Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Awareness and Impact of Non-pharmaceutical Interventions During Coronavirus Disease 2019 Pandemic in Renal Transplant Recipients

Andrea Monaco, Tommaso Maria Manzia, Roberta Angelico, Giuseppe Iaria, Carlo Gazia, Yousef Al Alawi, Konstantinos Fourtounas, Giuseppe Tisone, and Roberto Cacciola

Department of Surgery Science, Transplant and HPB Unit, University of Rome Tor Vergata, Rome, Italy; and King Salman Armed Forces Hospital, Tabuk, Kingdom of Saudi Arabia

ABSTRACT

The concerns generated by coronavirus disease 2019 (COVID-19) pandemic are having profound impact on solid organ transplantation (SOT). Non-pharmaceutical interventions (NPI) are currently the only measures available to contain COVID-19 in the general population and in more vulnerable recipients of any organ transplant.

In this cross-sectional case control study from a patient survey undertaken in 2 transplant centers (TxC) in the Kingdom of Saudi Arabia and Italy, we aimed to appraise awareness of the NPI implemented by respective these governments. We have also evaluated the impact of COVID-19 on our kidney transplant (KT) recipients and a control group of kidney living donors (KLD).

In our series, there were zero cases of COVID-19 among 111 KT recipients and 70 KLD of the control group. Demography, transplant type, immunosuppression regimes, and, importantly, the different COVID-19 prevalence in the 2 regions of the TxC did not appear to influence incidence of COVID-19 in our KT recipients.

The absence of COVID-19 cases in our series was unexpected. Our findings suggest that awareness of NPI is associated with a successful containment of COVID-19 in vulnerable, immunosuppressed KT recipients.

The coronavirus disease 2019 (COVID-19) pandemic is currently affecting solid organ transplantation (SOT) worldwide [1]. A sudden decrease of SOT activity has been reported since the World Health Organization (WHO) announced a global emergency on January 30, 2020; subsequently, COVID-19 was declared a pandemic on March 11, 2020 [2].

The pandemic is not sparing any country; however, the observation that some countries are affected less than others is a matter of constant comparison and analysis. Interestingly, large regions, that are part of countries afflicted by relevant incidence of COVID-19, have a limited number of infected cases.

Italy and the Kingdom of Saudi Arabia (KSA) are witnessing different incidence of COVID-19 with substantially different rates of mortality and hospitalization. Furthermore, the 2 transplant centers (TxC) involved in this study, linked by an ongoing collaboration, are located in regions with remarkably different incidence of COVID-19 compared to their respective national averages.

The growing concerns of severe acute respiratory syndrome caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) transmission led to the suspension or restriction of SOT to immediately life-saving procedures [1,3]. Kidney transplantation (KT) is particularly affected by the current health care crisis because it is rarely an immediately life-saving procedure; therefore, numerous kidney TxC have completely suspended their activities of both living donor kidney transplant (LDKT) and deceased donor kidney transplant (DDKT) [1].

Andrea Monaco and Tommaso Maria Manzia contributed equally to this work.

*Address correspondence to Roberta Angelico, MD, PhD, FEBS, Department of Surgery Science, Transplant and HPB Unit, University of Rome Tor Vergata, Viale Oxford 33, 00133, Rome, Italy. Tel: 0620908294; Fax: 0620908294. E-mail: roberta.angelico@gmail.com

© 2020 Elsevier Inc. All rights reserved.
230 Park Avenue, New York, NY 10169

Transplantation Proceedings, 52, 2607–2613 (2020) 2607
The legitimate concerns are accrued by the absence of specific antiviral treatment and vaccination against COVID-19. In this context, non-pharmaceutical interventions (NPI) represent the main measures that can be applied to protect the wider population [4,5] and in particular to shield the more vulnerable, immunosuppressed recipients of any organ transplant.

In our observational study, we appraised the level of awareness of NPI, implemented by respective governments in the KSA and Italy, of the KT recipients in both institutions.

Subsequently, we evaluated the impact of COVID-19 on our KT recipients. The analysis also included a control group of patients who were not immunosuppressed; for this purpose, we extended the same evaluation on the kidney living donors (KLD) of both institutions.

Finally, our study aimed to assess whether the KT recipients hosted different outcomes in substantially different geographic areas with different incidence of COVID-19.

MATERIAL AND METHODS

NPI in the KSA and Italy

Since the COVID-19 was declared a pandemic, the governments of the KSA and Italy promulgated emergency legislation aiming to guarantee the containment of the COVID-19 spread by the implementation of the NPI. Both countries adopted similar policies on the use of NPI, which are summarized in Table 1.

Study Population

We evaluated all KT recipients attending the post-transplant follow-up clinics at the TxC of King Salman Armed Forces Hospital in Tabuk, KSA, and Tor Vergata University Hospital in Rome, Italy. We did not apply any clinical selection criteria.

In order to create a control group of nonimmunosuppressed patients, we also evaluated the KLD of our patients who received an LDKT.

Survey Design

We designed a survey based on the available evidence on COVID-19 and its impact on SOT, focusing more specifically on KT recipients. We reviewed the NPI aimed to contain COVID-19 implemented in the recent legislation of the KSA and Italy (Table 1).

The questionnaire aimed to appraise awareness of NPI, as well as to cover clinically relevant events related to COVID-19 over a period of 13 weeks, extending from February 1, 2020, to May 3, 2020. These dates embrace the time period extending from the day after the WHO declared COVID-19 a global health emergency to the relaxation of strict restrictions enabled by the governments of the KSA and Italy.

The survey was structured following discussion with the lead clinicians of both institutions in the KSA and Italy. The final version of the survey was approved by the lead clinicians and wider transplant team members involved in the study, including a nurse specialist, nephrologist, and transplant surgeons.

Survey Organization

The survey started on May 4, 2020, and was completed on May 18, 2020; it was carried out by telephone or in person during attendance at follow-up clinics. Our specialist nurses and junior staff with consultant supervision have carried out the survey in both institutions.

The information regarding the type and date of transplant, induction, and maintenance immunosuppression were obtained from our out-patient clinic database and cross referenced with our patients during the survey.

Survey Structure

The survey was articulated in 2 main areas of questions aimed to achieve a cross-sectional analysis of NPI awareness and clinical status of KT recipients, members of their household, and KLD in relation to the COVID-19 pandemic.

In the first area of the survey, we focused on the appraisal of KT recipients and KLD on their awareness of the NPI aimed to prevent COVID-19. All patients underwent 2 screening questions to evaluate their knowledge of the current pandemic and vulnerability as recipients of SOT. Subsequently, we inquired about their awareness of the NPI.

The second area of the survey aimed to identify any clinically relevant events related to COVID-19 in KT recipients, members of their households, and KLD. Those events included the observation of any symptoms suggesting COVID-19, including any combination of fever, dyspnea, headache, and anosmia [6]. We inquired about any admission to hospital with pneumonia and whether the patient was tested for COVID-19. All the answers to the questions were also cross-referenced with our electronic hospital record systems.

National and Regional Difference of COVID-19 Incidence

The official data of the Ministry of Health in the KSA [7] and Italy [8] were extracted from the open-access database in order to calculate regional incidence of COVID-19 cases.

The same official ministerial data in conjunction with official census data were used in order to calculate the regional prevalence of COVID-19.
Data Evaluation and Statistical Analysis

In the first qualitative area of the survey, awareness of NPI was considered an independent single outcome and was analyzed as unique event. After the completion of the survey, we scored the awareness of KT recipients and KLD for each group of NPI with a mark of 1 or zero according to their answers. The scoring system is summarized in Table 2.

The total score obtained from the answers to each group of NPI was categorized as poor (0 to 2), acceptable (3), good (4), and excellent (5).

In the second quantitative area of the survey, the KT recipients’ characteristics were first analyzed separately by type of transplant, either LDKT or DDKT. Subsequently, we merged LDKT and DDKT into a single group of KT recipients and compared their clinical outcomes with the control group of KLD. Where appropriate, Fisher exact and \( \chi^2 \) test was performed using IBM SPSS 26.0 software (IBM, Inc, Chicago, Ill, United States) for Windows. We reported a significance level using \( P < .05 \). The regional differences of reported COVID-19 cases and related mortality were also analyzed with a G test.

### RESULTS

#### Study Population

One hundred and eleven KT recipients participated to the survey (LDKT = 58/111 [52.2%] and DDKT= 53/111 [47.8%]). Characteristics of the study population are reported in Table 3. The median follow-up from transplantation was 14 (interquartile range [IQR] 9-33) months for the patients in the LDKT group and 8 months (IQR 5-11) for the DDKT group. The median ages of LDKT and DDKT recipients were 35.5 years (IQR 28-51) and 56 years (IQR 47-63), respectively (\( P < .001 \)).

The induction immunosuppression with thymoglobulin was significantly different in the LDKT group (\( P < .001 \)), as was the avoidance of induction immunosuppression in DDKT group (\( P < .001 \)). There were no differences in the maintenance immunosuppression regimes (Table 3).

All patients in both LDKT and DDKT groups were fully adherent to their medications and follow-up clinic attendance.

The control group consisted of 70 KLD; the majority were men 51/70 (72.8%) with a median age of 33 (IQR 27-41.65) years. The median follow-up after the donor nephrectomy was 23 (IQR = 9-32) months.

#### Survey Analysis: NPI Awareness

Our survey has shown that, in the study period, 111/111 (100%) of our KT recipients (LDKT and DDKT) were...
COVID-19 free, with zero cases of SARS-CoV-2 infection reported and zero hospital admissions.

Symptoms that could have raised concerns of possible COVID-19 infection were observed in 11 (10%) KT recipients, of whom only 1 patient reported all symptoms of fever, cough, headache, and anosmia. The patient had a negative test for COVID-19 and developed a spontaneous regression of symptoms after 24 hours, without requiring hospital admission.

In the study period, 5 (4.5%) KT recipients were admitted to the hospital with pneumonia and tested negative for COVID-19.

Similarly, the control group of KLD has also shown that 70 (100%) were COVID-19 free, with zero cases reported and zero hospital admissions.

Among the members of the households of the survey participants, there were no reported cases of COVID-19. Out of these, there was 1 person admitted to the hospital with pneumonia who tested negative for COVID-19 and 1 person who reported symptoms of cough and fever not requiring hospitalization who was not tested.

National and Regional Difference of COVID-19 Incidence

The COVID-19 pandemic had very different impact in the 2 regions of the 2 TxCs (Table 5).

In the northwest region, the COVID-19 cases represented 1.15% of the total cases reported in the KSA [6], whereas, in the Lazio region, the COVID-19 cases represented 3.23% of the total cases reported in Italy [7].

The calculated COVID-19 prevalence was 0.013% in the northwest region of the KSA and 0.11% in the Lazio region. Notably, the number of cases and mortality in the 2 regions was statistically significant ($P = .001$).

**DISCUSSION**

Our survey was prompted by the concerns generated by a growing number of case reports and database analysis [9], indicating an increasing morbidity and mortality of KT recipients from COVID-19. Notably, preliminary report from countries heavily affected by the pandemic have indicated a mortality rate ranging between 21% and 23% among KT recipients with COVID-19 [8].

There is a need to monitor for potential cases of COVID-19 in KT recipients, as they may represent a high-risk group. The implementation of NPI in hospitals is crucial to prevent the spread of COVID-19 and protect KT recipients from potential complications. However, future studies are needed to assess the long-term outcomes of KT recipients infected with COVID-19 and the impact of NPI on their health outcomes.
The correct divulgence of the risks related to COVID-19, together with the implementation of clear NPI aiming to contain COVID-19, have undoubtedly contributed to the development of a collective responsibility in both countries. Such event reinforces the concept that patient awareness and associated adherence to medical advice represents a useful metric of future clinical outcomes, including attention to public health matters [11]. Similarly, it has been demonstrated that high levels of awareness are linked with a diligent adherence to medication and protocols [12].

The recipients of any organ transplant currently represent one of the most vulnerable categories of our society. Therefore, ensuring that our KT recipients with the members of their households have a sufficient awareness may represent an effective measure to enhance their safety during the COVID-19 pandemic.

In the period of our study, the NPI were also enforced by new legislation, urgently brought forward by the respective governments. It certainly explains the excellent awareness we have observed in the appraisal of our patients.

In our opinion, it is also possible that our patients’ excellent awareness and reported adherence to NPI might have also been affected by the geographic and temporal distance from the national and global epicenters of COVID-19.

In our study, there is the possibility of a nonintentional bias, represented by the fact that our cohort of patients may be a self-selected group of highly compliant individuals. In point of fact, our KT recipients are conscious of the risks linked to the immunosuppression regimes they follow.

Though the methodology of direct questioning is demonstrated to be a valuable tool to assess adherence, in the future, it may be necessary to apply more sophisticated methods to evaluate the adherence to NPI, particularly if there are new clusters of COVID-19 among KT recipients.

Importantly, the currently recommended NPI may be tailored differently in regions and countries with variable prevalence of COVID-19 once advanced contact tracing technology is available [4]. It is relevant to note that the beneficial effect of NPI on the general population in China [13], Hong Kong [10], and the UK [5] were recently demonstrated with mathematical modeling; but to date, there are no large studies evaluating the effects of NPI on KT recipients. Importantly, it may never be possible to perform a comprehensive prospective evaluation of NPI in KT recipients.

We acknowledge the scientific limitations, dictated by the character of a cross-sectional evaluation, in a relatively small cohort of patients in 2 different countries. However, the association of excellent awareness of the NPI, with
absence of COVID-19 cases in our group of patients, remains a relevant finding.

It was not in the original aim of the study to perform a strict comparison between 2 cohorts of patients in different countries; our study suggests that an excellent level of awareness of the NPI may be associated with the same beneficial effect on KT recipients, even if residing in countries and regions with significantly different impacts of COVID-19.

It is worth considering the possible different virulence and pathogenicity of COVID-19 in the KSA and Italy. However, the hypothesis of a progressive weakening of COVID-19 is currently strongly debated, and it remains to be fully demonstrated [14].

In our series, the absence of COVID-19 cases was not influenced by the demography of our patients or by the type of transplant (LDKT or DDKT) received. Furthermore, the induction and maintenance immunosuppressive regimes did not appear to affect, at present, the incidence of COVID-19 in our cohort of patients.

Although our survey did not reveal any differences between recipients of an LDKT with those who received a DDKT, we cannot state with confidence that all KT recipients may have the same risk of COVID-19 infection. However, we do believe that LDKT may be implicitly safer than DDKT, having the benefits of being a planned procedure that allows close screening of both donors and recipients. The close screening and clinical observation preceding LDKT may also contribute in reducing the risk of a false-negative test, thereby offering further added safety to our practice.

Our survey included 15 (13.5%) KT recipients who received their transplant after February 1, 2020. Significantly, there were 12 DDKT performed at Tor Vergata University Hospital during the highest peak of the pandemic in Italy. The observation that this subgroup of KT recipients has not hosted any COVID-19 cases may, very cautiously, be considered an indicator of effectiveness of NPI in newly immunosuppressed KT recipients. Furthermore, the availability of adequate infrastructures—allowing dedicated patients a pathway, as developed in our hospitals—may offer further protection to our patients.

The overall risk of infection from COVID-19 in KT recipients cannot be realistically calculated at present; therefore, this lack of evidence is preventing us from offering our patients a scientifically valid measure of the risk. More importantly, we are not yet in a position to compare the actual risk of COVID-19 infection with other forms of renal replacement therapy.

For this purpose, we have given our survey the status of prospective audit with the plan to repeat it at a 3-month interval. Also, we have the ambition to extend the close monitoring of patients with a KT of other neighboring units, including patients receiving other modalities of renal replacement therapy. We do believe that having a close regional monitoring of COVID-19 may add further strength to the national and international observations that are currently guiding our practice [15].

The transplantation regulatory bodies worldwide have the immensely difficult task of advising and ensuring safe SOT practice. It may be possible to enhance the safety of organ donation, procurement, and transplantation by applying contact tracing technology to SOT. Enabling the recognition of potential viral contact may remarkably enhance future safety measures.

Considering the uncertainty dictated by the risks of a second wave of the pandemic, it may be taken under careful consideration, as well as seen as a realistic option, the possibility of channeling SOT in those regions and TxC with lower incidence of COVID-19. In particular, conveying LDKT to safer “hubs” may be amenable; it may have the added benefit of preserving the viability of the kidney paired donation schemes already in place. Necessarily, future collaborations between TxC will require the creation of new transplant consortia and alliances able to operate at regional, transregional, national, and even international levels.

The challenges posed by COVID-19 are bound to influence SOT activity worldwide for the foreseeable future and until effective remedies become available. The international transplant community is facing a remarkable and unexpected dilemma: weighing risk avoidance and cautious risk management. Undoubtedly, we will need the prompt implementation of innovative, comprehensive, and adequate strategies aimed at mitigating the secondary mortality caused by the reduction of SOT inflicted by the current health care crisis.

ACKNOWLEDGMENTS

We thank our colleagues Mr Majed Lafeid, Ms Maha Suliman Almushouri, Ms Bedoor Salem Alatawi, and Ms Amani Basher Albalawi, who provided insight and expertise that greatly assisted the research, and for the assistance with database work and patient contact.

REFERENCES

[1] Boyarsky BJ, Chiang TP-Y, Werbel WA, Durand CM, Avery RK, Getsin SN, et al. Early impact of COVID-19 on transplant center practices and policies in the United States. Am J Transplant 2020;20:1809–18.

[2] World Health Organization. WHO director-general’s opening remarks at the media briefing on COVID-19 - 11 March 2020. https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19—11-march-2020; 2020 [accessed 12.03.20].

[3] Angelico R, Trapani S, Manzia TM, Lombardini L, Tisone G, Cardillo M. The COVID-19 outbreak in Italy: initial implications for organ transplantation programs. Am J Transplant 2020;20:1780–4.

[4] Ferguson NM, Laydon D, Nedjati-Gilani G, et al. Impact of non-pharmaceutical interventions (NPIs) to reduce COVID-19 mortality and healthcare demand. Imperial College London. https://doi.org/10.25561/77482, accessed March 3, 2020.

[5] Davies NG, Phil D, Kucharski AJ, Eggo RM, Gimma A, Edmunds WJ. Effects of non-pharmaceutical interventions on COVID-19 cases, deaths, and demand for hospital services in the UK: a modelling study. Lancet 2020;5:375–85. https://doi.org/10.1016/S2667-2667(20)30133-X.

[6] Ministry of Health, Government of the Kingdom of Saudi Arabia. Novel coronavirus (COVID-19). https://www.moh.gov.sa/
[7] Ministero della Salute, Governo Italiano. Covid-19, situation report update at 3 May 2020, http://www.salute.gov.it/portale/news/p3_2_1_1_1.jsp?lingua=italiano&menu=notizie&p=dalministero&id=4667; 2020 [accessed 06.03.20].

[8] ERA/EDTA Registry, COVID-19: information on registry initiatives. https://era-edta-reg.org/index.jsp?p=COVID-19 [accessed 04.08.20].

[9] Kim Y, Kwon O, Pack JH, Park WY, Jin K, Hyun M, et al. Two distinct cases with COVID-19 in kidney transplant recipients. Am J Transplant 2020;26. https://doi.org/10.1111/ajt.15947, accessed March 8, 2020.

[10] Cowling BJ, Ali ST, Ng TWY, Tsang TK, Li JCM, Fong MW, et al. Impact assessment of non-pharmaceutical interventions against coronavirus disease 2019 and influenza in Hong Kong: an observational study. Lancet Public Health 2020;5:e279–88. https://doi.org/10.1016/S2468-2667(20)30090-6.

[11] Gharoro EP, Ikeanyi EN. An appraisal of the level of awareness and utilization of the pap smear as a cervical cancer screening test among female health workers in a tertiary health institution. Int J Gynecol Cancer 2006;16:1063–8.

[12] Gokoel SRM, Gombert-Handoko KB, Zwart TC, van der Boog PJM, Moes DJAR, de Fijter JW. Medication non-adherence after kidney transplantation: a critical appraisal and systematic review. Transplant Rev (Orlando) 2020;34:100511.

[13] Lai S, Ruktanonchai NW, Zhou L, Prosper O, Luo W, Floyd JW, et al. Effect of non-pharmaceutical interventions to contain COVID-19 in China. Nature 2020.

[14] Cyranoski D. Profile of a killer: the complex biology powering the coronavirus pandemic. Nature 2020;581:22–6.

[15] The Transplantation Society. Guidance on coronavirus disease 2019 (COVID-19) for transplant clinicians. https://tts.org/tid-about/tid-presidents-message/23-tid/tid-news/657-tid-update-and-guidance-on-2019-novel-coronavirus-2019-ncov-for-transplant-id-clinicians; 2020 [accessed 14.03.20].