transplantation, reasons for impaired general condition, immunosuppression after transplantation ("intention to treat") **Transplant** date,

donor type (living / deceased / parent / sibling / offspring), transplantation frequency (first / second / third or more transplantations), primary function **Donor** age, sex, race, blood group, EBV/CMV status, HLA phenotype, cold ischemia time, cause of death (trauma/cardiovascular/other), medical diagnosis of arterial hypertension, non-heart beating donor (currently not legally permitted and not practiced in Germany)

Liver Transplantation:
The following information is requested: **Recipient** Name, age, sex, race, smoking history, current antidiabetic therapy, current antihypertensive therapy, blood type, HCV/HBV/EBV/CMV status, CMV prophylaxis, HLA phenotype, preformed panel reactive antibodies (PRA in %), CDC crossmatch, occurrence of donor specific antibodies (Luminex Single Antigen Assay, positive beads in%/highest MFI), induction therapy before transplantation (+method), MELD score before transplantation, underlying disease (type of cirrhosis, sclerosing cholangitis, biliary atresia, fulminant hepatitis, acute liver failure, tumor, metabolic, other), clinical general condition before transplantation, reasons for impaired general condition, immunosuppression after transplantation ("intention to treat").
Transplant date, donor type (living / deceased / parent / sibling / other), transplant frequency (first / second / third or more transplantations), urgency (high urgency / urgent / normal), graft size (for this study only full-size liver), in case of re-transplantation, number of days previous graft functioned.
Donor age, gender, race, blood group, HCV/HBV/EBV/CMV status, HLA phenotype, cause of death (trauma/cardiovascular/other), medical diagnosis of arterial hypertension, non-heartbeating donor (currently not legally permitted and not practiced in Germany)

Collection of relevant Covid-19-associated data for possible participation in the Pre-Transplant Covid-19 Serum Study ("PRE-TX SARS-CoV-2-Specific Questionnaire")
To participate in the Pre-Transplant Covid-19 Serum Study, the treating physician will also receive a SARS-CoV-2 infection-specific questionnaire to fill out (see also Appendix, **PRE-TX SARS-CoV-2-Specific Questionnaire**, modified according to Global COVID-19 Clinical Platform RAPID CORE CASE REPORT FORM (CRF) of the WHO, WHO Reference Number: WHO/2019-nCoV/Clinical_CRF/2020.4).
The following will be queried:
Transplant center, organ recipient (for identification), transplant date, date of onset of symptoms; **SARS-CoV-2 associated morbidity at time of transplantation** Cerebrovascular (yes/no), cardiovascular (yes/no), pulmonary (yes/no), renal failure (yes/no), thromboembolic complications (yes/no), other morbidity (which?); **course of Covid-19 disease**: hospitalization (yes/no), intensive care (yes/no), invasive ventilation (yes/no).

Sample collection for additional laboratory diagnostics for participation in the <u>Pre</u>-Transplant Covid-19 Serum Study (Figure 1)

Participating study patients with a history of SARS-CoV-2 infection before transplantation <u>and</u> the next two matched transplanted controls without SARS-CoV-2 infection history:

Before transplantation (day 0):

- 1 x 1–2 ml serum (for determination of DSA, sCD30, and SARS-CoV-2 antibodies and their subgroups)
- 1 x 10 ml EDTA blood from recipient and donor (for full 2-field 11 locus HLA typing)

Year 1 after transplantation:

- 1 x 1–2 ml serum (determination of DSA, sCD30, and SARS-CoV-2 antibodies and their subgroups)

Sample collection for additional laboratory diagnostics for participation in the Post-Transplant Covid-19 Serum Study (Figure 1)

For SARS-CoV-2-hospitalized study patients:

Day of hospitalization:

- 1 x 1–2 ml serum (for determination of DSA, sCD30, and SASR-CoV-2 antibodies and their subgroups)
- 1 x 1–2 ml serum before transplantation (if available, for reliable dnDSA evaluation))
- 1 x 1–2 ml serum before infection (if available, for reliable dnDSA evaluation)
- 1 x 10 ml EDTA-blood from both donor and recipient or the full 2-field 11 locus HLA typing info.

Day 60–90 after hospitalization:

- 1 x 1–2 ml serum (for determination of DSA, sCD30, and SARS-CoV-2 antibodies and their subgroups)

Year 1 after hospitalization:

- 1 x 1–2 ml serum (for determination of DSA, sCD30, and SARS-CoV-2 antibodies and their subgroups)

Two matched controls without SARS-CoV-2 infection:

Day of inclusion:

- 1 x 1–2 ml serum (for determination of DSA, sCD30, and SARS-CoV-2 antibodies and their subgroups)
- 1 x 10 ml EDTA-blood from both donor and recipient or the full 2-field 11 locus HLA typing info

Year 1 after inclusion:

- 1 x 1–2 ml serum (for determination of DSA, sCD30, and SARS-CoV-2 antibodies and their subgroups)

The samples from the externally participating centers will be frozen at –20° and sent to Heidelberg at specific time points (March 31, 2021; October 18, 2021; February 7, 2022) for DSA, sCD30, and SARS-CoV-2 antibody determinations.

Collection of Covid-19-associated data 60–90 days after hospitalization for SARS-CoV-2 for participation in the Post-Transplant Covid-19 Serum Study ("POST-TX SARS-CoV-2-Specific Questionnaire")

60–90 days after hospitalization, the treating physician will receive a SARS-CoV-2 infection-specific questionnaire for completion (see also Appendix, POST-TX SARS-CoV-2-Specific Questionnaire, modified according to Global COVID-19 Clinical Platform RAPID CORE CASE REPORT FORM (CRF) of the WHO, WHO Reference Number: WHO/2019-nCoV/Clinical_CRF/2020.4). The following data will be queried:
Organ recipient (for identification), transplant date, evaluation date; **initial** date of onset of symptoms; **Covid-19-specific therapy**: antiviral therapy (yes / no), if yes: Remdesivir (yes / no),

corticosteroids (yes / no), if yes: dose and preparation, experimental therapy (request to specify which), systemic anticoagulation (yes / no); **supportive therapy**: intensive care (yes / no), duration of intensive care, oxygen therapy (yes / no), ventilated (yes / no), intubated (yes / no), ventilation duration (days), ECMO (yes / no), catecholamine required (yes / no), acute renal failure, dialysis, acute liver failure, drug therapy: SARS-CoV-2 specific medication (yes / no), if yes, please specify; change in transplant specific medication (yes / no), if yes, please specify.
Additional laboratory findings collected on the day of hospitalization and 60–90 days after hospitalization: Serum creatinine (mg/dl) or µmol/L, proteinuria (yes/no), if yes: xx g/g creatinine or xx g/mol creatinine, if liver-TX: well-functioning graft / limited graft function

d. Matching of the control groups

For each participant of the Pre-/Post-Transplant Covid-19 Serum Study, 2 control patients will be matched. The matching will be done by donor type, age category, and gender, and in the post-transplantation study also by the time after transplantation (0–180, 181–365, 366–1095, 1096–2555 and >2555 days). Age categories are defined as 18–34, 35–59, and 60–75 years. Smaller centers will not be able to match by gender and age in the pre-transplant study, but this will be taken into account in the multivariate analyses.

10. Accompanying therapy

There are no restrictions with regard to the accompanying therapy. An investigational drug is not used.

11. Safety laboratory

The investigations are performed in the laboratories of the Immunology Department of the Heidelberg University Hospital. The determination of the general clinical-chemical parameters is done in the Analysis Center of the Heidelberg University Hospital, the detection of SARS-CoV-2 antibodies in the Virology, and the Immunology Department of the Heidelberg University Hospital.

12. Termination criteria

a. Individual termination criteria

Each participant has the right to withdraw his or her consent to participate in the study at any time. In addition, the study director reserves the right to exclude the patient from the study for the following reasons:

- Ineligibility (which became apparent during the study or was missed retrospectively at screening)
- Significant deviation from study protocol
- Significant non-compliance with the study protocol or medical therapy
- An adverse event that requires discontinuation/reduction of medical therapy or endangers further participation in the study
- Loss to follow-up

The data collected up to the termination will be included in the statistical evaluation as far as possible and the patient’s consent is present.

b. Termination criteria for the entire study

An accumulation of adverse events is not to be expected, since the examinations presented here are performed as part of routine follow-up after kidney or liver transplantation. There are therefore no fixed termination criteria that would justify terminating the entire study.

13. Undesirable events

An undesirable event is defined as any unexpected change in body functions or body structures. In principle, this includes all events that deviate from the expected sequence of events. We do not expect any undesirable events in this study, as it is a purely prospective observational study without intervention.

14. Benefit/risk assessment for conducting the study during the Covid-19 pandemic

The current Covid-19 pandemic poses a major challenge not only clinically but also in terms of our research. The Working Group of Medical Ethics Committees in the Federal Republic of Germany has published on its website various ethical aspects that have to be considered especially during the Covid-19 pandemic. We are aware that the transfer of data and samples to other research institutions for research on Covid-19-associated pathologies, here especially in transplantation research, requires the consent of the participants and sufficient information. We also note that patients with acute Covid-19 infection are considered a particularly vulnerable group (according to Art. 19 Declaration of Helsinki). If these patients are treated as inpatients, their autonomy may be largely restricted. If the course of the disease is severe, we will examine whether the patient can still make a self-determined decision for or against participation in the study. If the patient is unable to give consent, we will inform the legal representative or other decision-makers about the possibility of participating in the study.

We are aware that in the current pandemic the type and number of visits should be reduced. We are committed to a careful risk/benefit balance. A replacement visit in the form of a telephone or video visit is not possible in our study, as a blood sample is required. However, it is clear from the structure of our study that potential study participants will always present themselves at our outpatient clinic for important and necessary transplant aftercare. Therefore, we do not currently see any additional risk for our patients from participating in the study.

At the Heidelberg University Hospital, the measures generally specified by the Baden-Württemberg government to protect the population and prevent further progression of the Covid-19 pandemic apply.

15. Ethical and legal aspects

The examination is carried out in accordance with the Declaration of Helsinki and the Professional Code of Conduct for Physicians of the Medical Association of Baden-Württemberg in its current versions. The participation of patients and healthy volunteers in the examination is voluntary. However, the above inclusion criteria apply, thereby limiting participation to renal and liver transplant patients with or without SARS-CoV-2 infection. The consent can be withdrawn at any time without giving reasons and without disadvantages for further medical care. The study participants will be informed orally and in writing about the nature and scope of the planned study,

in particular about the possible benefits for their health and possible risks. Since this is an observational study, there are minimal burdens and risks for the study participants. In particular, the fact that significant findings on the improvement of health of the investigated group can be obtained justifies the inclusion of the test subjects in this scientific study and a possible retrospective analysis of already asserted samples (consent available). A refusal to participation in the study on the part of the test subject will be respected at all times.

The consent is documented by the signature of the participant or a legally authorized decision maker on the declaration of consent. The exact procedure for this has already been described in detail in Section 9b "Patient Collective & Patient Recruitment". In the event of withdrawal from the study, any (data) material already obtained will be destroyed or the patient will be asked whether he or she agrees to the evaluation of the material. The study protocol will be submitted to the Ethics Committee of the Medical Faculty of Heidelberg for review before the study starts. The inclusion of patients and healthy volunteers according to above mentioned inclusion/exclusion criteria will not be initiated until the written, consenting vote of the Ethics Committee has been received. Information leaflets and consent forms will be made available to the other participating centers in English/Spanish/Portuguese and French. By signing the participation form, the participating centers undertake to provide sufficient information (by means of the informed consent form) and to obtain the patient's consent to participate in the study (by means of a signed consent form). The signed consent forms remain with the respective transplant center.

The names of the study participants and all other confidential information are subject to medical confidentiality and the provisions of the Basic Data Protection Ordinance (DSGVO) as well as the State or Federal Data Protection Act (LDSG or BDSG). Data of study participants may only be passed on in pseudonymized form.

16. Patient insurance

The project is covered by Heidelberg Hospital's public liability insurance. This insures possible damages resulting from participation in the scientific study.

17. Expense allowance for the study participants

Financial compensation for study participants is not provided for.

18. Study financing and conflicts of interest

The study is financed by own funds of the Institute of Immunology Heidelberg. Furthermore, project funding by third parties is intended. Conflicts of interest (both financial and personal) do not exist for any of the departments or persons involved in the study.

19. Data protection

All data with identification of the study participants are only accessible to the supervising physicians and nursing staff as well as laboratory staff, doctoral students, and the CTS study IT team. For all other persons involved in the study, the data is encrypted in pseudonymized form. Likewise, only pseudonymized patient data are used in publications. The list for the assignment of participant code and participant name is only available to the physicians, laboratory staff, and PhD students of the Renal Center, Surgical Clinic, Medical Clinic and Immunology of the Heidelberg University Hospital

who are involved in the study. Decryption of the pseudonymized data is only permitted in justified cases. This is the case, for example, if important new findings regarding the diagnosis and therapy of the underlying disease become known in the course of the study. In this case it is possible to assign the data collected to the respective patient. Re-identification is also permissible if a study participant wishes to assert his or her right to information or revocation. In accordance with Good Clinical Practice (GCP) guidelines, the data collected will be stored indefinitely in the database of the Collaborative Transplant Study Heidelberg. The exact retention period of the biomaterials and data cannot be stated precisely, as it is currently not foreseeable which studies on the study blood regarding organ transplanted patients with SARS-CoV-2 infection might still be relevant in the future. Therefore, it results that the biomaterials will be kept indefinitely and made available for further, medical research regarding transplanted patients with SARS-CoV-2 infection. We will review every five years whether further retention of the biomaterials and data is still necessary. The personal data will be anonymized as soon as this is possible according to the research purpose.

20. Registration at the regional council

As this study is not a drug study, it is not necessary to report it to the regional council.

21. Statistical design

The presented study will be conducted as a pilot study. An explorative data evaluation will be performed. It is a multicenter, controlled study. An exact number of patients to be recruited cannot be accurately predicted due to the multicenter international nature of the studies and the unpredictable development of the pandemic and vaccination. In the planned recruitment period of one year, we expect to recruit 300–600 SARS-CoV-2 patients and 600–800 control patients per study and per organ. If these numbers are not reached in one year, we would like to extend the recruitment period to 2 years.

A 5% significance level case number estimate based on the log-rank test comparing Kaplan-Meier estimates for 5-year graft survival and DSA-free survival and an assumed 10% survival difference between SARS CoV-2 patients and controls at 1:1 matching and assuming no follow-up losses provides a required case number for:

5-year graft survival of approximately

- 400 –600 patients for the pre-TX serum study
- 300 –400 patients for the post-TX serum study

for 5-year DSA-free survival of about

- 400 – 600 patients for the pre-TX serum study
- 300 –400 patients for the post-TX serum study

depending on the proportion between living and deceased donations (case number estimate according to Table 1A Freedman, STATISTICS IN MEDICINE, VOL. 1, 121-129 (1982))

For the 1:2 matching study design applied here, the required number of SARS-CoV-2 patients will decrease with an increase in the total number of patients by about 30%. If one assumes additional follow-up losses of 20%, the number of cases will increase by another 25%.

A cumulative incidence of 20% in the controls was assumed for DSA development after 5 years (Everly et al.). For transplant survival, 5-year survival was calculated for the corresponding groups

using the CTS data (live and deceased kidney donation for the pre-TX study, influence of tacrolimus trough level for the post-TX study).

For Cox regression, depending on the quality of the matching and the resulting number of confounders, an increased number of cases must be expected in order to detect the same differences in a statistically significant manner.

The statistical analysis will be done with the help of a biometrician. For statistical evaluation R version 4.0.3 will be used.

A detailed descriptive statistics (mean, standard deviation, minimum, median, quartiles (Q1, Q3), maximum, 95% confidence interval for continuous variables and n-number and percentage for categorical variables) of all collected data will be performed. It will be tested for significant differences at a 5% significance level ($p<0.05$).

Pre-Transplant Covid-19 Serum Study

In this study, the incidence of dnDSA in transplanted patients with a history of SARS-CoV-2 infection prior to transplantation will be calculated by descriptive statistics at the time of 1 year after transplantation and correlated with matched control patients (transplanted without previous SARS-CoV-2 infection). Using Kaplan-Meier curves, transplant survival and total mortality can be represented. The course of antibody concentrations after infection or vaccination can also be calculated descriptively.

Univariate Kaplan-Meier and multivariate Cox analyses of graft survival and all-cause mortality will also be performed using data from the Collaborative Transplant Study at 1, 2, 3, and 5 years after transplantation.

Post-Transplant Covid-19 Serum Study

To evaluate whether hospitalized transplant recipients show poorer transplant and patient survival, poorer organ function, and a higher incidence of rejection reactions and infections at 1, 2, 3, and 5 years after hospitalization compared to the control group, Cox regression analyses are performed and Kaplan-Meier curves are calculated (using available Collaborative Transplant Study data). To evaluate whether hospitalized transplant recipients with SARS-CoV-2 infection are more likely to form dnDSA, a comparative analysis to matched control patients will be performed at the time of "follow-up" (60–90 days after the start of hospitalization or 1 year after hospitalization) (univariate with Fisher's Exact Test and multivariable with logistic regression). Comparative analyses will also be performed to determine whether dnDSA formation after 60–90 days after hospitalization or 1 year after hospitalization has an influence on mortality, organ function, and rejection. Whether a certain blood group or HLA phenotype is present in patients with Covid-19 after transplantation can be determined by descriptive statistics. The change in antibody subgroups can be calculated by descriptive statistics.

22. Signature page

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Date/Version of the study plan: 15.12.2020 – Version 1.2

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APPENDIX

(see also https://www.ctstransplant.org/downloads/centerarea/Liver.pdf)

CTS COVID-19 SERUM STUDY

PRE-TX SARS-CoV-2-SPECIFIC QUESTIONNAIRE

RECIPIENT (Last Name, First Name or Center ID) _____

TRANSPLANT DATE _____ (Day/Month/Year)

DATE OF SARS-CoV-2 SYMPTOM ONSET _____ (Day/Month/Year)

SARS-CoV-2-ASSOCIATED MORBIDITIES AT TIME OF TRANSPLANT

Cerebrovascular	☐Yes ☐No
Cardiovascular	☐Yes ☐No
Lung disease	☐Yes ☐No
Kidney failure	☐Yes ☐No
Thromboembolic complications	☐Yes ☐No
Dermatologic	☐Yes ☐No
Psychiatric	☐Yes ☐No

Other morbidities _____
Specify

COURSE OF SARS-CoV-2 INFECTION

Hospitalization	☐Yes ☐No
ICU or high dependency unit admission	☐Yes ☐No
Invasive ventilation (any)	☐Yes ☐No
Extracorporeal (ECMO) support	☐Yes ☐No

_____ Transplant Center

_____ Date

_____ Completed by

Please return to: Prof. Caner Süsal
Transplantation Immunology
Heidelberg University Hospital
Im Neuenheimer Feld 305
69120 Heidelberg - GERMANY

or fax to: +49 6221 564200

CTS COVID-19 SERUM STUDY

POST-TX SARS-CoV-2-SPECIFIC QUESTIONNAIRE

RECIPIENT (Last Name, First Name or Center ID) _____

TRANSPLANT DATE _____ (Day/Month/Year)

DATE OF SARS-CoV-2 SYMPTOM ONSET _____ (Day/Month/Year)

SUPPORTIVE CARE

ICU	☐Yes ☐No	Days of stay in ICU _____
Oxygen therapy	☐Yes ☐No	
Non-invasive ventilation	☐Yes ☐No	
Invasive ventilation	☐Yes ☐No	Days on ventilation _____
Extracorporeal (ECMO) support	☐Yes ☐No	
Inotropes/vasopressors	☐Yes ☐No	
Acute kidney injury	☐Yes ☐No	
Dialysis	☐Yes ☐No	
Acute liver failure	☐Yes ☐No	

MEDICATION

SARS-CoV-2 specific medication ☐Yes ☐No

If yes, specify: _____

Change in transplant-related medication ☐Yes ☐No

If yes, specify: _____

LABORATORY FINDINGS

Day of hospitalization

Serum creatinine	_____ mg/dl or _____ µmol/L
Proteinuria	☐Yes ☐No If yes: _____ g/g crea or _____ g/mol crea
If liver-TX:	☐good functioning graft ☐impaired graft function but no failure

60–90 days after hospitalization

Serum creatinine	_____ mg/dl or _____ µmol/L
Proteinuria	☐Yes ☐No If yes: _____ g/g crea or _____ g/mol crea
If liver-TX:	☐good functioning graft ☐impaired graft function but no failure

_____ Transplant Center

_____ Date

_____ Completed by

Please return to: Prof. Caner Süsal
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