

Title

COVID-19 pandemic deteriorates aftercare attendance in heart transplant recipients independently of perceived impact on social life

Short Title

COVID-19 deteriorates aftercare in HTx

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Abbreviations and Acronyms

- HTx = *Heart Transplantation*
- vs. = *versus*
- SARS-CoV-2 = *severe acute respiratory syndrome coronavirus type 2*
- COVID-19 = *coronavirus disease 2019*
- MMF = *Mycophenolate mofetil*
- ISHLT = *International Society of Heart and Lung Transplantation*
- pAMR = *pathological Antibody Mediated Rejection*

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- *CKD = Staging definition of Chronic Kidney Disease according to KDIGO*

Author contributions statement

- Designed research/study: Udo Boeken
- Performed research/study: Daniel Oehler, Udo Boeken
- Responsibility for treatment decisions and data collection: Daniel Oehler, Raphael Romano Bruno, Ralf Westenfeld, Udo Boeken
- Analyzed data: Daniel Oehler, Udo Boeken
- Wrote paper: Daniel Oehler
- Critical revision of the manuscript: Daniel Oehler, Raphael Romano Bruno, Ralf Westenfeld, Udo Boeken
- Supervision: Udo Boeken, Ralf Westenfeld, Malte Kelm, Artur Lichtenberg

Proposed Tweet:

COVID 19 pandemic associates with non-attendance behavior in HTx and is independent of the general perceived impact on daily life. Reduced attendance is mainly driven by previously attendant patients. [Visual Abstract]

Abstract

Background: Heart transplant (HTx) recipients are at increased risk of developing infections or malignancies due to immunosuppressive medication. Thus, regular aftercare in those patients is of utmost importance. The extent of collateral damage due to the COVID-19 pandemic (delayed or canceled clinical visits and diagnostics) on high-risk patients is yet unknown. We believe that, especially for HTx-patients, data acquisition on potential pandemic-related non-attendance is crucial to improve clinical care in the future. Therefore,

we aim to decipher possible COVID-19-related alterations in attendance to clinical care post-HTx using a survey-based approach.

Methods: HTx recipients two years beyond transplantation were selected (n=75). We filed a paper-based questionnaire or an online survey containing nine items about COVID-19 related exceptional circumstances. Fifty-two patients (69%) returned fully answered questionnaires.

Results: A perceived impact on daily life was evident with 79% of all patients reporting moderate to severe negative influence of COVID-19 pandemic on daily routine. We detected increased non-attendance of clinical care during the COVID-19 pandemic compared to pre-pandemic time (38% vs. 6%, $p<0.0001$). The various diagnostic modalities of aftercare were heterogeneously affected, ranging from 2% non-attendance for influenza vaccination and 18% for colonoscopy. Off note, non-attendance to clinical care within the pandemic was independent of perceived impact of the pandemic on daily life ($p>0.68$).

Conclusions: For the first time, we objectively demonstrate significant decrease in attendance to clinical care in HTx recipients during COVID-19 pandemic. Efforts are needed to increase attendance in this highly vulnerable patient cohort.

Keywords: COVID-19, Clinical Care, Heart Transplantation

Introduction

Since the beginning of 2020, the COVID-19 pandemic has influenced nearly every aspect of social life, including mental health^{1,2} and medical care^{3,4}. Recently, it was reported that patients on the waiting list for heart transplantation in Spain suffered from increased mortality in 2020 due to pandemic restrictions⁵. Following transplantation, HTx-recipients remain at

increased risk of allograft rejection⁶, infectious diseases⁷, and are prone to malignancies due to immunosuppression^{8,9}. Steady aftercare is crucial to prevent or treat those complications early. In our centre we experienced HTx-recipients skipping routine follow-up visits due to concerns about potential transmission of SARS-CoV-2 during outpatient visits, with one patient dying from an acute cardiocirculatory failure, presumably due to acute rejection.

Infection control policies in Germany were differing throughout the pandemic. For the current study, 2020 and the beginning of 2021 are from importance here. In March 2020, first governmental advisory was given to cancel bigger events, resulting finally in a “lockdown” including contact restrictions and quarantine regulations for returnees from other countries. While due to the dynamic changes in infection incidence in May 2020 restrictions were slightly lifted, in October and December 2020 regulations were increasing again with even stricter contact restrictions (so called “hard lockdown”) and thereafter, within the time horizon of this study, remained unchanged. Restrictions never excluded patients from medical care *per se*, however it cannot be excluded that arranging of medical appointments were hindered through those regulations indirectly.

The overall extent of this collateral damage due to the COVID-19 pandemic (delayed or canceled clinical visits and diagnostics) on high-risk patients is yet unknown. We believe that, especially for HTx-patients, data acquisition on potential pandemic-related non-attendance is crucial to improve clinical care in the future. Therefore, we aim to decipher possible COVID-19-related alterations in attendance to clinical care post-HTx using a survey-based approach.

Patients and methods

Study population

We selected all HTx recipients two years beyond transplantation (n=75) to include only those patients which had both pre- and within pandemic experiences in aftercare to be reported. The study conformed to the principles of the Declaration of Helsinki and Good Clinical Practices. All subjects participated voluntarily. The study was approved by our local ethics committee.

Data collection

Letters with the explanatory note were sent to all patients, including the option to either fill in an attached paper-based questionnaire or use the online survey. Recruitment started 22nd of March 2021 by sending invitation letters by mail, and data acquisition terminated on the 22nd of May 2021. Fifty-two patients (69%) returned fully answered questionnaires, while 23 (31%) did not.

Access to the Online Survey tool ('Qualtrics'; Qualtrics, Munich, Germany) was granted by individual link as well as QR-Code to use mobile devices. The short link led to individual access to the survey. People were informed about pseudonym-based data acquisition. Data acquisition was performed according to European and German Data protection regulations. Apart from German, patients could ask for translated questionnaires in English, Arabic, Russian, and Turkish. Data was stored with a pseudonym on the server and downloaded for offline statistical analysis.

The questionnaire contained nine items concerning COVID-19 related exceptional circumstances (see supplements), including:

- Items concerning the perceived impact on daily life in general

- Items on pandemic-related exceptional circumstances, e.g. items on subjective or organizational/ logistical limitations/restrictions due to the COVID-19 pandemic
- Items regarding the direct involvement of COVID-19, e.g. infection with SARS-CoV-2 or quarantine

Additional clinical data

Clinical data were obtained from the patients' records, including age, sex, time after transplantation, comorbidities such as hypertension, diabetes and kidney failure, and transplant-specific complications as history of rejection, clinically relevant infections, or cancer with diagnosis after heart transplantation. Additionally, the latest immunosuppressive medication was recorded.

Statistical analysis and figure making

Qualitative variables were compared by the Pearson Chi-square test or, when its application conditions were not met, by Fisher's exact test. The tests were performed bilaterally, and the threshold of significance was set at .05. Statistical analysis was performed using GraphPad Prism and IBM SPSS Statistics software (SPSS). Figures were made using GraphPad Prism, Microsoft PowerPoint, and Power-user add-in for Microsoft Excel.

Results

Baseline Clinical Characteristics

From all patients eligible (n=75, see methods), fifty-two patients (69%) returned fully answered questionnaires and could therefore be included (baseline characteristics in table 1), while twenty-three patients (31%) were excluded (characteristics in table S01). The majority of all included patients were male (79%, n=41), the mean age was 57.5 years. At the time of data collection, patients were on average 58 months after transplantation and

maintained mostly on a triple immunosuppressive regimen including tacrolimus, corticosteroids and either everolimus (54%, n= 28) or mycophenolate mofetil (MMF, 37%, n= 19). Most patients suffered from comorbidities such as diabetes (49%, n=25), hypertension (64%, n=33) and chronic kidney failure with at least CKD III (72%, n=37). Concerning allograft rejection, history of cellular rejection with ISHLT-Grade > 1R was present in 27% (n=14), while history of humoral rejection (pAMR 1) occurred in 23.1% (n=40). Medical records of history of clinically relevant rejection with the need for additional therapy was documented in 31% (n=16) of all cases. Clinically relevant infections after transplantation were present in 54% (n=28) and cancer with first diagnosis after heart transplantation was seen in 12% (n=6). A minority reported either about history of infection with SARS-CoV-2 (8%, n=4) or being quarantined due to contact with SARS-CoV-2-positive individuals (and 4%, n=2).

General concerns on COVID-19

Investigating the perceived impact of COVID-19 on daily life, only a minority (21%) reported no or low negative influence on daily routine (Figure 1, A). Accordingly, the majority reported moderate (44%) and severe or very severe (35%) subjective limitations.

Impact on clinical care

Of all patients, 39% (n=20) reported non-attendance to aftercare because of logistical restrictions or concerns about possible infection with SARS-CoV-2 during pandemic (Figure 1, B, right bar). The diagnostic modalities were heterogeneously affected (Figure 2): The lowest value for non-attendance were detected for vaccination against Influenza virus (2%). Abdominal sonography and chest X-ray were not performed in around 9%, and non-attendance to dental examination was in the same range as endomyocardial biopsy, transplant outpatient clinic visits, or monitoring of immunosuppressive drugs (each

approximately 12%). The highest values for refusal of necessary diagnostics were observed for urological or gynecological examinations, skin cancer screening and colonoscopy (13 to 18%).

Of those showing non-attendance during pandemic (n=20), 20% reported about no or mild and each 40% about moderate and severe perceived impact on their daily lives due to COVID-19 (Figure 3, yellow bar). Those reporting regular clinical care (Figure 3, green bar) were affected similarly in their everyday life (no/mild 22%; moderate 46%, severe 32%). Accordingly, non-attendance to clinical care within the pandemic was independent of the degree of perceived impact on daily life ($p>0.68$).

Non-attendance significantly increased during the COVID-19 pandemic compared to reported pre-pandemic behavior (Figure 1, B, left bar; 38 % vs. 6%, $p<0.0001$). On the other hand, 94% (n=49) reported attendance to clinical care pre-pandemic, changing during pandemic with 37% showing non-attendance then. This transition within the pandemic leads to 95% (n=19) of the non-attending patient cohort within pandemic coming from previously attendant patients (Figure 4).

Discussion

This study aimed to enlighten potential COVID-19-associated changes in attendance to clinical aftercare post HTx using a survey-based approach.

We report two major findings:

1. Non-attendance behavior within our heart transplant cohort during the COVID-19 pandemic is independent of the general perceived impact of the pandemic on daily life.

2. Non-attendance to clinical care in our heart transplant recipients is significantly higher during COVID-19 pandemic and reduced attendance is mainly driven by previously attendant patients.

General influence of COVID-19 pandemic restrictions on heart transplant recipients

Although it could be shown that hospitalizations due to heart failure and acute myocardial infarction declined during the pandemic with parallel increase of severe symptoms and worse outcome^{10,11}, impact of COVID-19 on HTx recipients in general is unknown.

For HTx recipients, especially the link between general effects of the COVID-19 pandemic on their everyday life and the specific disease management has not been reported before. In the current study, we could see a perceived strong negative influence on daily routine, including worries about infection due to the COVID-19 pandemic. This is in the same range as the reported numbers from Cousino et al. in patients with congenital heart disease¹² (75% vs. 79%). Interestingly, even our cohort feels a strong influence on their daily life, non-attendance during the pandemic was independent of that. Therefore, it can be hypothesized that, as HTx recipients are educated to be compliant whatever the circumstances are, general feelings concerning pandemic dynamics are less important than concrete restrictions.

Specific impact of COVID-19 on clinical aftercare attendance

We demonstrated non-attendance to aftercare in HTx recipients reaches 38% during the COVID-19 pandemic. In line with our observations, Cousino et al.¹² displayed in 38% of all patients with congenital heart disease delay of pre-pandemic scheduled cardiac surgery and 46% postponed cardiac clinic visits. Compared to non-cardiac patients, our cohort seems to be more compliant, as Vogel et al. could show that in a cohort of multiple sclerosis

patients¹³, 64% cancelled a medical visit, 22% a neurologist visit, and 11% an MRI. Interestingly, in our cohort, non-attendance to diagnostics during COVID-19 revealed a more heterogeneous pattern, in that not all diagnostics modalities were influenced to the same extent. Potential reasons could be that some diagnostic procedures were more challenging to undertake due to COVID-19 restrictions or that patients canceled those visits they thought were less needed, especially in those periods where strict regulations (“lockdown”) were in place (for Germany, as mentioned above, this was in the scope of this study mainly true for beginning and end of 2020 as well as beginning of 2021).

Pandemic-related increase of non-attendance

Although prospective, well-powered studies on attendance in HTx, in general, are missing and demanded¹⁴, Helmy et al., as part of the pre-pandemic BRIGHT cohort study¹⁵, could show that medication non-attendance of immunosuppressants was 17%. To our knowledge, none of the current studies compared pre- and pandemic non-attendance directly, and non-attendance was only investigated through medication intake. In the current study, we illustrate a significant pandemic-related increase of non-attendance to aftercare (from 6 to 38%), underlining the impact of COVID-19 on clinical care in this vulnerable cohort additionally. Additionally, we could show that pre-pandemic behavior did not predict pandemic non-attendance and that worsened attendance is mainly driven by previously attendant patients.

Strengths and limitations

The present study has some strengths and limitations. First, the reporting rate is 69%, which is above average compared to other patient-related COVID-19 surveys, where reporting rates usually range below 50%^{16,17}. Secondly, we selected only HTx recipients with transplantation dates above two years, as this was necessary to compare COVID-19 related

effects due to the specific time point of this study. However, this could lead to a selection bias we cannot entirely exclude. Third, the sample size is small, but even with low numbers of patients in the current study, we could see significant statistical and clinically meaningful effects concerning attendance behavior. Fourth, a potential selection bias due to inclusion of only patients handing in the fully answered questionnaire and thereby hypothetically more compliant by doing so cannot be excluded. However, as the baseline characteristics of those patients not answering our questionnaire are comparable (see also figure S01) and our study shows statistically different effects within the given study cohort, it is likely that a possible selection bias would even strengthen the effects we could observe rather than weaken it. Last, there is a potential bias due to the time corridor we accepted answers, as pandemic restrictions are highly dynamic. However, as our findings are comparable to other patient-related studies, this bias seems to be neglectable.

Conclusion

We report here for the first time reduced attendance to clinical care in HTx recipients during COVID-19 pandemic. This effect was independent of perceived threat from COVID-19 and was mainly driven by non-attendance in previously adherent HTx recipients. Efforts are needed to improve attendance in this highly vulnerable patient cohort.

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Conflict of Interest and funding Statement:

The authors have no conflicts of interest to declare.

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Table 1: Baseline characteristics of study cohort.

Baseline Characteristics		Total n=52	
Sex	Men (n, %)	41	78.8
Age (mean, SD)		57.5	± 12.2
Time after transplantation, mo (mean, SD)		57.7	± 29.7
Diabetes mellitus (n, %)		25	48.1
Hypertension (n, %)		33	63.5
Kidney Failure (n, %) ^a	CKD I	4	7.7
	CKD II	11	21.2
	CKD III	26	50.0
	CKD IV	7	13.5
	CKD V	4	7.7
History of cellular rejection in biopsy ^b (n, %)	0R	13	25.0
	1R	25	48.1
	2R	13	25.0
	3R	1	1.9

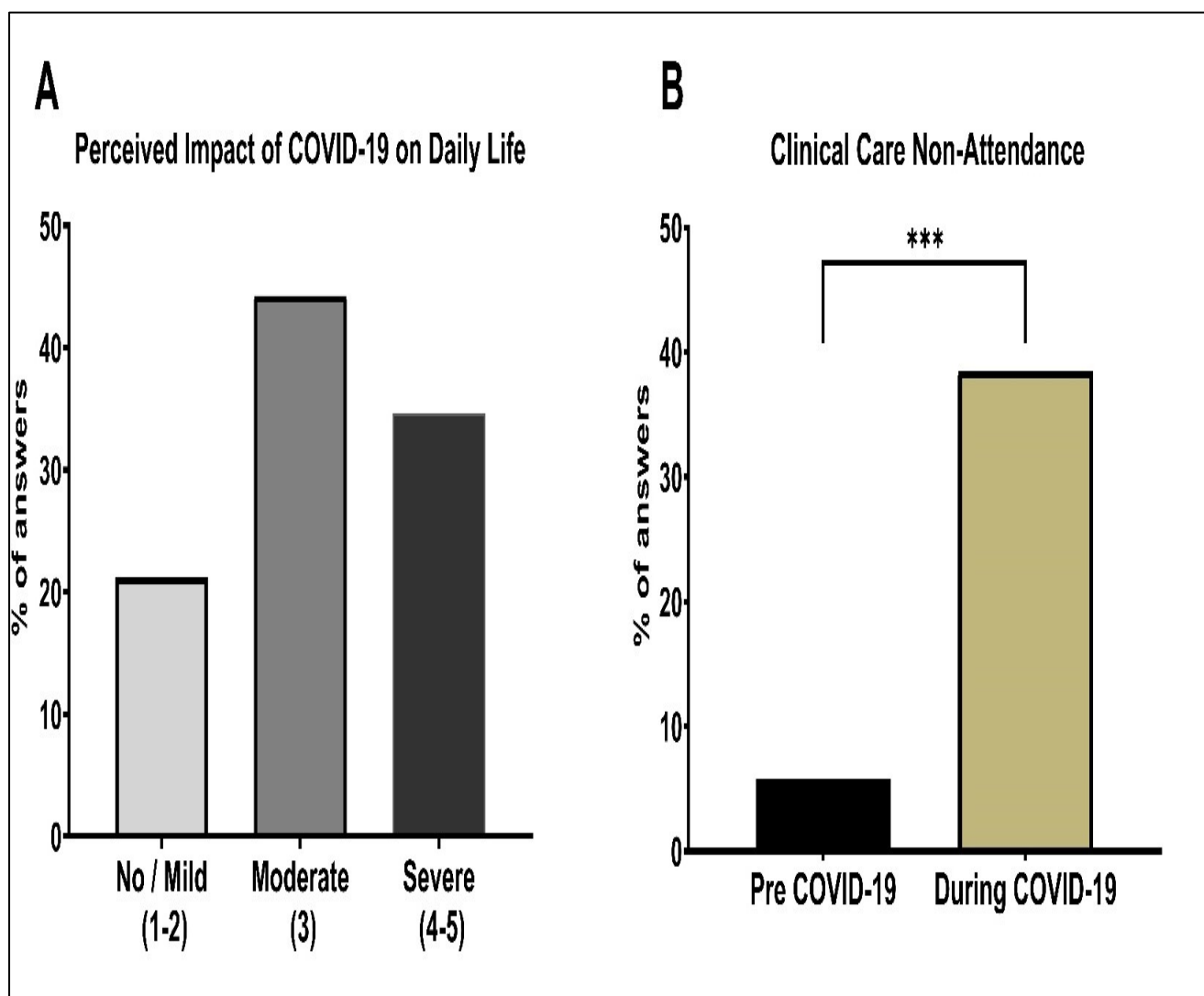
History of humoral rejection in biopsy ^b (n, %)	pAMR 0	40	76.9
	pAMR 1	12	23.1
History of clinically relevant rejection (n, %)		16	30.8
History of Infections (n, %)		28	53.8
History of Cancer (n, %)		6	11.5
History of Drug-induced complications (n, %)		5	9.6
Immunosuppressive medication (n, %)	Tacrolimus/Everolimus/Prednisone	28	53.8
	Tacrolimus/Everolimus	2	3.8
	Tacrolimus /Sirolimus	1	1.9
	Tacrolimus/MMF/Prednisone	19	36.5
	Tacrolimus/MMF	2	3.8

^a Staging definition of *Chronic Kidney Disease* according to KDIGO.

^b If more than one episode was present, only worst counted

Figure Legends

Figure 1: Pandemic influence on daily life and clinical care. **A.** Perceived impact of COVID-19 on Daily Life. Shown is the percentage of patients who perceived no or mild (21%, left column), moderate (44%, middle column), or severe (right column, 35%) impact on daily life during the pandemic. **B.** Non-attendance to clinical care pre-and within the pandemic as a percentage of all answers at distinct timepoint. Pre-pandemic, 6 % (left column) had experienced limitations, while during the pandemic, this increases to 39 % (right column), resulting in a significant difference (***) = $p < 0.0001$). Details see text.



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Figure 2: Details of non-attendance to clinical care as a heatmap. Percentage of all patients who could not attend a specific follow-up diagnostic: While Influenza and Pneumococcal Vaccinations were not reported as compromised (2%), this changes with cardiac diagnostics like endomyocardial biopsy (12%). Non-attendance is highest in colonoscopy (17%) resp. Gynecological exam (women only, 18%). Details see text.

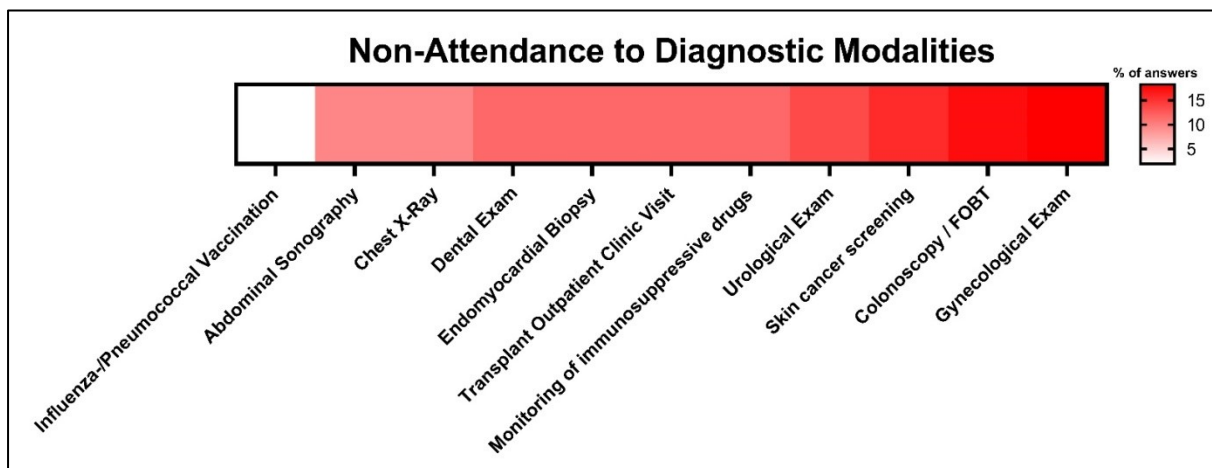


Figure 3: Relation between the perceived impact on daily life and particular attendance on clinical care. Groups are separated according to Figure 1, A. No correlation could be observed between the pandemic influence on daily life and clinical care attendance ($p>0.68$).

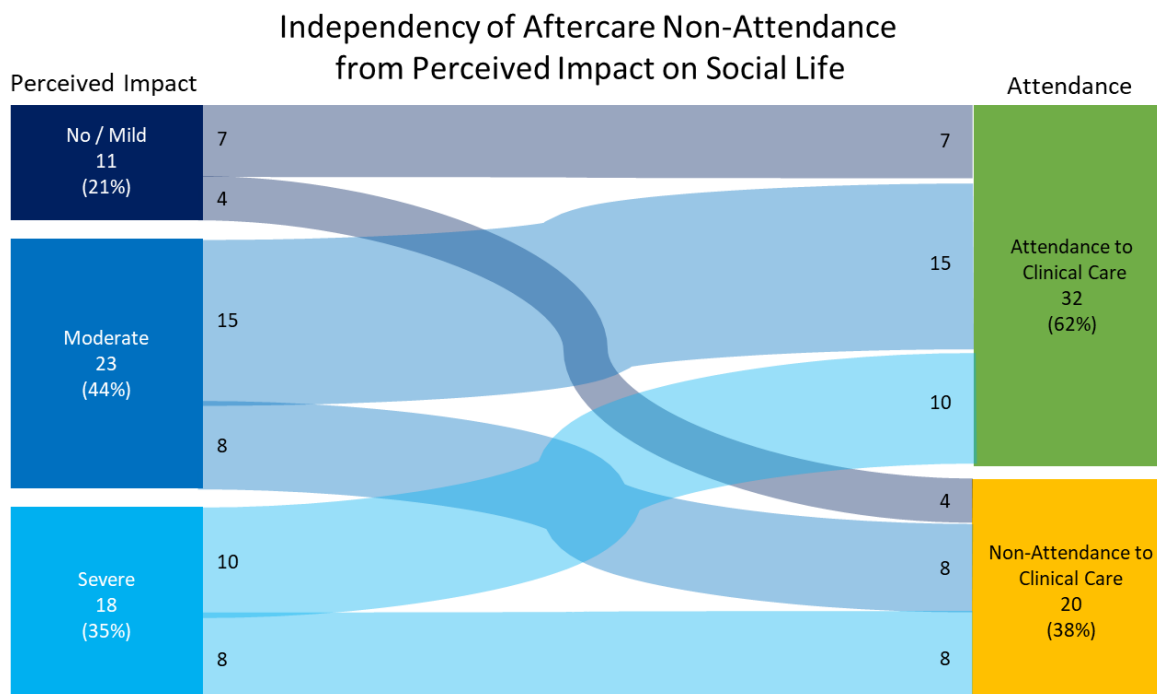


Figure 4: Transitions of attendance pre- and within pandemic. The majority of all reported non-attendance within the pandemic (n=19, 37%) originates from those who reported regular clinical care before pre-pandemic. Those reporting non-attendance before pandemic (6%) only play a minor role. Details see text.

