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Living well after organ transplantation

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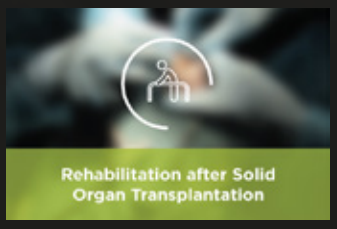

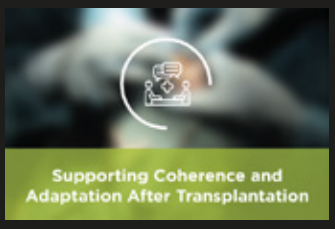

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SPECIAL ISSUE EDITORIAL
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Editorial: Living Well After Organ Transplantation

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Keywords: organ transplant recipients, life participation, wellbeing, quality of life, transplant care

Editorial on the Special Issue

Living Well After Organ Transplantation

Solid organ transplantation can offer many patients with end-stage organ failure improved survival and better quality of life compared to pretransplant. For transplant recipients, being able to participate in meaningful activities of life is a critically important outcome after transplantation [1–3]. However, complications, co-morbidities, medication side-effects and treatment burden can impair physical, mental, and social outcomes, which in turn might undermine a recipient's capability to "live well" with their transplant.

Physicians, nurses, and allied health professionals have a key role in supporting transplant recipients in managing their physical and psychosocial health. However, addressing quality of life in transplant recipients remains a clinical challenge. With this special issue, we draw attention to under-investigated aspects of the quality of life of transplant recipients and highlight interventions and innovative care models that may have potential to improve quality of life and related outcomes in transplant recipients.

First, to support transplant recipients in being able to "live well," it is important to understand the perspectives of transplant recipients on what good quality of life means to them. Therefore, the first section of this special issue is dedicated to the patient's voice, in which three transplant recipients shared their views on how care should be provided to support patients to live well after transplant (Fowler; Sipma et al.; Schneider et al.). From diverse backgrounds (advocacy, business, and dietetics), all three recipients call for an integrated and person-centered care approach and urge transplant providers to not only focus on medical aspects but to take all aspects of transplant recipients' daily life into consideration. Several suggestions were made to accomplish this goal, e.g., by integrating the patient's voice into regular care, by using patient-reported outcome measures (PROMs), by adopting new models of care, or by establishing clear guidelines regarding integrated supportive care. Moreover, it was advocated that transplant recipients should see themselves as drivers of their own wellbeing by taking control over their own life, while transplant professionals take on a role of supporting better self-management and facilitating access to relevant healthcare services and programs.

The authors of the other manuscripts in this special issue endorse this plea as that healthcare professionals should strive for person-centered care and the integration of tailored interventions to support psychosocial and behavioral dimensions of transplant recipients care pathway. However, some key initiatives need to be taken to better align the needs and capabilities of transplant recipients with the type of care being provided by transplant professionals. More specifically, transplant professionals need insight into the prevalence and associated factors of key health issues after transplantation before appropriate interventions can be implemented. For instance, Hoteit et al. examined excessive daytime sleepiness, which was present in 12.7% of kidney transplant recipients.

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This was associated with Diabetes Mellitus and obesity and had a negative effect on recipients' physical functioning. Hence, measuring daytime sleepiness or other sleep-related problems in transplant recipients is relevant and can be achieved through using appropriate PROMs which provide a basis for further intervention planning.

Second, transplant professionals' insights into correlations or determinants of psychosocial and behavioral or quality of life issues allows them to identify at-risk patients and to target modifiable determinants through targeted interventions. In this special issue, two studies describe barriers for medication adherence in heart transplant recipients. Denhaerynck et al. showed that primarily personal barriers, for example, sleepiness, being away from home and forgetfulness, were related to non-adherence to the immunosuppressive regimen. These findings were supported by the study of Marston et al., who showed that intentional non-adherence, i.e., recipients consciously deciding to reduce their dosing frequency or number of medications or discontinue treatment, is, alongside financial and accessibility barriers, mainly driven by personal barriers. Both studies show that multilevel determinants drive patient behavior pointing to the needs for multilevel interventions, i.e., not only targeting transplant recipients yet also healthcare provider, organization of care and healthcare system aspects.

Third, transplant professionals need to have knowledge about post-transplant outcomes that reflect how recipients feel and function, and their associated factors. Life participation, the ability to participate in meaningful activities of life, has found to be the most important outcome for kidney transplant recipients [1]. However, employment status, as part of life participation, has received limited attention. In a registry-based study, Mols et al. found that of the 40% of heart transplant recipients eligible for labor market participation, most (30%) were employed and 10% were unemployed. Unemployment was associated with multimorbidity and being socioeconomically disadvantaged. Although many transplant centers already address return to work as an important outcome post-transplant, the authors call for additional strategies to support workforce reintegration, particularly in those vulnerable groups.

Knowledge of patient-reported outcomes is also needed to support shared decision-making. Kidney transplantation, for example, is in general the treatment of choice for people with kidney failure as it offers better survival and quality of life compared with dialysis. The paper of De Boer et al. showed that this also applies to older (≥65 years) kidney transplant recipients as they perceived their physical and mental health-related quality of life as better when compared to older waitlisted kidney transplant candidates. This evidence can help older transplant candidates to make an informed decision whether to pursue a transplant or not.

Next to positive effects, potentially negative effects on outcomes should also be addressed. In their viewpoint article, Stylemans et al. describe the pros and cons of physical activity after transplantation. Although engaging in physical activity is beneficial for the health of transplant recipients, strenuous physical activity may come with potential adverse outcomes such as overuse injuries, increased risk of infections, and cardiovascular events. The authors state that the line between health benefits and potential harm of physical activity lies in the dosage administered, indicating that interventions to support recipients in living well posttransplant should always take the persons capabilities into consideration.

Lastly, it is important to evaluate if interventions or new models of care are effective in improving transplant outcomes, including those related to self-management and quality of life. The study of van Zanten et al. examined the effectiveness of a nurse-led, tailored intervention to promote self-management skills in solid organ transplant recipients. Although participants were positive about the program and reported added value, in terms of goal setting and providing tools to move forward after transplantation, the intervention was only effective for recipients with lower self-management skills at the start of the study. This indicates that a one-size fits all approach might not be effective and that it is important to identify transplant recipients who will benefit the most from an intervention based on certain characteristics, for example, health literacy, level of knowledge or skills, or demographic characteristics or economic status.

One specific aspect related to self-management is the monitoring of signs and symptoms by healthcare professionals during post-transplant follow-up care visits. Advancements in telemedicine and eHealth nowadays make it possible for transplant recipients to self-monitor their signs and symptoms in a reliable way at home. Hezer et al. studied the feasibility of implementing home-monitoring as standard care after kidney transplantation. The authors found that most kidney transplant recipients were open for home-monitoring, adhered to the protocol, were positive about the home-monitoring system and reported lower care needs due to home-monitoring. This study shows the potential of telemedicine and eHealth interventions in supporting self-management, especially in the light of the ever-growing transplant population. However, the effectiveness of home-monitoring still needs to be evaluated in a real-world setting with a focus on implementation in the clinical workflows.

Mielke et al. addressed another aspect of transplant care that is important when trying to achieve personalized care, a trustful relationship between transplant recipients and transplant professionals. Trust in the transplant team is gaining attraction as a relevant system level factor related to quality of care and as a determinant of health behavior. In their study, the authors found that heart transplant recipients who received care based on an integrated model of care, combined with longer consultation time and a chronic illness management approach, had greater trust in their transplant team, and showed better outcomes regarding dietary adherence. The authors conclude that trust and transplant care based on the principles of chronic illness management are key factors for reengineering transplant care aiming to optimize transplant outcomes.

In conclusion, based on the plea for person-centered transplant care made in this special issue by transplant recipients and transplant professionals, the time is ripe for reengineering transplant care. By providing care based on the needs and capabilities of transplant recipients, we can improve long-term outcomes after transplantation and enable transplant recipients to live well after transplantation. We hope the papers

included in this special issue serve as a powerful source of inspiration for transplant programs across the globe.

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POSITION PAPER
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Life After Kidney Transplantation: The Time for a New Narrative

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The first successful kidney transplant in December 1954 between the Herrick brothers ushered in a new field of medicine. Over the almost seventy years, thousands of lives have been saved and patient survival has improved. There is one area of kidney transplant patient care that has been overlooked. Patient quality and ability to participate in life have not been adequately studied. This is due in part to the false narrative of life after kidney transplantation. The false narrative has developed due to the patient voice not being heard due to a variety of factors. The development and implementation of Patient Reported Outcome Measures into clinical practice and clinical trials is the first step ensuring the patient voice is heard systematically. By enabling the patient voice to be heard, I hope this result in a new narrative that is patient centered.

Keywords: kidney transplant, patient reported outcome measures, patient advocacy, life participation, post kidney transplant

INTRODUCTION

When I was contacted to serve as a co-editor, I was thrilled for the opportunity to contribute. For myself and for many other kidney transplant recipients, we only truly feel understood by fellow recipients. The lack of understanding by some members of the medical community and sometimes our loved ones can create a sense of isolation and loneliness during different parts of our journeys. The objective of this issue of Transplant International is to provide similar insights for the transplant community. It is my hope that these insights will be acted upon so that systemic changes are made in the way transplant care is provided. Before change can be initiated, the argument for change must be articulated through an honest narrative on life after kidney transplantation. Through my personal and professional experience, the objective of this article is to educate this audience why a new narrative for life after kidney transplantation is needed.

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LIFE BEFORE TRANSPLANTATION

Prior to my kidney failure, I was seen by a primary care physician. Since my mother had Autosomal Dominant Polycystic Kidney Disease (ADPKD), I was aware that I had a 50% chance of inheriting her medical condition. After witnessing my mom suffer on hemodialysis and die at 52, I lived in fear that I would suffer the same fate as her. My primary care physician monitored my kidney function for any signs of changes in kidney function. According to my physician, my kidney function was normal, and I had nothing to be concerned about in the near-term future. Later that year after my annual appointment, I experienced back pain during the Holiday Season. Initially, I attributed it to firewood that I had picked up. Since flank back pain can be a symptom of ADPKD, I decided to determine if I had the same disease. I contacted my doctor and requested an ultrasound test. This test would determine definitively whether I had ADPKD.

The test confirmed that I had inherited ADPKD. In contrast to the earlier optimistic prognosis, my doctor informed me that I would be in kidney failure in 3–5 years. He informed me that I would either start dialysis or have a kidney transplant in the time frame provided. I instinctively and immediately declined the offer. The doctor that said my kidney function was fine was now making a nephrology referral. I trusted my intuition that I needed to advocate for myself. Through my self-advocacy I was able to receive the best treatment for kidney failure. My ability to trust my instincts enabled me to seek the best treatment option, and to live my best life afterwards.

I called a physician friend at an Academic Medical Center requesting his recommendation for a nephrology referral. He recommended a colleague, and I scheduled my appointment with the nephrologist. On the first appointment, my doctor informed me that I was a good candidate to receive a pre-emptive kidney transplant. This treatment would provide the best long-term outcomes for End Stage Kidney Disease (ESKD) while also avoiding dialysis. While I was overjoyed to learn this information, I was left wondering why this was the first time I was learning about this treatment option.

As I came to learn later, in the United States (US) only 3.5% [1] of incident kidney failure patients receive a pre-emptive kidney transplant. This is because most patients with kidney disease are unaware of their condition. In fact, approximately 40% of kidney failure patients crash into dialysis. In other words, these patients are unaware that they are progressing into kidney failure until dialysis is administered to save their lives. When the US Medicare End Stage Renal Disease benefit was passed into law in 1973 [2], it eliminated the need to ration dialysis treatment. While it assured that ESKD patients would have access to dialysis treatment, it failed to evolve over time until the Advancing American Kidney Health Executive Order was issued in 2019 [3].

As my kidney function continued to decline, my nephrologist created an environment for me to develop self-management skills such as understanding my lab values, and how to prepare for the day when I would receive a kidney transplant. There is one area that stands out among all aspects of my patient care. He explained the cardiovascular risks post kidney transplant, and educated me on the benefits of routine exercise to prepare for my kidney transplant. I started doing an elliptical machine workout three to five days weekly. This habit helped me to manage an uncertain future. The decision to exercise was something within my sphere of control. I would have thoughts constantly of whether I would be able to find a donor or whether my kidney transplant would be successful. The decision to choose to exercise was an act of centering in the present moment and helped to quiet my anxious thoughts. Later, I learned that it was not a common practice for nephrologists to educate their patients on the benefits of exercise [4].

TRANSITIONING TO A NEW LIFE

The first-year post-transplant was one of immense gratitude while adjusting to a new life. The sense of joy and profound gratitude can never be adequately described. The selfless act of my living donor combined with the support that I received from my wife and community was so powerful that I knew my life was changed permanently. Amidst this sense of awe and wonderment, there were aspects of my new life that I had not been adequately educated upon prior to my transplant.

The first challenge was psychological. I was 43 years old, and during that first year, I struggled with my own mortality. Our children were very young, and I ruminated constantly on whether I would be around to see them grow up. When I had my follow up appointments with my transplant team, the discussion always centered upon lab values, ensuring I was taking my transplant medications, etc. There was never any discussion about how I was adapting to my new life with chronic immunosuppression. I clearly sensed there was an implied message that I should be grateful for my kidney, and that I should get on with my life.

The second challenge was adjusting to my kidney transplant medications. Within a year after my kidney transplant, I began to experience cognitive issues and fogginess. When I reported this to my transplant team, my experience was not validated. Rather, they stated that this condition was not caused by my medications. The conversation shifted to reminding me that I should be grateful to have received a pre-emptive kidney transplant. Contrary to what my transplant team was telling me, I knew something was not right. I was looking for a member of my care team to validate my experience, and no one did. The psychological and medication challenges combined with the pressures of a job promotion became too much for me to handle. Eventually, I experienced deep depression. I could not find any answers to my questions. Frustrated at not feeling understood with diminished quality of life, I drew upon the lessons of my pre-transplant nephrologist.

WEATHERING THE STORMS POST-TRANSPLANT

I remembered the lessons on the benefits of exercise. I started exercising to regain some control back in my life. After I exercised, I would feel better not only physically but mentally. The physical activity resulted in improved cerebral blood flow to my brain. Routine exercise became a staple in my life because of its ability to counteract the side effects of tacrolimus. I took this action out of desperation to feel better. I needed to feel better so that I could perform my job. I started journal writing, and it provided the benefit of re-framing my new life. Rather than ruminating on thoughts on the length of my life, I shifted my efforts to towards empowering myself by taking acting action over what was in my sphere of control. I had control over whether I exercised, prepared for my medical appointments, etc. I read a book on the history of kidney transplantation, "The Puzzle People" [5], and this book made a lasting impression upon me. In the book, transplant recipients shared that they probably would never have made their life achievements without having a kidney transplant. The kidney transplant experience provided them with a greater sense of purpose with the awareness of the brevity of life. The decision to choose how I wanted to frame my life empowered me to move forward. For

example, I framed my own experience as an example for our children to learn from. Over time, I added meditation to my routine of vigorous exercise and journal writing. In turn, the net benefit of my discipline was that I created a ballast to manage the ongoing challenges of managing a chronic disease.

The set of challenges after transplant have been constant and unremitting. There have been multiple hospitalizations due to infections. Once hospitalized, there was the challenge of ensuring physicians were not using nephrotoxic medications or the risk of having an acute kidney injury. There have been multiple MOHs surgeries due to squamous cell carcinoma and melanoma cancer. I have had a radical prostatectomy and three covid episodes. On top of all of that, there has been the constant challenge of managing the never-ending ups and downs of lab results while ensuring I have access to my transplant medications and access to health insurance. In the back of my mind, there is always the constant worry of my kidney failing. My routine of discipline has prepared me to effectively manage the ongoing challenges.

COUNTERING THE ESTABLISHED NARRATIVE FOR KIDNEY TRANSPLANTATION

Prior to my kidney transplant, I was led to believe that everything would be ok once I received my new kidney. While it is true that my health was restored, the adjustment post-transplant was something that I was not prepared for. I was under the impression that I would have my kidney transplant, and my life would return to normal. This perception was formed in part by my kidney transplant team, and the narrative surrounding kidney transplantation. Before my transplant, I read all the celebratory stories of organ donation and kidney transplantation. No where in these stories was there any acknowledgement about some of difficulties experienced due to chronic immunosupression, or guidance to overcome the challenges. This perception has only been reinforced by published studies that tout improvement in kidney transplant survival without addressing quality of life [6].

Upon closer examination the established narrative of transplantation is contrary to published evidence. In response to a request from the Social Security Administration the National Academies of Science, Engineering, and Medicine conducted a day and a half meeting on *Organ Transplantation and Disability: A Workshop* [7]. The workshop included presentations on the functional outcomes for individuals who are recipients of organ transplants: including those of the kidney, heart liver, and lung.

The evidence presented contrasted sharply with the public perception of transplantation. Employment the first year after transplantation was quite low for all organ recipients. For kidney, liver, heart, and lung it was 31%, 21%, 21% and 14% respectively. The causes of low employment are multifactorial: lack of physical rehabilitation, side effects of transplant medications, depression, absence of patient reported outcome measures (PROMs), etc. PROMs would play a key role in enabling transplant recipients to acknowledge what they are feeling. Recently, Allison Jaure PhD published in Kidney International *Validation of a Core Patient Reported Outcome Measure for Kidney Transplant Recipients: the SONG Life Participation Instrument* [8]. The novel instrument measured activities that are important to patients such as ability to work and participate in family activities. In other words, it measures the value of the kidney transplant to the recipient. When I assess the value of my kidney transplant, I measure its value in being able to work the entire time, put my children through college, and see them grow into young adults.

The process to improve life after transplants starts with a baseline assessment of the population. To that end, the American Society of Transplantation has issued a comprehensive patient survey for all transplant recipients on a broad number of domains. One of the domains is patient reported quality of life. When the results are published, it should provide additional support for the implementation of PROMs into clinical practice. My personal example of life post-transplant and low employment for solid organ transplant recipients are just two aspects that counter the prevailing narrative of life after transplant. It is difficult to advance the field of transplantation if payors, regulators, policymakers, and patients themselves do not perceive the need for improvement. I have provided three recommendations to begin the process of initiating systemic change bu.

Patient Reported Outcome Measures (PROMs)

As I have described above, there Is a need to implement PROMs into clinical practice. The adoption of PROMs would initiate the process for the patient voice to be heard and serve as a catalyst for patient engagement. In turn, patients would be directed to interventions to improve quality of life while additional research and resources should be increased to improving quality of life and employment. The inclusions of PROMs in pharmaceutical and device manufacturer clinical trials may offer also offer a path to differentiation in treatments and a path to regulatory approval.

New Care Model Pilots

In the US, the CMS Innovation (CMMI) Center has introduced value-based care models to incentivize increased use of home dialysis and kidney transplantation. With this as a precedent, CMMI can address the lack of rehabilitation post kidney transplantation. As a starting point, a pilot model that offers physical rehabilitation, psychological counseling, mentorship, etc. Would be a step forward in validating the patient experience while aligning with national policy. In the US expanding kidney transplant access and the volume of kidney transplants have been formalized through reform of the Organ Procurement Organizations. While this is a positive achievement, the full value of a kidney transplant will not be achieved without rehabilitation support. It is analogous to buying an expensive automobile without routine service.

Elevation of the Patient Voice With Regulatory Agencies

In recent years, the American Society of Transplantation (AST) and the European Society of Transplantation (ESOT) have taken

meaningful action to elevate the patient voice in their professional societies. The AST has formed the Transplant Advisory Council, and ESOT has formed the ESOT-European Transplant Patients Organization Alliance that has resulted in patient representation in meetings and workgroups. Through my experience in patient advocacy, I have observed a lack of alignment and coordination between regulatory agencies regarding kidney transplantation. For example, in November 2023 I attended the FDA Public Workshop on "Endpoints and Trial Designs to Advance Drug Development in Kidney Transplantation." Considering that the Social Security Administration conducted a workshop on organ donation and disability, their attendance at the meeting would have educated them on how the side effects and health risks of transplant medications can contribute to the difficulty of returning to work. My request is for AST and ESOT Is to leverage their patient councils to educate a broad number of regulatory agencies on the patient experience to gain a holistic understanding of the patient journey, and the unmet needs in kidney transplantation.

On December 23 2024, it was the 70th anniversary of the first successful kidney transplant. This extraordinary scientific and medical innovation has added life years to thousands of patients globally. It is now time to build upon improved patient survival and improve the quality of life of kidney transplant recipients. Acknowledging this unmet need can serve as a catalyst to engage with policymakers, regulators, Life Science companies, etc. To incentivize innovation in kidney transplantation while providing holistic patient care. I ask the global kidney transplant community to learn from the lessons of the American Society of Nephrology and the Kidney Health Initiative (KHI).

Since 2015, I have served as a Kidney Health Initiative volunteer through the Patient Family Partnership Council, and the Board of Directors. During my service, I have witnessed first-hand the transformation of nephrology patient care. The US nephrology community is in midst of changing from a system of care that financially rewarded placing patients on dialysis to one that prioritizes the detection and early intervention of kidney diseases. This change never would have happened so quickly if not for the American Society of Nephrology (ASN) elevating the patient voice as a stakeholder.

My call to action is for the global kidney transplant community to learn the ASN lessons. I would like to see the global kidney transplant community prioritize listening to the patient voice. To that end, I would like the community to focus upon the implementation of PROMS in patient care. This would ensure the patient voice is heard in a systemic manner so that improvement in quality of life is a global priority.

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The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

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POINT OF VIEW
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"It's My Life and It's Now or Never"—Transplant Recipients Empowered From a Service-Dominant Logic Perspective

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Patient well-being after an organ transplant is a major outcome determinant and survival of the graft is crucial. Before surgery, patients are already informed about how they can influence their prognosis, for example by adhering to treatment advice and remaining active. Overall, effective selfmanagement of health-related issues is a major factor in successful long-term graft survival. As such, organ transplant recipients can be considered as co-producers of their own health status. However, although keeping the graft in good condition is an important factor in the patient's well-being, it is not enough. To have a meaningful life after a solid organ transplant, patients can use their improved health status to once again enjoy time with family and friends, to travel and to return to work -in short to get back on track. Our assertion in this article is twofold. First, healthcare providers should look beyond medical support in enhancing long-term well-being. Second, organ recipients should see themselves as creators of their own well-being. To justify our argument, we use the theoretical perspective of service-dominant logic that states that patients are the true creators of real value-in-use. Or as Bon Jovi sings, "It's my life and it's now or never."

Keywords: service-dominant logic, organ transplant, value creation, quality of life, value-based healthcare

Point of View

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INTRODUCTION

In 2021, when the Corona virus pandemic resulted in many planned transplant operations being postponed, around 144,000 organ transplants were still performed globally. Most of these were kidney transplants (66%), followed by liver (24%), heart (6%), and lung (4%). Those 2021 data are based on the Global Observatory on Donation and Transplantation (GODT) data, produced by the WHO-ONT collaboration [1]. Organ transplants are generally the preferred treatment to improve the lives of patients suffering from organ failure [2, 3]. It is safe to say, thanks to the current high standards in organ transplant procedures, and despite the serious conditions of patients suffering from these life-threatening diseases, that, in 2021, many lives were not only saved but also improved through organ transplants. Through this, many of the organ transplant recipients and their families are now able to resume their life in a more-or-less normal way. This is an impressive worldwide achievement of all the professionals involved.

As an illustration of this, the first author (WS) of this paper is a kidney transplant recipient who has regained his well-being. He has also been a volunteer for the Dutch Kidney Patients Association for over a decade and is therefore familiar with the topic of living well after an organ transplant.

It is important that organ transplant recipients understand their personal responsibility in protecting the functioning of their new organ. In this article we distinguish two domains where patients are responsible. The first domain is "responsibility from a medical perspective," the second is 'about "responsibility from a personal well-being perspective." In the first domain, healthcare professionals encourage patients to take all the necessary steps to protect the functioning of their new organ. This includes adhering to the prescribed medication, maintaining a healthy diet and having sufficient physical activity. This first domain is part of normal medical practice, also referred to as 'the health factory' [4], and falls within the scope of healthcare services as "diagnosing and treating illness and promoting health." The second domain is about personal well-being, including quality of life. The sense of well-being has been associated with feelings such as experiencing positive emotions, of having self-control to a certain extent, and a sense of purpose [5]. In 2001, the World Health Organization (WHO) described well-being as a subjective state of mind that goes beyond "the mere absence of disease" and is rather "a state of complete physical, mental and social well-being" [6, 7]. Our view is that, within the personal domain, patients create their own value of living, their quality of life, and their feeling of well-being. To justify our argument, we use the theoretical framework of the service-dominant (S-D) logic. S-D logic is a holistic approach to delivering healthcare services with an active role for patients to create value. S-D logic has several similarities and differences compared to the integrated care concept and chronic care management (hereafter referred to as integrated care). In the next section we introduce S-D logic and we compare S-D logic with integrated care. Then, we discuss the relationship between S-D logic and well-being. Finally, we suggest four themes in introducing of the S-D logic in practice.

SERVICE-DOMINANT LOGIC AND INTEGRATED CARE

During the past decades the S-D logic framework has been developed to present a different perspective on value (co-) creation [8–10]. The traditional view in service innovation on the creation of value has been that providers deliver value to the customer, hence the service provider is the value creator [10, 11]. The S-D logic, however, distinguishes between value creation from the perspective of the provider and of the customer [10, 12–15]. According to the S-D logic, the service provider creates *potential value* in the provider sphere, whilst the provider and the customer together *co-create value* in the joint sphere. In healthcare the doctor and the patient interact in the joint sphere and co-creation is realized because doctors and patients know different things and integration of their knowledge and dialogue may lead to improved and personalized interventions [4]. Furthermore, the patient, in this case the organ recipient, is the independent creator of value-in-use (*real value)* in the customer sphere (**Figure 1**, adapted from Grönroos and Voima [16]). Once dismissed from the hospital after surgery the patient is on his own and, beyond self-management on health-related issues, is working hard to regain his normal life activities. This is all done in the customer sphere and highly determines the patient's well-being.

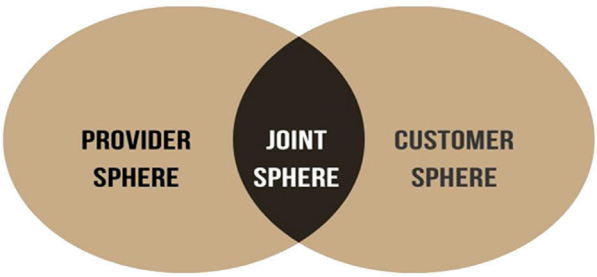

FIGURE 1 | Value Creation Spheres (adapted from Grönroos and Voima [16]).

A central theme in the S-D logic is "value-in-use" (or real value), stressing that a service in itself has no value and that value comes from its use. For transplant recipients this means that after surgery and the first recovery they resume their lives as well as possible. Patients are the creators of value and well-being in their personal lives, for instance by getting back to work. The S-D logic, with value-in-use as the core value-driver, has already been applied to healthcare [4, 17–20]. As is illustrated in the example above, S-D logic views patients as the creators of value in their private lives after having received medical care, in this case after having received a new functioning solid organ. This calls for a thorough understanding of patients' daily environment because their home situation (customer sphere in **Figure 1**) is key to value creation and personal well-being. In the context of living well after an organ transplant, the S-D logic framework highlights the importance of a supportive environment for recipients since well-being is more than "just" a well-functioning new organ. A practical example in the consulting room is that, when informing patients about the possibilities of an organ transplant, the doctor mentions "you might get back to work again" (value-in-use perspective) instead of "we can transplant you with a new organ" (medical service perspective).

S-D logic can be compared with the integrated care approach. Integrated care is a well-known approach in healthcare service delivery and was developed as an answer to fragmented specialization in healthcare and especially adds value to the service of patients with chronic care needs [21–26]. Integrated care focuses on coordinated medical support to improve healthcare through the lens of patients, although it can also be considered as a multipurpose approach to develop a cost-effective, coherent care system [24, 26]. Similar to S-D logic, integrated care models are associated with interprofessional partnerships, interorganizational collaboration, patient engagement and setting patients in the heart of health service [14, 17, 27–30].

We argue that integrated care, in terms of S-D logic, is mainly focused on the joint sphere (**Figure 1**), the area where a variety of healthcare providers and patients interact. Where integrated care models promote a system that delivers coordinated and optimal care for and together with patients, S-D logic considers the patient as an asset, an active producer of value. We argue that

this is a different way to patient involvement than described in current integrated care models. In integrated care the patient is a receiver of care whereas in the service-dominant logic approach patients are (co-)creators of value in their home environment and doctors are considered as facilitators, enabling patients to create value. We argue that this is an important and valuable addition to the role of the patient in healthcare services that aim to improve patients' well-being. Therefore, the implementation of the S-D logic in healthcare offers a different perspective on service for patients than the paradigm that the set of medical interventions themselves deliver value, which we feel is the common premise of integrated care. A quote from an oncologist illustrates this: "Oncology practice provides treatment, but that is a fraction of the patients' needs" [31]. To facilitate organ recipients in moving on with their lives requires supportive facilities in the patient sphere. In practice, this means that patients and care providers need to discuss what is needed for the patient to live well after an organ transplant, which specialized care within or outside the hospital can be utilized and what challenges the patient foresees. These services might go beyond the medical profession and could be offered by different professionals. To realize this, a culture of collaboration and an external orientation is needed along with patients' awareness of their active role [10, 32]. Where patients cannot fully bear that responsibility themselves, interaction with the care provider becomes especially important. In summary, both S-D logic and integrated care promote patient centeredness. However, in our view S-D logic goes a step further by considering the patient as a resource and (co-creating) value goes beyond cooperation [33]. Value-in-use is created by the patient in the patient sphere and outside the sight of the medical profession [14, 30], which is less addressed in integrated care.

WELL-BEING OF ORGAN TRANSPLANT RECIPIENTS

If we consider the organ recipients' well-being from the S-D logic perspective and in terms of value-in-use, we can argue that well-being is created by the organ recipients themselves after discharge from the hospital and independent of the monitoring by healthcare professionals. This creation of value by organ transplant recipients is a process that evolves out of the sight of the medical profession. During the period when patients are restoring their sense of well-being, for instance by once again socializing with their family, finding the energy to read a book, enjoying cooking, visiting cinemas and theatres, continuing their studies, reintegrating into the workplace and daring to travel again, the well-functioning of their new organ facilitates this process. In essence, this is the key message of the S-D logic: medical health services, providing diagnoses, surgery, and aftercare, should be seen as facilitators (or enablers) for patients to attain the highest possible level of well-being. The organ transplant is an indispensable starting point for patients to regain their lives, but after the operation, they have to move forward themselves. We were told of a case of a nephrologist who asked a kidney transplant patient during a regular consultation: "How are you doing?", and the patient responded, "I think my kidney is doing well." However, this was not what the nephrologist, who was also interested in the broader context of the patient's well-being, meant. For the professional, the most important outcome of an organ transplant is also that organ recipients regain their lives. Although this point of view may not be groundbreaking, to serve organ recipients based on the S-D logic raises some issues. We therefore now discuss four themes related to the introduction of the S-D logic in the daily practice of organ transplant actions: the awareness that healthcare providers are facilitators, the complex process of achieving well-being, managing an S-D logic-oriented service network and rethinking value-based healthcare.

Healthcare Providers Are Facilitators

First, transplant healthcare providers (tHCPs) should acknowledge that they are a crucial, but not the only, part of their patients' struggles to regain their lives. While tHCPs offer potential value, this still has to be converted into value-in-use by their patients. The tHCP's role is to facilitate patients to give meaning to their lives, and a successful complex health intervention such as an organ transplant alone is not enough. In addition to saving a life, tHCPs can have an important role in patients having a life. After providing a correct diagnosis, an organ transplant and high-quality care, the creation of real value by the organ transplant recipient continues. Here, value-in-use should be focused on well-being, which is up to the patient, possibly with support of other, possibly non-medical, facilitating health services. For instance, it is acknowledged that having a job is an important factor in a patient's feeling of well-being [34]. Although it is certainly recognized by physicians that they can contribute to patients returning to work, it is not yet part of the collective mindset in hospitals [35]. There is a need to admit that healthcare services, even if excellent, are a part of what a patient needs: transplants are not the complete story of the patient's journey but a necessary step that should open up a broader, more holistic, view on life after an organ transplant.

The Complex Process of Achieving Well-Being

Second, it needs to be recognized that creating well-being is a process that involves various actors surrounding the sphere of the patient, and that achieving patients' psychological ownership of their well-being is complex [36]. Further, the development of services to support the creation of well-being affects the entire healthcare service system. Well-being is multidimensional and is influenced by many aspects such as health, employment, income, and relationships [37] and, given that these influences may change over time, it is not an easy task for tHCPs to identify their role in this complexity. For instance, it is suggested that recovering and regaining quality of life after a liver transplant is influenced by the occurrence of depression before a transplant [38], illustrating the complexity of achieving well-being. We can picture two roles for tHCPs beyond their core medical task: a) to motivate the organ transplant recipient to take personal responsibility for the creation of well-being; and b) to have

some knowledge on related services that might help patients who are confronted with issues such as loneliness or loss of income or job.

Managing an S-D Logic-Oriented Service Network Partnership

Third, management has the responsibility to make decisions on the scope of services to be offered by the organization, either at the unit (department) or at the organization (hospital) level. The scope of services that are offered beyond medical care should be discussed. These extended services should aim to support organ recipients in creating well-being in their daily lives. For instance, since employment is considered an important influence on well-being [39, 40], a possible service would be to support work retention. Similarly, budget coaching and relationship coaching are possible additional services because coping with chronic illness may affect income and relationships [41, 42]. There is no need for hospitals to offer these extended health services themselves, there may be other more suitable providers to turn to for support. Here, the role of the hospital would be to connect with external providers and align the provided service levels. The S-D logic refers to these extended health services, offering collaborative care to realize a holistic service approach, as the service ecosystem [18, 43]. This ecosystem is characterized by multiple actors, most likely from different organizations, that together create a context to enable value creation by the organ recipient. Although moving a hospital to an S-D logic-oriented service network partnership is a managerial challenge [32], we believe that transplant recipients may benefit from this transition.

Rethinking Value-Based Healthcare

Fourth, when adopting the value-in-use paradigm, there is a need to rethink the concept of value-based healthcare (VBHC). Value-based healthcare focuses on 'what matters most to patients' and relates these outcomes to costs [44], although what this means in practice is somewhat unclear [45]. In practice, the concept of VBHC focuses mainly on the direct healthcare context and less on the broader context of well-being as described in this paper. We notice that the majority of quality metrics in solid organ transplantation focuses on safety and effectiveness although a plea is made for more patient involvement and a focus on what really matters to patients in an broader healthcare context [46]. Patient reported outcome measures (PROMs) are considered to represent the patient's perspective but are hardly used in the clinical practice of kidney transplants [47]. However, the benefits of PROMs are mainly described in terms of better doctor-patient communication and improved healthcare self-management of patients [48] thus leaving out the possibilities of value creation in the patient's sphere. We can imagine that in the future PROMs, being the backbone of value-based healthcare (VBHC), evolve and take the daily life of transplant recipients into consideration. In our view, accepting the paradigm that healthcare organizations are the enablers of value creation, and that organ transplant recipients are the creators of value-in-use, would lead to a more prominent role for patients' self-determination [49]. Whereas VBHC is aiming to create value *for* the patient, we argue that value is created *with and by* the patient. On this basis, we would urge the intensification of patient involvement in designing healthcare services on the grounds that patients are the co-creators of value in healthcare and well-being [50–54].

CONCLUSION

The well-being of organ transplant recipients is not only realized through good medical practice. Keeping the graft in good condition and sustaining long-term graft survival are important facilitators for organ recipients to regain their lives. Embracing the paradigm of S-D logic by the professional transplant community may lead to a supportive healthcare service system that in addition to high medical quality transplants, also takes into consideration the capabilities of transplant recipients to regain their daily life, in all its aspects. After all, transplant recipients could sing along with Bon Jovi "It's my life and it's now or never."

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

WS drafted the original manuscript, MdJ and KA provided feedback on different versions of the manuscript. All authors were involved during the whole process from idea generation until finishing the manuscript.

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Dietary Guidelines Post Kidney Transplant: Is This the Missing Link in Recovery and Graft Survival?

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The physiology of a transplanted kidney is affected from the moment it is separated from the donor. The risk of complications arising from surgery are highly associated with ischemic-reperfusion injury (IRI) due to the effects of hypoxia and oxidative stress during the procurement, preservation and reperfusion procedures. Hypoxia promotes the formation of reactive oxygen species (ROS) and it seems apparent that finding ways of optimising the metabolic milieu for the transplanted kidney would improve recovery and graft survival. Studies have demonstrated the benefits of nutrition and antioxidant compounds in mitigating the disturbance of energy supply to cells post-transplant and at improving long-term graft survival. Particularly in patients who may be nutritionally deficient following long-term dialysis. Despite the high incidence of allograft failure, a search of the literature and grey literature reveals no medical nutriti on therapy guidelines on beneficial nutrient intake to aid transplant recovery and survival. This narrative review aims to summarise current knowledge of specific macro and micronutrients and their effect on allograft recovery and survival in the perioperative period, up to 1-year post transplant, to optimise the metabolic environment and mitigate risk to graft injury.

Keywords: kideny transplantation, nutrition guidelines, graft survival, post kidney transplant care, diet post transplant

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INTRODUCTION

The physiology of a transplanted organ is affected from the moment it is separated from the donor. The risk of complications arising from surgery are highly associated with ischemia-reperfusion injury (IRI) due to the effects of hypoxia and oxidative stress during the procurement, preservation and reperfusion procedures [1, 2]. As hypoxia promotes the formation of reactive oxygen species (ROS), it seems apparent that finding ways of improving antioxidant levels would optimise the milieu within which the transplanted organ is placed.

Nutrition is broadly accepted as playing a role in optimizing patients' health pre- and post-transplant, and requirements for different nutrients change significantly as kidney function declines. Renal insufficiency is associated with significant changes in electrolyte handling and cellular balance of sodium, potassium, phosphate and calcium, all of which are biologically vital. Dietary restriction contributes significantly to reducing kidney disease progression in more advanced disease [3, 4]. Dietary restrictions limit the options of access to whole foods rich in these minerals, such as vegetables, dairy and nuts, which can cause patients to increase their intake of ultra processed foods (UPF). UPFs typically contain additives, preservatives, artificial sweeteners, and emulsifiers, with

limited dietary fibre, all of which impact the biodiversity of the microbiome [5]. Kidney transplant recipients (KTR) are therefore at risk of nutritional deficiencies by the time they receive their donor organs, affecting antioxidant status, and potential imbalance in the gut microbiota, with increased production of uremic toxins [4, 6, 7].

The Role of the Gut Microbiome

Evidence suggests that gut microbiota play an important role in the metabolism, storage, and expenditure of energy and nutrients, and play a pivotal role in host immunity, and metabolic function [8, 9]. The integrity of the gut microbiome therefore affects the host's ability to absorb nutrients and regulate immunity [9].

Dysbiosis of intestinal flora is associated with complications in KTR, and many patients experience dysbiosis particularly in the first month post-transplant [10–12]. The causes of dysbiosis are multifactorial and can be assigned to the use of preparative regimens prior to transplantation as well as prophylactic antibiotics and immunosuppressant drugs [13]. Dysbiosis may influence graft outcomes, causing acute rejection, infection, renal fibrosis, and modification of drug metabolism [8, 14, 15].

Given the ability of the microbiota to influence isoimmunity and drug metabolism, data suggest that modifying the microbiota could contribute to more targeted immunosuppressive and post-transplant complication therapies, to improve graft survival and patients' quality of life (QoL) [13, 16, 17]. Diet modification particularly the inclusion of prebiotic and prebiotic foods is beneficial in altering an abnormal microbiota to produce the host's own antimicrobial substances, thereby improving immune function and graft survival [18, 19]. These prebiotic foods contain high amounts of fibre which serve as a food source for many of the gut microbiota, and a commensal partnership exists between the host and these bacteria [20].

While there is consensus on the increased risk of foodborne infection, especially in the first 6 months post-transplant, recommendations for the avoidance of consuming fresh fruit and vegetables vary across national guidelines [21, 22]. Several studies have questioned whether these protective diets provide any significant benefit in terms of infection rates, compared to a non-restrictive diet and may contribute to nutritional deficiencies [23, 24]. A common metric of gut health is the diversity of microbial species, and any acute changes can modify this composition within just 24 h [25, 26]. There is currently a lack of relative evidence referring to the microbiota in renal transplantation, with most studies conducted on animals [8, 27]. Research is therefore needed to understand the implications of chronic dysbiosis and its effect on graft survival in humans.

As nutrition is a vast subject, we acknowledge that this review does not cover all aspects of nutrition that might affect individual patients. We therefore focus specifically on nutrients that are highly monitored during ESKD to determine their effect on allograft health post-transplant and highlight the relevance of continued monitoring particularly in the critical early (up to 1 year) period post post-transplant.

MATERIALS AND METHODS

Published data were searched using the Medline National Library of Medicine, MEDLINE and Embase. No date restriction was applied, to broaden the search, however only English language papers were included. Search terms used included Diet, Nutrition Therapy, Dietary Guideline*Intervention* Nutrition*, Policy, AND Transplant*, Renal, Kidney Transplantation. 68 papers were identified, and after initial review of titles and abstracts for relevance, three duplicates were removed. A secondary review revealed no papers focused specifically on dietary guidelines post kidney transplant, although 20 covered individual macro and micronutrients which served as thematic insight for this paper. A grey literature search within the major national and international Kidney transplant organisations was also conducted to confirm whether any nutrition guidelines were available for post-transplant support. None were found (**Figure 1**). A narrative review, adopting a systematic synthesis of the available evidence of the individual macro and micronutrients was conducted with all papers reviewed by authors. Thematic analysis was identified by the primary author and confirmed by author 2 and 3. These themes will be discussed here.

RESULTS

Our findings show a paucity of specific dietary recommendations for KTR, and the studies currently available focus on single nutrient intakes, and not on the overall eating pattern. Considering that individuals do not typically consume nutrients in isolation it is challenging for single nutrient interventions to demonstrate conclusive effects and modifying dietary patterns as a whole may present a more realistic alternative or provide a complementary approach to single-nutrient interventions. We discuss these individual nutrients here, and demonstrate how the composition of the diet, particularly one that focuses on lower carbohydrate intake may be of increased relevance to graft survival.

Macronutrients: Protein

Protein requirements change during various phases post-transplant. The first few weeks post-transplant are characterized by increased nutritional demands due to the associated stress of surgical insult to the body and the high doses of immunosuppressive medications [28]. During this critical phase large glucocorticoid doses cause accelerated protein catabolism to achieve positive Nitrogen balance and improve wound healing while conserving muscle [29, 30]. There are currently no agreed guidelines on a recommended protein intake for KTR, although a review by Chadban et al [29] recommends around 1.4 g/kg/day protein intake during the first 4 weeks post transplantation to reverse negative Nitrogen balance and increase muscle mass. This was also found protective in reducing the risk of increased fat mass and muscle loss up to 1 year post transplant. Once patients are on a maintenance diet, research suggests a distinction be made between diabetic and

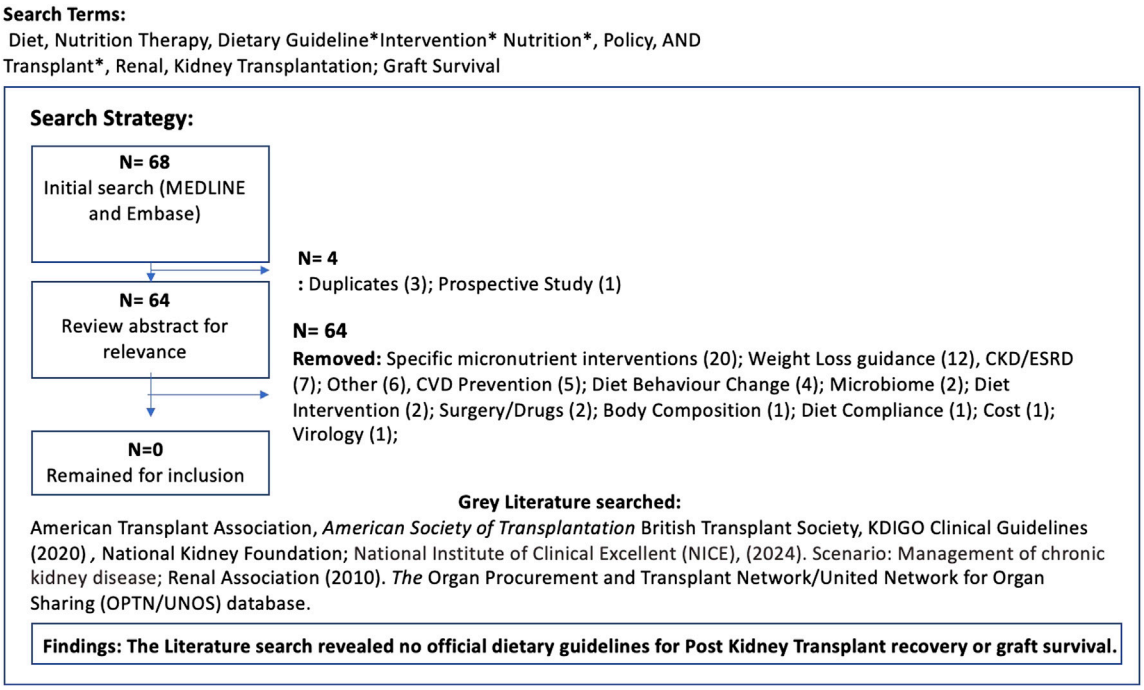

FIGURE 1 | Literature review strategy: post kidney transplant dietary guidelines.

non-diabetic KTR patients, advocating slightly higher protein requirements in diabetic patients (0.8–0.9 g/kg/day vs. 0.6–0.8 g/kg protein/day) based on the beneficial effects of protein in stabilising blood glucose [31, 32].

KTR frequently suffer with severe fatigue, which ultimately affects quality of life (QoL), and the role of protein in muscle repair, energy metabolism and neurotransmitter production (such as dopamine and serotonin) are well documented [33, 34]. A cross-sectional study, involving 730 stable KTR [median age 58 years (IQR 48–65), 57% male] with a mean protein intake of 82.2 ± 21.3 g/d were assessed to examine the association of protein intake with fatigue and QoL. Moderate and severe fatigue were present in 254 (35%) and 245 (34%) of KTR. Higher protein intake was significantly associated with lower risk of moderate fatigue (OR 0.89 per 10 g/d; 95%CI 0.83–0.98, $p = 0.01$), severe fatigue (OR 0.85; 95%CI 0.78–0.92, $p < 0.001$) and was associated with higher physical component summary scores for QoL (β 0.74 per 10 g/d; 95%CI 0.39–1.09, $p < 0.001$) [35]. This suggests that higher protein intake is independently associated with lower risk of moderate and severe fatigue and better QoL in KTR. It is important to note that enhanced protein intake alone, without resistance training may limit this benefit, due to the anabolic stimulus that exercise provides in muscle maintenance [36].

Several studies have however found that restricting dietary protein in KTR with chronic allograft nephropathy or chronic rejection may be beneficial, with respect to kidney function; however, further research is needed to identify the magnitude of benefit and a safe level of intake for this patient group [37, 38].

Carbohydrates

Metabolic disorders after kidney transplantation are common, and various dietary approaches have been studied regarding their effects on co-morbidity progression such as weight gain, hypertension, hyperlipidaemia, and insulin resistance [39]. Exposure to immunosuppressive medications such as glucocorticosteroids can cause or worsen preexisting hyperglycemia and weight gain [40–44], and regulating blood glucose has favourable downstream implications in slowing kidney disease progression [45–47].

As carbohydrates are the major contributor to post prandial hyperglycemia, increasing evidence highlights the benefits of very low-carbohydrate (ketogenic) diets to reduce inflammation, maintain euglycemia and weight, by improving satiety, reducing hyperglycemia and hyperinsulinemia. [48–50]. These diets are generally cautioned against for individuals with impaired kidney function, partly due to concerns about increased protein intake, which is associated with hyperfiltration and potentially, a decline in kidney function [51–53]. While classification of these diets differ greatly within the literature, differences are based on the proportion of total daily energy from carbohydrate and/or absolute carbohydrate intake [54]. Dietary analysis of very low carbohydrate studies usually report daily protein intake from 0.6 g/kg to 1.4 g/kg; which is below the high protein threshold (≥2.0 g/kg) believed to be of concern [55, 56].

The available literature on very low carbohydrate diets in KTR is scarce, although several studies recommend it as a therapy for preventing or assisting in recovery from ischemic and traumatic injuries [57–59]. The extensive topic of ketone

body metabolism is beyond the scope of this article, but in brief, when following a keto diet (KD) or during fasting, fatty acids are relocated from adipocytes to liver cells, and transformed into the Acyl-CoA form, then transported to the liver to produce ketone bodies, which provide an alternative form of ATP energy [60]. Since disturbances in the energy supply of cells during ischemia cause a transient interruption of normal blood flow to the kidney, there is an increase in oxidative stress and inflammation [61]. Ketone bodies have demonstrated nephroprotective effects in IRI, due to their ability to suppress the concentration of proinflammatory factors, such as tumour necrosis factor alpha, interleukins including IL-6; IL-1β, IL-18, IFN, and decreased expression of the NF-κB and MCP-1 which induce the expression of various proinflammatory genes [57, 62]. The natriuretic and diuretic effect of the KD may also provide additional kidney protection by helping to alleviate sodium retention and improve systemic and glomerular blood pressure [63, 64].

As there is currently no agreement on isocaloric comparisons recommending a specific carbohydrate intake for KTR, clinicians are challenged to provide risk assessments and guidance [65]. While the KD implies an increased intake of fat, this definition is not standard across studies, and it is important to distinguish between the types of fat and their ratios in the overall diet, which will be discussed in the section below [66].

Fats

There are currently no specific recommendations for dietary fat intake post kidney transplant, and patients are advised to follow the recommendations for the general population [31]. There is also no consensus on what the optimal ratio of n-6: n-3 polyunsaturated fats (PUFA) should be. Few studies investigate Essential Fatty Acid (EFA) deficiency in KTR, although low intakes have been attributed to renal hypertension, mitochondrial activity disorders, Cardiovascular Disease (CVD), type 2 diabetes, and decreased resistance to infection [67, 68].

Inflammation is part of the body's immediate response to injury or infection, and it begins the immunological process of eliminating pathogens and toxins to repair damaged tissue [69]. Although inflammation is a normal response, when it occurs in an uncontrolled or inappropriate manner excessive damage and disease to the affected tissue(s) can ensue. Dyslipidaemia is a known risk factor for CVD and evidence suggests that KTR have significantly lower serum content of potentially beneficial Polyunsaturated Fatty Acids (PUFA) compared to CKD patients not on dialysis [70]. PUFAs help regulate the antioxidant signalling pathway and modulate inflammatory processes. Both Omega 6 and Omega 3 play a key part in balancing inflammation to achieve homeostasis. Several sources suggest that humans evolved on a diet that had a ratio of omega-6 to omega-3 EFA of about 1:1; whereas today, Western diets have a ratio of approximately 10:1 to 20:1 [71, 72]. While pro-inflammatory omega 6 plays an important part in host defence, by creating a hostile environment for microbes and later by initiating tissue repair, recovery, and maintenance of homeostasis, prolonged (unresolved) inflammation can cause tissue damage and metabolic changes [73]. By contrast, Omega −3 (n-3) have shown improved renal and cardiovascular prognosis, and protective benefits against inflammation and overall mortality in KTR, due to their antithrombotic, anti-inflammatory, and antiarrhythmic effects [74–77].

In one study investigating the effects of n-3 PUFA supplementation on kidney allograft function and lipid profile, 60 long-term, first time KTR were assigned to 2 groups: a CON group ($n = 28$), who continued with their usual diet, and the DIET group ($n = 32$), who followed an n-3-PUFA rich diet for 6 months to investigate changes in n-3 PUFAs intake; the n-6: n-3 PUFAs ratio, systemic inflammation markers, and renal function. At 3 and 6 months the DIET group had significantly higher n-3 PUFA levels and a markedly lower n-6: n-3 PUFA ratio than baseline. This group also had reduced systemic inflammation with decreased plasma total cholesterol, triglycerides, C-reactive protein, and decreased interleukin (IL)-6. While eGFR remained unchanged, this group also experienced 50% reduction in proteinuria and microalbuminuria compared to baseline [78].

Further clinical studies are needed to confirm beneficial ratios of n6: n3, particularly in the initial weeks and months post-transplant, to gauge the positive effects of controlled inflammation as part of the healing process, and the protective effects of n3 in renal function long term.

Micronutrients

Sodium

The literature regarding sodium intake and hypertension in KTRs is scarce and gaps in knowledge still exist on the exact amount needed to optimize graft outcomes and reduce the risk of CVD. This is mostly due to the lack of clarification on the best methods to measure sodium intake; and the often-complex co-morbidities experienced by KTR. The 2012 KDIGO Clinical Practice Guideline recommend a salt intake to <90 mmol (<2 g)/day of sodium (corresponding to 5 g of sodium chloride) for CKD patients with high blood pressure, the same as for the general population [79]. The supporting evidence for this recommendation is of low quality as it references only an adequate intake for adults aged 19–50 years, "based on meeting sodium needs of apparently healthy individuals." This infers that the guidelines are relevant to those who are moderately active, live in a temperate climate and have no metabolic diseases or compromised kidney function, which does not apply to KTR.

A 2024 literature review by Afsar et al investigating sodium intake and renal transplantation showed continued inconsistencies [80]. Some studies found no relationship between sodium intake and hypertension [81–83] while others found a positive association, although these studies were conducted on rats [84, 85]. Contrasting views also found no association between sodium intake and proteinuria/albuminuria in graft function [86] while others showed a positive association [87, 88].

Numerous studies highlight the effect of insulin on renal sodium transport and metabolism; and demonstrate that

TABLE 1 | Variations in potassium recommendations across the general and CKD population.

US food and nutrition board (IOM. 2005) [101]	The World Health Organization (WHO, 2012) [102]	K/DOQI, National Kidney Foundation (2000) [103]	Comprehensive review by Kalantar-Zadeh et al., (2017) [104]
4.7 g (120 mmol) per day in healthy adults	3.9 g (100 mmol) per day or at least 90 mmol/day (3,510 mg/day) in healthy adults. No specific guidelines for kidney disease (CKD stage 1–5)	Unrestricted potassium intake in non-dialysis dependent patients with CKD stage 1–5 In hemodialysis patients, up to 2.7–3.1 g/day and in peritoneal dialysis patients up to 3–4 g/day	Intake of 4.7 g/day in the early stages of CKD without risk of hyperkalaemia, but a dietary potassium restriction of less than 3 g (77 mmol) per day in CKD patients prone to hyperkalaemia

individuals with arterial hypertension have reduced insulin sensitivity and hyperinsulinemia, compared to subjects with normal blood pressure [89–91].

As a mineralocorticoid, insulin plays an important role in sodium balance, particularly in conditions of elevated circulating plasma insulin concentrations. Plasma insulin stimulates sodium reabsorption by the distal nephron segments, causing hyperfiltration and a rise in intra-glomerular pressure [64]. As carbohydrates are the major contributor to post prandial hyperglycemia and subsequent insulin secretion, it seems logical that to achieve sodium balance and insulin homeostasis it is necessary to modify the diet, by substitution of carbohydrates with lower carb alternatives [45, 92].

Prospective long-term, randomised controlled studies of the effect of the KD in KTR are warrened specifically investigating their effect on electrolyte imbalance, hyperfiltration and the downstream effects on allograft function [93].

Potassium

Disturbances of potassium balance is a frequent complication among KTR notably immediately post-transplant, and in those with suboptimal graft function and higher calcineurin inhibitor levels [94, 95]. Despite the high incidence and potential life-threatening implications, consensus on potassium management in KTR is lacking – with post-transplant medications and dietary induced hyperkalemia associated with decreased glomerular filtration rates and impaired sodium delivery in the distal nephron [96].There is currently a lack of research on the specific consequences of untreated hyperkalemia to KTR, although insights from CKD populations highlight the importance of maintaining normal serum K+ concentrations particularly in IRI post transplantation, where cells experience metabolic shifts that lead to the inhibition of sodium-potassium ATPase. This inhibition disrupts ion homeostasis, contributing to increased ROS production and subsequent cellular damage [97]. Potassium also helps regulate the inflammatory response by influencing the activation of immune cells and the release of cytokines. Post transplant K+ balance is also vital for cardiovascular and renal outcomes [98–100].

Dietary guidelines for potassium vary greatly across the literature and none are specifically directed at KTR (**Table 1**). KTR that do experience hyperkalemia are frequently advised to avoid high-potassium plant-based foods, although the associated effectiveness is weak as the bioavailability and metabolism of K+ is naturally influenced by the other nutrients consumed [105–107]. K+ from plant-based sources in particular have proved beneficial, as they provide alkali and antioxidant vitamins, trace elements and fibre, which promotes intracellular entry and excretion of K+ in stool by increasing faecal volume [108]. As constipation is a frequent symptom in KTR, restricting fibre-rich foods can impact intestinal microbiota composition and increase the risk of metabolic acidosis and inflammation [109–111].

The Influence of Insulin on K+ Balance

Multiple compensatory mechanisms are enhanced in CKD to maintain potassium homeostasis. Insulin facilitates the uptake of K+ into the cells by activating the Na+/Ka+-ATPas pump [112].

In hyperglycemia, elevated glucose leads to osmotic diuresis, causing significant loss of water and electrolytes, including K+, resulting in an apparent elevation of serum K+ while depleting cellular stores [100]. Studies show that reducing insulin requirements through reduced carbohydrate consumption improves insulin sensitivity which in turn helps to stabilise K+ levels [100, 113].

As new onset diabetes after transplant (NODAT) is a common complication occurring in up to 50% of KTR, there is a need for more specific dietary guidelines to optimise insulin balance [114]. Latest guidelines from *KDIGO (2023)* [115] contain no references to dietary recommendations for K+, despite commendation that "a healthy diet should be maintained."

Vitamin D

Numerous studies demonstrate a high prevalence of vitamin D deficiency in KTR, likely due to the effects of immunosuppressive regimens and renal function impairment which affects the ability of the kidneys to convert 25-hydroxyvitamin D [25(OH)D] into 1,25-dihydroxyvitamin D [1,25$(OH)_2$D] (the active form), and advice that transplant recipients avoid sunlight to minimise the risk of skin cancer [116, 117]. Existing research in KTR highlights the challenges of achieving adequate vitamin D through diet alone and that even after successful kidney transplantation, the activity of 25-dihydroxyvitamin D may not fully normalize [118]. Supplementation is therefore considered more effective, particularly in vitamin D deficiency and excessive immune inflammation [119–121].

Vitamin D has an established function in immunological health, due to its role in calcium homeostasis and restoring mitochondrial membranes by regulating intracellular Ca^{2+} concentrations to decease ROS production in IRI [122]. Several studies show that low levels of 25(OH) vitamin D can

have deleterious effects on renal allograft health and increase the risk of NODAT [123–127]. Severe vitamin D deficiency is defined as having a serum 25OHD concentration of <10 ng/mL (25 nmol/L) [128]). KDIGO (2020) guidelines for patients with CKD (stage 1–5) suggest that vitamin D deficiency and insufficiency be treated using strategies recommended for the general population. However, a 2015 study of 289 KTR showed that vitamin D status is negatively affected by calcineurin inhibitors (specifically tacrolimus), the most commonly used immunosuppressant, but not experienced in newer mTOR inhibitors, such as sirolimus and rapamycin [117]. Appropriate management of immunosuppression therapy and monitoring of vitamin D status in KTR therefore warrants a more careful and individualised approach compared to the general population.

It is worth noting that studies on vitamin D deficiency in KTR only proves association and adverse outcomes, but not causality. Continuation of the primary disease (i.e.,: presence of CKD) or a *de novo* disease in the kidney graft could also contribute to proteinuria, worse kidney function and mortality [120]. Larger prospective and interventional RCTs are needed to fully assess the influence of vitamin D on post-transplant outcomes, and the benefits of long-term supplementation.

Vitamin C

KTR are prone to vitamin C deficiency mostly due to the potential remnant long-term effects of dialysis and higher requirements due to the enhanced pro-oxidative and pro-inflammatory status following IRI [129, 130]. Vitamin C is a powerful biological antioxidant which serves as cofactor for several enzymes involved in anti-inflammatory responses, collagen hydroxylation, carnitine and catecholamine biosynthesis [131]. KTR with low levels of vitamin C are therefore at increased risk of poor wound healing and infection immediately post-surgery, and face higher risk of long-term graft failure, due to reduced biosynthesis of collagen and regulatory T cells [132–134].

In a trial assessing Vitamin C in 598 KTR at 3-, 6-, 12-, 24-, and 60-month post-transplantation, Vitamin C deficiency was defined as plasma vitamin C ≤ 28 μmol/L [135]. At all measurement points, KTR had lower plasma vitamin C than potential donors (30–41 μmol/L vs. 58 μmol/L), with deficiency ranging from 46% (6-month post-transplantation) to 30% (≥1-year post-transplantation). Dietary vitamin C intake and vitamin C supplementation were associated with lower odds (OR per 100 mg/day 0.38, 95% CI 0.24–0.61 and OR 0.21, 95% CI 0.09–0.44, respectively). This suggests a strong need for vitamin C analysis and potential supplementation, particularly in individuals with delayed graft function.

Supplemental doses of vitamin C of 90 mg to 3 g/day are considered safe, with mild adverse effects, including gastrointestinal disturbances [136]. Studies on long term, high dose supplementation show increased risk of kidney stones (particularly in males with renal insufficiency), due to increased urinary excretion of oxalate [137, 138]. This risk is not replicated in dietary vitamin C due to the saturable absorption of vitamin C from the gastrointestinal tract [139], and the fact that most dietary sources (such as fruit and vegetables) include a high water content.

The Effect of Vitamin C on Delayed Graft Function

In IRI, endothelial cells are activated by the upregulation of pro-inflammatory cytokines. Vitamin C reduces inflammation and endothelial permeability by increasing pro-inflammatory cytokines and phagocytes that contribute to ROS reduction [41, 42, 140, 141]. In a small (19 participant) double-blinded RCT, investigating the effect of vitamin C on delayed graft function (DGF), KTR in the treatment group received an intravenous vitamin C infusion (70 mg/kg diluted in 0.45% saline), with the control group receiving only the dilute solution. The incidence of DGF was not significantly different between the groups after a single dose of vitamin C, although the duration of DGF was substantially shorter in the vitamin C group than the placebo group (7.33 ± 5.68 versus 19.66 ± 0.57 days; P = 0.02) [142]. It is important to note that this study did not include the nutrition status of participants and therefore those with higher deficiency rates may have experienced more dramatic outcomes. Additionally, considering the short half-life of the vitamin and the nature of surgical delays, a bolus intravenous dose of vitamin C may have produced more accurate results.

While vitamin C supplements, particularly in the first month post-transplant might provide a safer and more measurable form of intake, the sodium content of vitamin C preparations should be considered, particularly in sodium-restricted patients [70, 136].

DISCUSSION

Our research showed a positive association between poor nutrition status and impact on allograft recovery and survival. There is consensus grounded in evidence that transplant patients have distinct nutritional needs, with many KTR being nutritionally deficient by the time they receive their donor organ, placing them at increased risk of IRI, graft failure and mortality [143, 144]. There are currently limited studies investigating the longitudinal dietary intake of KTR, yet as this group are still considered a subset of patients with CKD they remain at high risk for progression to dialysis and mortality [145]. Our research highlights the difficulty of investigating the effect of individual macro- and micronutrients on allograft health although there is sufficient evident to highlight the negative impact of higher glycaemic diets, due to the downstream effects on renal sodium transport and the effects of hyperinsulinemia on intra-glomerular pressure. While most metabolic disorders post-transplant cannot be modified, diet and obesity are two factors that can safely be manipulated particularly in preventing metabolic disorders such as NODAT and CVD [146]. Obesity is associated with the prevalence and progression of CKD and low carbohydrate diets are recognised as an effective treatment in weight loss [147, 148]. In a context where the prevalence of nutrition-related health conditions is growing, there is an urgent need for nutrition education for physicians, who receive on average less than 24 contact hours of nutrition instruction across the medical degree [149]. Many do not feel comfortable, confident, or adequately prepared to provide

nutrition counselling and this gap in knowledge is contributing to poorer patient outcomes [150, 151].

Findings on PUFA intake demonstrated that the beneficial effects of anti-inflammatory n-3 depend primality on the dietary n6: n3 ratio. There is no consensus in the literature on what constitutes an optimal ratio, but the benefits of PUFA homeostasis demonstrate that for KTR there is a need for further research particularly to understand whether a higher n-6 ratio in the period immediately post-transplant might enhance immunity, tissue repair and recovery. Longer term maintenance strategies which include a reduction in carbohydrates will naturally have a higher percentage of protein and fat to compensate for the reduced calories [54] and future guidelines are needed to guide patients on optimal composition of dietary fats at various stages post-transplant.

Evidence on protein requirements post-transplant remain contentious and updated research is needed to ascertain a safe level of intake. It is likely that future guidance on protein intake will be based on prevailing renal function and the magnitude of benefit of higher intake to counteract protein catabolism and muscle protein wastage. Literature on hypovitaminosis D in KTR suggest that low sunlight exposure and the accelerated catabolism of vitamin D secondary to glucocorticoid use increases the risk of renal allograft failure and development of NODAT [123]. Evidence suggests that the general population in the UK are deficient of vitamin D, specifically in the winter months [122]. There is therefore a case for individualised monitoring and replacement therapy in this group.

KDIGO clinical guidelines (KDIGO, 2020) recognise that immunosuppression and graft function are only one component of healthcare, yet it makes no mention of the role of nutrition on allograft health and survival. This research demonstrates that monitoring of nutritional status post-transplant should be a clinical priority, with personalised dietary recommendations and provision for self-management strategies.

CONCLUSION

Despite significant medical advances over the last few decades, kidney transplants frequently do not function for the lifetime of the recipient, with more than a third of kidney grafts failing within 10 years following transplantation [152, 153]. It is widely known that nutrition influences all metabolic disease, health and recovery and more specific research is needed on the beneficial effect of targeted nutrition in establishing an optima metabolic milieu for the transplanted organ to thrive. Clear guidelines which are accessible to patients and clinicians are we suggest, essential since these will provide the missing link in post-transplant care.

AUTHOR CONTRIBUTIONS

Diagnosed with Type 1 diabetes (T1D) at age 11, the lead author (SS) has lived experience of the challenges of managing chronic health through diet. Later diagnosed with end stage renal disease and placed on a dialysis diet, she used this knowledge and experience to write her MSc thesis on the lived experience of the diet and lifestyle challenges of following a highly restrictive dialysis diet. Post kidney-transplant the lack of guidance was starkly evident, making the transition of adapting to managing the health of her new kidney extremely difficult. This lived experience insight has contributed to the detailed analysis and interpretation of the literature included in this review. All authors contributed to the article and approved the submitted version.

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Sleepiness and Health-Related Quality of Life Among Kidney Transplant Recipients in a Low-Middle Income Country: A Cross-Sectional Study

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This study aims to describe daytime sleepiness and health-related quality of life (HRQoL) among Lebanese kidney transplant (KT) recipients and to examine the medical, psychosocial and transplant factors related to them. It is a cross-sectional multi-center study involving KT recipients >18 years. Daytime sleepiness was assessed using ESS Questionnaire. HRQoL was measured using the SF-36 questionnaire. Social support was self-reported. A multivariable regression analysis evaluated factors associated with daytime sleepiness and HRQoL in our sample. 118 patients were recruited over a 2 years period. Excessive daytime sleepiness was prevalent in 12.7%. It was associated with Diabetes Mellitus (OR 3.97, 95% CI 0.94–16.81, $p = 0.06$) and obesity (OR 1.13, 95% CI 1.02, 1.27, $p = 0.02$). Social support and higher eGFR were associated with better scores on the MCS (β 24.13 $p < 0.001$ and β 0.26 $p < 0.01$) and the PCS (β 15.48 $p < 0.01$ and β 0.22 P 0.02). Conversely, depression and hospitalization were negatively associated with the MCS (β –27.44, $p < 0.01$ and β –9.87, $p < 0.01$) and the PCS (β –0.28.49, $p < 0.01$ and β –10.37, $p < 0.01$).

Keywords: kidney transplant, sleepiness, quality of life, social support, low-middle income, BMI

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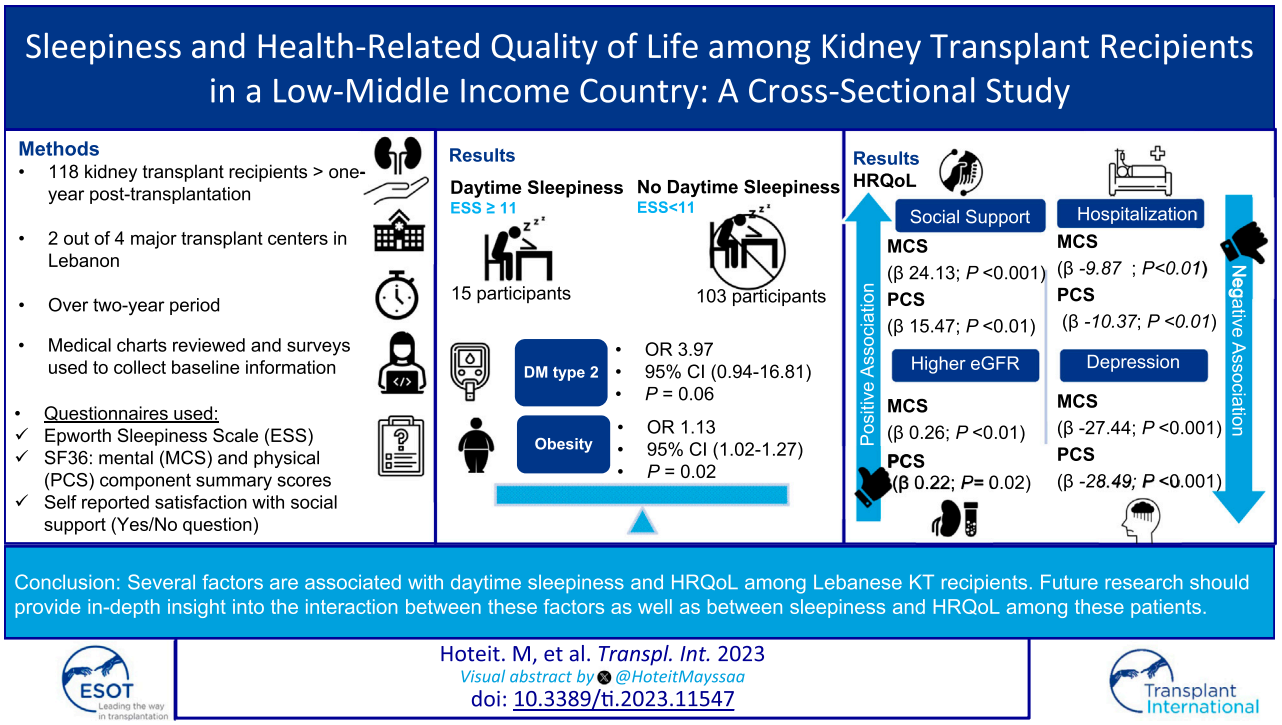
Abbreviations: BMI, Body Mass Index; CAD, Coronary Artery Disease; CKD, Chronic Kidney Disease; CKD-T, Chronic Kidney Disease in Kidney-Transplant; DM, Diabetes Mellitus; ESS, Epworth Sleepiness Scale; GAD-7, Generalized Anxiety Disorder; HRQoL, Health Related Quality of Life; IQR, Inter-Quartile Range; KT, Kidney Transplant; MENA, Middle East and North Africa; MCS, mental component summary score; OSA, Obstructive Sleep Apnea; PHQ9, Patient Health Questionnaire; PCS, physical component summary score; SD, standard deviations; SF 36, Short-Form Health Survey.



GRAPHICAL ABSTRACT |

INTRODUCTION

Kidney transplantation restores kidney function and alleviates many uremic symptoms and complications. Hence, sleep deficiency and poor sleep quality are less prevalent among Kidney transplant (KT) recipients than patients on maintenance dialysis. However, sleep deficiency and daytime sleepiness are still more common among KT recipients than the general population [1, 2]. In fact, poor sleep quality is widespread among KT recipients, with a frequency ranging from 30% to 62%, according to the Pittsburgh Sleep Quality Index (PSQI) [3]. Sleep disorders can either persist in chronic kidney disease (CKD) patients after transplantation, or develop as a *de novo* condition. Several biological and psychosocial factors may predispose KT recipients to increased prevalence of sleep deficiency and daytime sleepiness. In addition, immunosuppressive drugs can interfere with sleep and has been linked to non-adherence [4–6].

Regardless of the underlying sleep disorder, poor sleep quality and sleep deficiency culminate in daytime sleepiness. The latter can have a substantial impact on the health and wellbeing of patients. Nonetheless, it may also be associated with increased morbidity and mortality, as well as significant economic consequences such as increased healthcare utilization and lost productivity. Furthermore, poor sleep quality can weaken a KT recipient's immune system. It has recently been established that even a minor disruption in sleep results in a reduction in natural immunological responses as well as a drop in the generation of T-cell cytokines [4, 7]. Hence, sleep deficiency is a critical matter for KT recipients. Proper screening and management may enhance patient survival, halt the progression of chronic kidney disease (CKD-T), and extend the much-needed graft survival, in addition to improving their Health-Related Quality of life (HRQoL) [6].

Another fundamental component of KT recipients' wellbeing is HRQoL. For this particular population, HRQoL plays a crucial role in their overall satisfaction with life after transplantation and the impact of the transplant on their daily function and emotional state. HRQoL is rather a well-studied topic in KT recipients. Better HRQoL has been associated with better adherence to medications, enhanced social engagement and better long-term graft outcomes [8, 9].

Both sleep and HRQoL has biopsychosocial and cultural determinants. There is some evidence that older adults who possess robust social support networks might experience better sleep quality than those who do not [10]. Cultural factors such as eating habits, food content, race/ethnicity, gender roles, social class and cultural practices have been shown to affect sleep length [11]. Besides, cultural beliefs and values tend to shape our perception and experience of HRQoL. Factors such as social support, access to healthcare, spirituality and religion can influence our health behaviors and influence our perception of HRQoL. Thus, it is crucial to study sleep and HRQoL within the context of a specific culture/region.

Studies evaluating sleep disorders and HRQoL in KT recipients in the MENA region are almost non-existent. Lebanon belongs to the MENA region, which consists of

geographically, and culturally close countries. Our study aims to describe daytime sleepiness and HRQoL among Lebanese KT recipients and to examine the factors linked to them, in order to better understand and serve this patient population.

MATERIALS AND METHODS

Study Design, Settings and Participants

The study used a cross-sectional design, with participants recruited from the outpatient clinics of two major university hospitals in Lebanon over a 2 years period, from 1st June 2019 to 31st May 2021. Both hospitals are major transplant referral centers in the country, which has a total of four hospitals performing kidney transplants. Eligibility criteria were age >18 years old and kidney transplant performed >1 year at the time of recruitment.

Patients were first screened for eligibility by their primary nephrologist. Patients who agreed to participate, were contacted by the research assistant. If the participant had poor literacy, a trained research coordinator would go over the informed consent and questionnaires with them and a witness will co-sign the informed consent.

Measurements

Outcomes of Interest

Daytime Sleepiness

This study aimed to determine the prevalence of daytime sleepiness and HRQoL among KT recipients who are ≥1 year post-transplant. The Epworth Sleepiness Scale (ESS) Questionnaire was used to assess the presence of daytime sleepiness. The ESS is a validated eight-item questionnaire to measure a subject's expectation of dozing (falling into a light sleep) in eight situations. Dozing probability ratings range from 0 (no probability) to 3 (high probability) [12]. The score is divided into four categories: <6 is lower normal daytime sleepiness; 6–10 higher normal daytime sleepiness; excessive daytime sleepiness is above 10 and severe excessive daytime sleepiness is above 16. The participants were categorized into two groups: those scored < 11 as "Normal daytime sleepiness" group and those with a score ≥ 11 as "Excessive daytime sleepiness" group.

Health-Related Quality of Life

The Short-Form Health Survey (SF-36) was used to assess HRQoL perception. It is a widely used generic HRQoL measure with eight domains: physical functioning, role functioning-physical, role functioning-emotional, vitality, pain, general health, social functioning, and mental health [13]. The score for each domain ranges from 0 to 100. The higher the score, the more favorable the health outcome is. The SF-36 survey scores can be aggregated into two summaries: Mental component summary (which includes vitality, social functioning, role-emotional, and emotional wellbeing) and physical component summary (which include physical functioning, role limitations due to physical health problems, pain, general health).

Participants could choose between two languages: Arabic and English. Arabic is the official language of Lebanon and the MENA region. These instruments were chosen because they were the only ones validated in Arabic language [14–17] (**Supplementary Material**).

Data Collection and Covariates

In addition to collecting demographic data, the survey collected data on several factors, which were grouped under several themes: psychosocial variables, medical variables including cardiovascular risk factors and co-morbidities, and kidney transplant related variables. Mental health scores for anxiety and depression were assessed using the Generalized Anxiety Disorder 7 Questionnaire (GAD7) and the Patient Health Questionnaire (PHQ9), respectively.

The GAD7 is a seven-item questionnaire used to assess the severity of anxiety. Participants were categorized into two groups based on their scores: "No/mild anxiety" for scores ≤ 9, and "Moderate/severe anxiety" for scores ≥ 10. The PHQ9 is a nine-item tool to screen and measure severity of depression. Participants were categorized based on their scores into two groups: "No/mild depression" for scores ≤ 9, and "Moderate/severe depression" for scores ≥ 10. Both anxiety and depression severity are based on the frequency of the occurrence of DSM-IV criteria in the previous 2 weeks.

We measured perceived social support. It was self-reported and evaluated using a single question "Are you satisfied with your social support?" with a yes/no answer. Demographic information (participant's age, gender, educational background, marital and employment status and social habits including smoking and alcohol consumption) were self-reported. Information on the presence of comorbidities, body mass index (BMI), type of donor, time on dialysis, type of immunosuppression and laboratory data were retrieved from the patients' hospital files.

Ethical Considerations

The study was approved by the American University of Beirut's institutional review board and carried out in accordance with the 1975 Helsinki Declaration. All participants signed an informed consent form before being included in the study.

Statistical Analyses

Descriptive statistics were performed for all sample characteristics and outcome measures. For continuous variables, means and standard deviations (SDs) were reported and when non-normally distributed, medians and interquartile range (IQR) were reported. Categorical variables were described as numbers and percentages. When comparing participants with normal vs. excessive daytime sleepiness, comparisons of continuous variables were done using the independent t-test or the Mann-Whitney test and comparisons of categorical variables were based on Chi-Square test. We then performed age- and sex-adjusted logistic regression analysis to estimate association of each category of factors (psychosocial, medical and kidney transplant-related) with excessive daytime sleepiness defined by an ESS score ≥ 11. A multivariable logistic regression was then performed as a sensitivity analysis to assess the association of social support with excessive daytime sleepiness (taking into consideration two ESS thresholds:

TABLE 1 | General characteristics of the total number of patients.

	Total *N* = 118
Socio-demographics	
Age, years, mean ± SD	51.01 ± 13.62
Sex, M/F, n (%)	78/40 (66/34)
Marital Status, n (%)	
Married	85 (72)
Other (divorced/single/widowed)	33 (28)
Number of children, mean ± SD	2.37 ± 2.22
Boy child, median (IQR)	1 [0, 2]
Girl Child, median (IQR)	1 [0, 2]
Number of grand-children, median (IQR)	0 [0, 0]
Occupational Status, n (%)	
Working	67 (56.8)
Other (retired/never worked)	51 (43.2)
Highest Educational level, n (%)	
University	48 (40.7)
Illiterate and school level	70 (59.3)
Satisfied with social support, n (%)	97 (82.2)
Medical factors/CV risk factors/Comorbidities	
Hypertension, n (%)	96 (81.4)
CAD, n (%)	15 (12.7)
Diabetes mellitus, n (%)	39 (33.1)
Dyslipidemia, n (%)	38 (32.2)
Cancer	5 (4.2)
Autoimmune disease, n (%)	3 (2.5)
Smoking status, n (%)	
Never	56 (47.5)
Ex-smoker	37 (31.4)
Current	25 (21.2)
Alcohol consumption, n (%)	
Never	99 (83.9)
Social	17 (14.4)
Drinker	1 (0.8)
Binge	1 (0.8)
Height, mean ± SD	166.69 ± 8.98
Weight, mean ± SD	79.25 ± 17.74
BMI, mean ± SD, Kg/m^2	28.10 ± 5.39
Medical factors/Kidney transplant related	
Years of transplant, mean ± SD	9.27 ± 6.55
Type of transplant, n (%)	
Cadaveric	8 (6.8)
Living unrelated	44 (37.3)
Living related	66 (55.9)
Hospitalization last year, n (%)	46 (39.0)
Visit to psychiatrist, n (%)	4 (3.4)
Immunosuppression, n (%)	
Prednisone	112 (94.9)
Mycophenolate Mofetil	109 (92.4)
Cyclosporine	29 (24.6)
Azathioprine	2 (1.7)
Sirolimus	5 (4.2)
Tacrolimus	84 (71.2)
Everolimus	4 (3.4)
Regular medication intake, n (%)	118 (100)
Lowest serum creatinine, mean ± SD, mg/dL	0.96 ± 0.24
Delayed graft function, n (%)	4 (3.4)
Current serum creatinine, mean ± SD, mg/dL	1.50 ± 1.06
Current eGFR, mean ± SD, mL/min/1.73 m^2	55.89 ± 20.59
Mental health and SF-36 quality of life scores	
Known mental health problem, n (%) (one anxiety, one bipolar, on medications, one improved)	2 (1.7)
Anxiety, n (%)	
None or mild	89 (75.4)
Moderate or severe	29 (24.6)
Depression, n (%)	
None or mild	102 (86.4)
Moderate or severe	16 (13.6)
Daytime sleepiness, n (%)	
Normal daytime sleepiness	103 (87.3)
Excessive daytime sleepiness	15 (12.7)
Physical functioning, mean ± SD	76.86 ± 26.87
Role limitations due to physical health, mean ± SD	77.12 ± 38.61
Median (IQR)	100 (50–100)
Role limitations due to emotional problems, mean ± SD	84.46 ± 33.67
Median (IQR)	100 (100–100)
Energy/fatigue, mean ± SD	62.12 ± 24.51
Emotional wellbeing, mean ± SD	69.92 ± 21.23
Social functioning, mean ± SD	84.43 ± 25.31
Median (IQR)	100 (74.25–100)
Pain, mean ± SD	81.05 ± 27.26
Median (IQR)	100 (66.88–100)
General Health, mean ± SD	59.92 ± 23.02
Health change, mean ± SD	64.62 ± 28.18
Mental Component Score (MCS), mean ± SD	75.23 ± 19.86
Physical Component Score (PCS), mean ± SD	73.74 ± 21.27

(Continued in next column)

TABLE 1 | (*Continued*) General characteristics of the total number of patients.

Note. Categorical variables are presented as numbers (n) and percentages (%). Continuous variables are presented as means and standard deviations (SD) if normally distributed and as medians and interquartile range (IQR) if skewed.

≥10 and ≥11) by adjusting for medical indicators (BMI and diabetes, which were significantly associated with daytime sleepiness in age- and sex-adjusted models).

As for the HRQoL, internal consistency between the eight dimensions of the SF-36 questionnaire was evaluated by calculating Cronbach's alpha. Age and sex adjusted linear regression analysis was done for sociodemographic and medical factors associated with the mental and physical component summaries of the SF-36 score (MCS and PCS). We had multiple variables that we were interested in and we wanted to run a consistent method for all, to facilitate comparisons as well as interpretations, and for most part, there was not large violations of using linear regression models. All analyses were conducted using Statistical Package for Social Sciences (SPSS), version 25.0.

RESULTS

General Characteristics

A total of 124 adult kidney transplant recipients were approached to participate: 118 agreed to participate while six (5%) refused. The sociodemographic characteristics, comorbidities, kidney transplant related factors, mental health characteristics and SF-36 HRQoL scores of the participants are summarized in **Table 1**. Their mean age was 51 years and 66% were males. 91% of them were Lebanese while the remaining 9% were from neighboring

TABLE 2 | Comparison between those with normal daytime sleepiness versus those with excessive daytime sleepiness.

	Normal daytime sleepiness *n* = 103	Excessive daytime sleepiness *n* = 15	*p*-value
Socio-demographic factors			
Age, years, mean ± SD	50.91 ± 13.71	51.67 ± 13.38	0.84
Sex, M/F, n (%)	67/36 (65/35)	11/4 (73.3/26.7)	0.77
Marital status, n (%)			
Married	75 (72.8)	10 (66.7)	0.62
Other	28 (27.2)	5 (33.3)	
Number of children, mean ± SD	2.22 ± 2.04	3.4 ± 3.09	0.05
Number of grand-children, median (IQR)	0 [0, 0]	0 [0, 0]	0.50
Occupational status, n (%)			
Current or past working	95 (92.2)	14 (93.3)	0.78
Never worked	8 (7.8)	1 (6.7)	
Highest educational level, n (%)			
Illiterate/School level	58 (56.3)	12 (80)	0.09
University	45 (43.7)	3 (20)	
Satisfied with social support, n (%)	87 (84.5)	10 (66.7)	0.09
Medical factors/CV risk factors/Comorbidities			
Hypertension, n (%)	85 (82.5)	11 (73.3)	0.47
CAD, n (%)	12 (11.7)	3 (20)	0.40
Diabetes mellitus, n (%)	30 (29.1)	10 (66.7)	<0.01
Dyslipidemia, n (%)	34 (33)	4 (26.7)	0.77
Cancer, n (%)	5 (4.9)	0 (0)	0.99
Autoimmune disease, n (%)	3 (2.9)	0 (0)	0.99
Smoking status, n (%)			
Never	47 (45.6)	9 (60)	0.52
Ex-smoker	34 (33)	3 (20)	
Current	22 (21.4)	3 (20)	
Alcohol consumption, n (%)			
Never	87 (84.5)	12 (80)	0.71
Yes	16 (15.5)	3 (20)	
Height, mean ± SD, cm	166.47 ± 8.99	168.20 ± 9.03	0.49
Weight, mean ± SD, kg	76.96 ± 15.84	95.0 ± 22.29	<0.01
BMI, mean ± SD, kg/m^2	27.48 ± 5.06	32.40 ± 5.87	<0.01
Kidney transplant related factors			
Years of transplant, mean ± SD	9.50 ± 6.57	7.66 ± 6.39	0.31
Type of transplant, n (%)			
Cadaveric and living unrelated	47 (45.6)	5 (33.3)	0.37
Living related	56 (54.4)	10 (66.7)	
Hospitalization last year, n (%)	41 (39.8)	5 (33.3)	0.63
Visit to psychiatrist, n (%)	4 (3.9)	0 (0)	0.99
Immunosuppression, n (%)			
Prednisone	97 (94.2)	15 (100)	0.99
Mycophenolate Mofetil	94 (91.3)	15 (100)	0.60
Cyclosporine	25 (24.3)	4 (26.7)	0.99
Tacrolimus	73 (70.9)	11 (73.3)	0.99
Lowest serum creatinine, mean ± SD, mg/dL	0.97 ± 0.25	0.97 ± 0.17	0.97
Delayed graft function, n (%)	4 (3.9)	0 (0)	0.99
Current serum creatinine, mean ± SD, mg/dL	1.46 ± 1.04	1.78 ± 1.22	0.35
Current eGFR, mean ± SD, mL/min/1.73 m^2	56.75 ± 19.85	50 ± 25.11	0.33
Mental health and SF-36 quality of life scores			
Anxiety, n (%)			
None or mild	79 (76.7)	10 (66.7)	0.39
Moderate or severe	24 (23.3)	5 (33.3)	
Depression, n (%)			
None or mild	91 (88.3)	11 (73.3)	0.12
Moderate or severe	12 (11.7)	4 (26.7)	
Physical functioning, mean ± SD	79.71 ± 25.06	57.33 ± 31.50	<0.01
Role limitations due to physical health, mean ± SD	82.75 ± 34.39	45.83 ± 46.38	<0.01
Median (IQR)	100 (75–100)	25 (0–100)	

(Continued on following page)

TABLE 2 | (*Continued*) Comparison between those with normal daytime sleepiness versus those with excessive daytime sleepiness.

	Normal daytime sleepiness *n* = 103	Excessive daytime sleepiness *n* = 15	*p*-value
Role limitations due to emotional problems, mean ± SD	87.66 ± 30.22	66.68 ± 45.73	0.04
Median (IQR)	100 (100–100)	100 (0–100)	
Energy/fatigue, mean ± SD	62.33 ± 24.61	60.67 ± 24.56	0.81
Emotional wellbeing, mean ± SD	70.59 ± 20.85	65.27 ± 23.95	0.42
Social functioning, mean ± SD	86.37 ± 23.32	73.67 ± 33.14	0.15
Median (IQR)	100 (75–100)	100 (50–100)	
Pain, mean ± SD	82.51 ± 26.58	72.97 ± 30.30	0.26
Median (IQR)	100 (68–100)	80 (50–100)	
General Health, mean ± SD	59.42 ± 22.99	63.33 ± 23.73	0.55
Mental Component Score, mean ± SD	76.44 ± 18.91	66.92 ± 24.59	0.08
Physical Component Score, mean ± SD	75.64 ± 19.75	60.64 ± 26.94	<0.01

Note. Excessive daytime sleepiness is defined as ESS score ≥ 11. Continuous variables are compared using independent t-test and categorical variables are compared using Chi Square test.

TABLE 3 | Age and sex-adjusted logistic regression analysis for psychosocial and medical factors associated with excessive daytime sleepiness.

	Age and sex adjusted		
Variables	**OR**	**95% Confidence interval**	***p*-value**
Psychosocial factors			
Married	0.64	0.19, 2.16	0.47
Ref: other			
Number of children	1.25	0.99, 1.59	0.06
Education	3.05	0.81, 11.49	0.09
Ref: University level			
Working	1.03	0.30, 3.55	0.96
Ref: other			
Social support	0.353	0.09, 1.26	0.11
Depression	2.80	0.73, 10.76	0.13
Anxiety	1.62	0.50, 5.23	0.41
Comorbidities			
Hypertension	0.49	0.13, 1.84	0.29
CAD	1.76	0.40, 7.76	0.45
Diabetes mellitus	6.25	1.65, 23.61	<0.01
Dyslipidemia	0.66	0.18, 2.41	0.53
Smoking status: current	0.86	0.22, 3.38	0.83
Ref: other			
BMI	1.17	1.06, 1.30	<0.01
Kidney transplant-related factors			
Current serum creatinine	1.21	0.81, 1.79	0.35
Current eGFR	0.98	0.96, 1.01	0.26
Years of transplant	0.95	0.86, 1.05	0.33
Living related transplant	1.87	0.56, 6.26	0.31
Ref: Cadaveric and living unrelated			
Hospitalization last year	0.73	0.23, 2.32	0.59
CNI intake	0.61	0.12, 3.17	0.56

arab countries. 72% were married and 57% were working. The mean age of the graft was 9.27 ± 6.5 years. 81% had hypertension, 13% had coronary artery disease (CAD) and 33% had diabetes mellitus (DM). Their mean BMI was 28.1 ± 5.39. 39% were hospitalized in the last year prior to recruitment. Their mean eGFR was 55.89 ± 21 ml/min/1.73 m [2]. Among our sample, 25% had moderate/severe anxiety while 14% had moderate/severe depression. The mean/median scores for the individual and summary components of the SF-36 HRQoL scores are listed in **Table 1**. 82% answered that they were satisfied with their social support.

Daytime Sleepiness

Fifteen patients (12.7%) had excessive daytime sleepiness while 103 (87.3%) had normal daytime sleepiness. There was no difference in age, gender, marital status, and educational status

TABLE 4 | Multivariable logistic regression analysis assessing factors associated with excessive daytime sleepiness.

	OR	95% Confidence interval	*p*-value
Social Support	0.27	0.07, 1.09	0.06
Age	0.97	0.92, 1.02	0.25
Sex	1.20	0.29, 4.92	0.79
Diabetes	3.97	0.94, 16.81	0.06
BMI	1.13	1.02, 1.27	0.02

between the two groups. Those with excessive daytime sleepiness were more obese (mean BMI 32.4 ± 6 versus 27.48 ± 5.06, $p < 0.01$) and had more DM (67% versus 29%, $p < 0.01$). Among the different components of the SF-36 HRQoL scores, those with excessive daytime sleepiness scored significantly lower on physical functioning. The mean score for physical component score was 60.6 versus 75.6 ($p = 0.01$). Details about the differences between the two groups are summarized in **Table 2**. An Age and sex-adjusted logistic regression analysis (**Table 3**) followed by a multivariable logistic regression analysis showed that DM and BMI are associated with excessive sleepiness diabetes (OR 3.97, 95% CI 0.94, 16.81, $p = 0.06$) and obesity (OR 1.13, 95% CI 1.02, 1.27, $p = 0.02$, respectively) (**Table 4**).

Health-Related Quality of Life

The internal validity of the different components of the SF-36 scores in our transplant sample was tested using Cronbach's Alpha and it was very acceptable (**Supplementary Table S1**). All medical, psychosocial, and demographic factors were analyzed to assess their association with both the physical and mental component summaries of SF36 scores. Social support was associated with higher scores on both the mental and physical component summaries of the SF-36 (β 24.13, $p < 0.01$ and β 15.47, $p < 0.01$, respectively) as well as higher eGFR (β 0.26, $p < 0.01$ and β 0.22, $p = 0.02$, respectively). On the other hand, depression was associated with lower scores on both the MCS (β −27.44, $p < 0.01$) and the PCS (β −28.49, <0.01). The same applies to hospitalizations in the previous year (β −9.87, $p < 0.01$ and β −10.37, $p < 0.01$, respectively) (**Table 5**).

Social Support

84.5% of those with normal daytime sleepiness reported satisfaction with social support compared to 66.7% of those with excessive daytime sleepiness ($p = 0.09$). In a multivariate logistic regression, the association of social support with sleepiness varied according to the threshold of ESS used. When excessive daytime sleepiness was defined by a lower ESS threshold (score > 9), it was significantly associated with social support even after adjusting for depression (OR 0.17, 95% CI 0.04–0.75, $p = 0.02$) (**Supplementary Table S2**). With an ESS cutoff >10, satisfaction with social support was protective against excessive sleepiness but it did not reach statistical significance (OR 0.27, 95% CI 0.07–1.09, $p = 0.06$) (**Table 4**). This remained true when depression was added to the model (**Supplementary Table S3**). As for the HRQoL, social support remained significantly associated with the SF36 MCS score after adjusting-on top of age and sex-to depression (β 0.30, 95% CI 6.14–25.01, $p < 0.01$) (**Supplementary Table S4**).

DISCUSSION

Daytime sleepiness is rather prevalent among our KT recipients. Obesity and diabetes mellitus seem to contribute to it. Social support was positively associated with daytime sleepiness and its effect might be mediated by depression. Enhanced kidney function and perceived social support were linked with improved HRQoL ratings. Conversely, a history of hospitalization within the past year and the presence of depression exhibited connections with diminished HRQoL scores.

The prevalence of excessive daytime sleepiness in our transplant population was 12.7%. This is congruent with studies conducted in the general population, which revealed a prevalence ranging from 2.5% to 23% depending on the country of the study: 2.5% in Japan [18], 11% in Australia [19], 19% in Saudi Arabia [20], 21% in rural Canada [21], and 23% in Germany, [22]. There is not much published research on the prevalence and relevance of daytime sleepiness in KT recipients. The Epworth Sleepiness Scale data from three Swiss transplant hospitals found a 51% prevalence of daytime sleepiness [23]. This is significantly higher than our findings and could be explained by the lower ESS cutoff used (>6 vs. 11 in our study), as well as the older age of their study population (mean age 59 vs. 51). It is worth noting that the non-response rate in the Swiss study was 38%, with non-responders being much younger than responders. This could have contributed to the results being overestimated, as sleep difficulties are more common in older people. This is due to a combination of factors that come with aging rather than aging itself, such as physical and psychiatric illness, increasing medication use, changes in the circadian clock, and a higher prevalence of certain sleep disorders [24].

Our study showed that daytime sleepiness is positively associated with physical factors like obesity and DM. Weight gain is common during the first year after transplantation and thereafter [25]. Obesity (BMI ≥30 kg/m^2) has been linked to fatigue and sleep disorders such as daytime sleepiness and obstructive sleep apnea (OSA), with obese participants being twice as likely as non-obese people to have excessive daytime sleepiness [26, 27]. In the transplant population, increased BMI is particularly important because it may have more serious implications, such as reduced graft survival and increased cardiovascular risk [28, 29]. The presence of OSA may have mediated the association we observed between high BMI and daytime sleepiness. Unfortunately, we were unable to determine whether patients were diagnosed with or treated for OSA.

Additionally, sleep disorders are highly prevalent among adults with DM [30]. In fact, sleep disorders may be a novel risk factor for the development of insulin resistance and DM. Getting sufficient sleep is essential for proper insulin secretion and glucose metabolism. This is particularly important in the transplant population who are inherently predisposed to steroid and immunosuppression induced DM. On the other hand, sleep disturbances can be induced by pain from common consequences

TABLE 5 | Age- and sex-adjusted linear regression analysis for factors associated with the mental component summary and the physical component summary of the SF-36 health-related quality of life scores.

MCS				
	Standardized coefficient	**Unstandardized coefficient B**	**95% CI for B**	***p*-value**
Married	−0.030	−1.327	−9.700, 7.046	0.75
Ref: other				
Working	0.054	2.173	−5.908, 10.255	0.59
Ref: other				
Education	0.068	2.75	−4.499, 9.996	0.45
Ref: university level				
Social support	0.467	24.130	15.520, 32.741	<0.001
Depression	−0.475	−27.440	−36.820, −18.060	<0.001
Smoking	−0.031	−1.501	−10.321, 7.318	0.73
Hypertension	−0.147	−7.450	−16.925, 2.024	0.12
Coronary artery disease	−0.093	−5.512	−16.645, 5.621	0.33
Diabetes	−0.027	−1.122	−9.300, 7.055	0.78
Dyslipidemia	0.024	1.001	−7.161, 9.162	0.81
BMI	−0.148	−0.545	−1.210, 0.120	0.11
Years of transplant	−0.037	−0.113	−0.687, 0.461	0.69
Living related transplant	−0.033	−1.303	−8.933, 6.328	0.73
Ref: other				
eGFR	0.267	0.258	0.086, 0.430	<0.01
Hospitalization last year	−0.243	−9.869	−16.989, −2.749	<0.01
PCS				
	Standardized coefficient	**Unstandardized coefficient**	**95% CI**	***p*-value**
Married	−0.013	−0.611	−9.692, 8.469	0.89
Ref: other				
Working	0.150	6.432	−2.258, 15.123	0.14
Ref: other				
Education	−0.057	−2.450	−10.313, 5.413	0.54
Ref: university level				
Social support	0.279	15.468	5.346, 25.590	<0.01
Depression	−0.461	−28.492	−38.784, −18.200	<0.001
Smoking	0.073	3.782	−5.758, 13.322	0.43
Hypertension	−0.101	−5.499	−15.829, 4.831	0.29
Coronary artery disease	−0.160	−10.185	−22.156, 1.787	0.09
Diabetes	−0.021	−0.959	−9.825, 7.908	0.83
Dyslipidemia	0.028	1.267	−7.581, 10.114	0.77
BMI	−0.125	−0.494	−1.217, 0.230	0.18
Years of transplant	−0.019	−0.062	−0.685, 0.560	0.84
Living related transplant	0.047	1.995	−6.273, 10.263	0.63
Ref: other				
eGFR	0.216	0.223	0.034, 0.412	0.02
Hospitalization last year	−0.239	−10.371	−18.105, −2.637	<0.01

of DM such as peripheral neuropathy or nocturia from inadequate glycemic control [30–32].

Although the results were not statistically significant, daytime sleepiness was positively associated with perceived social support. Mechanisms that may relate social support with better sleep quality include shielding against loneliness and social isolation, dampening stress levels, providing emotional support, embracing healthy sleep habits, and entraining circadian rhythms. On the other hand, sleepiness leads to less social interest, motivation and interactions. All these points indicate that the link between sleepiness and social functioning is possibly bidirectional with each entity influencing the other [33–35]. This association between daytime sleepiness and social support might have been mediated by depression. Indeed, studies have shown that depression is linked bi-directionally with sleep disorders [36], and since KT recipients are prone to depression [37], this could imply more sleep disorders in this group. As a result, clinicians are urged to look for the other comorbid disorder when sleepiness or depression are identified. Although we cannot draw solid conclusions from our cross-sectional design - due to its limited scope, which involved a single question to assess social support, a solitary subjective questionnaire to screen for daytime sleepiness, and reduced statistical significance-, it is important to underscore the potential role of social support in KT recipients in mitigating daytime sleepiness.

Along the same line, our study demonstrated a positive influence of social support on HRQoL scores within our cohort. This appears to be consistent across various countries. A French study evaluating HRQoL based on four fundamental dimensions—self-esteem, financial assistance, informational guidance, and emotional backing—revealed a

significant association between deficient social support and lower HRQoL scores [38]. This correlation was observed in a Bahraini study as well, where married individuals exhibited notably higher HRQoL scores compared to their unmarried counterparts. This disparity was attributed to the additional social and financial support married participants received from their spouses and children, exerting a positive influence on their health and HRQoL [39]. Furthermore, a Chinese study identified social support, as gauged by the Social Support Rating Scale, as the primary determinant impacting adherence behavior and HRQoL [40].

Another positive link to higher HRQoL scores in our study was higher eGFR. This aligns with the outcomes observed by Legrand et al., wherein patients across all stages of CKD, including CKD-T, exhibited significantly lower physical HRQoL scores in comparison to the general population. Additionally, the adjusted mental component summary score was marginally lower among CKD-T patients compared to the general population, but statistically significant [41]. Furthermore, in a Japanese study involving KT recipients, scores of physical functioning, general health, and vitality closely correlated with serum creatinine levels. Individuals with a serum creatinine level exceeding 2 mg/dL displayed notably lower scores in contrast to those with levels below 1.5 mg/dL [42]. These findings illustrate the negative impact of graft dysfunction on HRQoL scores. On another hand, HRQoL scores are negatively impacted by recent hospitalization. A study by Gentile et al. found that hospitalization and recent critical illness were linked to worse HRQoL scores among KT recipients, similar to our findings [43]. Hospitalizations are linked to fatigue, deconditioning and anxiety; all these will affect HRQoL [44, 45].

Our study emphasized the well-known relation between depression and HRQoL in kidney transplant patients [46]. The experience of undergoing major surgery, managing complex medication regimens, coping with potential graft rejection, and adjusting to a new lifestyle can contribute to the development of depression in this population. Depression can affect their physical and emotional wellbeing as well as social and cognitive functioning. It can also interfere with adherence to medications, thereby affecting graft function and overall health [47]. Integrated care that includes psychological support, counseling, and, if necessary, pharmacological intervention, can play a pivotal role in managing depression and improving HRQoL in this patient population.

Limitations and Strengths

The study's main limitations were its cross-sectional design and small sample size. First, the cross-sectional design restricts our ability to establish whether daytime sleepiness observed post-kidney transplantation is a continuation of pre-transplant sleep problems or a new occurrence. Similarly, it hinders the ability to discern mediating or temporal links. Some features of social support, mental wellbeing, and quality of life may be overlapping and a cross sectional design may not capture the dynamic interaction between these issues. Second, our sample size was relatively small. It imposed limitations in detecting associations of smaller magnitude and we may have missed identifying other factors that contribute to the risk of sleepiness and deteriorating HRQoL. However, it is important to note that Lebanon is a small country with ~1,000 kidney transplant recipients. Unfortunately, recruitment was hindered by the COVID-19 pandemic. Third, the study only included two transplant centers, however these are the major referral centers, serving a substantial portion of the country's transplant recipients. Fourth, the absence of a healthy comparison group makes it challenging to determine whether the observed rates of sleepiness and HRQoL scores in the study sample differ significantly from those in the general population. Nonetheless, previous research has already demonstrated such differences. Fifth, the study relied on self-reported data for the assessment of daytime sleepiness and social support. Daytime sleepiness was evaluated through questionnaires rather than objective measures like polysomnographic sleep tests. Similarly, social support was perceived and evaluated based on a single question. While self-report screening questionnaires may not provide the same level of accuracy as objective diagnostic tests, they are efficient initial tools in any diagnostic process.

Despite these limitations, our study contributes valuable insights into the post-kidney transplant experiences of individuals in Lebanon, shedding light on important and often forgotten aspects of their post-transplant care such as sleep, social support, and HRQoL. The use of locally validated assessment tools among KT recipients may aid in the identification of those with excessive sleepiness or lower HRQoL scores, leading to the implementation of effective treatment strategies, to address these issues and improve their overall wellbeing.

CONCLUSION AND FUTURE DIRECTIVES

We have identified a variety of factors that are either positively or negatively associated with daytime sleepiness or HRQoL in kidney transplant recipients. Future research with larger and more diverse samples, longitudinal designs, and objective assessments could further elucidate the complex relationships among these variables. Exploring various dimensions of social support and their potential links to sleep disturbances warrants further investigation. Furthermore, a more in-depth understanding of the cultural differences contributing to sleepiness and HRQoL would enable the development of strategies to better address and manage these issues across diverse populations.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusion of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving humans were approved by the American University of Beirut's Institutional Review Board. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MH, AA, ME, LF, and SK contributed to the study conception and design. AA, RA, WM, HA, and SK performed the study execution and acquisition of raw study data. MA performed the statistical analysis. MA, ME, MH, and SK contributed to the analysis, and interpretation of raw study data. MH, AA, ME, MA, and SK contributed to manuscript preparation. All authors contributed to the article and approved the submitted version.

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontierspartnerships.org/articles/10.3389/ti.2023.11547/full#supplementary-material

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International Variability of Barriers to Adherence to Immunosuppressive Medication in Adult Heart Transplant Recipients. A Secondary Data Analysis of the BRIGHT Study

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Non-adherence to immunosuppressive medication among transplant patients is associated with poor clinical outcomes and higher economic costs. Barriers to immunosuppressives are a proximal determinant of non-adherence. So far, international variability of barriers to adherence in transplantation has not been studied. As part of the cross-sectional multi-country and multi-center BRIGHT study, barriers to adherence were measured in 1,382 adult heart transplant recipients of 11 countries using the 28-item self-report questionnaire "Identifying Medication Adherence Barriers" (IMAB). Barriers were ranked by their frequency of occurrence for the total sample and by country. Countries were also ranked the by recipients' total number of barriers. Intra-class correlations were calculated at country and center level. The five most frequently mentioned barriers were sleepiness (27.1%), being away from home (25.2%), forgetfulness (24.5%), interruptions to daily routine (23.6%) and being busy (22.8%), fairly consistently across countries. The participants reported on average three barriers, ranging from zero up to 22 barriers. The majority of the variability among reported barriers frequency was situated at the recipient level (94.8%). We found limited international variability in primarily person-level barriers in our study. Understanding of barriers in variable contexts guides intervention development to support adherence to the immunosuppressive regimen in real-world settings.

Keywords: heart transplantation, medication adherence, immunosuppressant nonadherence, immunosuppressant medication, barrier

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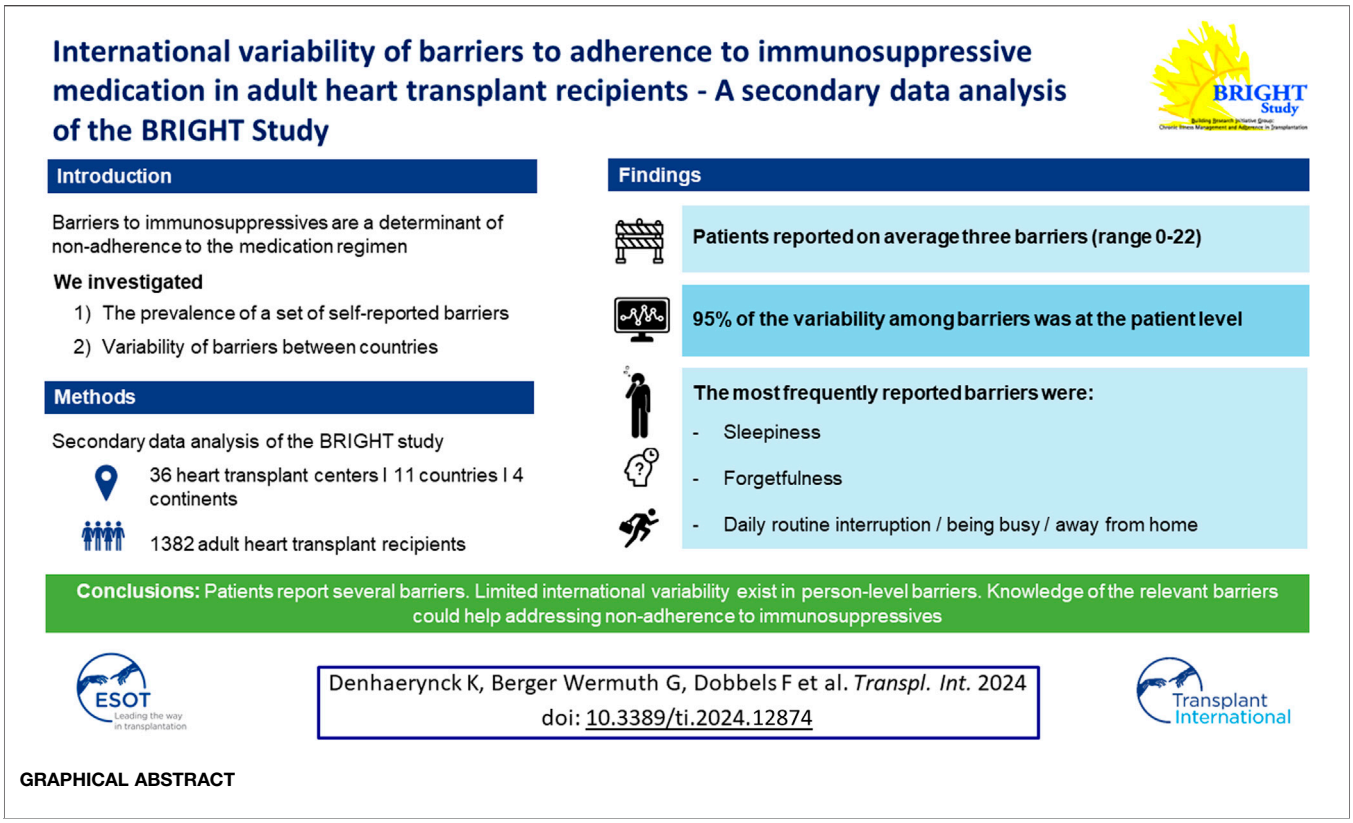
INTRODUCTION

Transplant recipients are required to adhere to a complex medical regimen of lifelong immunosuppressives (IS), supplemented by medications that prevent or treat co-morbidities [1, 2]. Optimal clinical outcome [3–5], and lower costs [6, 7] can be achieved by adhering well to the medication, which implies that the regimen 1) is *initiated* promptly, 2) *implemented* correctly as prescribed and 3) *persistently* continued over time [8]. In order to identify the patients at risk of



GRAPHICAL ABSTRACT

nonadherence and to know who to support in enhancing their medication taking behavior, knowledge of the determinants of (non)adherence is essential.

Appropriate theoretical models can guide the identification of relevant determinants. The Integrated Model of Behavioral Prediction integrates insights of the most prominent behavioral theories (i.e., the health belief model, theory of reasoned action, theory of planned behavior and the social cognitive theory) [9] into a limited number of determinants of behavior. The model assumes that intentions drive behavior, while their execution can be hindered by a number of non-intentional barriers. Barriers are defined as "a person's estimation of the level of challenge of social, personal, environmental, and economic obstacles to a specified behavior or their desired goal status on that behavior" [10]. Barriers frequently reported in the transplant literature are forgetfulness [11–21], interruptions to daily routine (e.g., being away from home) [12–17, 19, 22, 23], or having complex medication regimens (e.g., a high number of pills; several intakes per day; medication or dose changes) [14, 20–22, 24]. Barriers to medication taking are an undervalued problem within the transplant population [12, 25], because they are often not recognized strongly associated with non-adherence to immunosuppressives [20, 26], and are predictive of occurrence of acute rejections [27]. So far research has not explored variability in barriers in diverse transplant contexts and healthcare systems.

To overcome the limitations of the hitherto published studies on barriers, which included mostly limited numbers of patients, and limited cultural perspectives and care systems [28–30], the aim of our study was to assess a comprehensive set of barriers to medication adherence using a large multi-center sample of adult heart transplant (HTx) recipients participating in the BRIGHT study [1, 26], to rate the occurrence of the different barriers and assess its variability internationally.

MATERIALS AND METHODS

Design, Setting and Sample

This study is a secondary data analysis of the international multi-center cross-sectional Building research initiative group: chronic illness management and adherence in transplantation (BRIGHT) study [1, 26]. The purpose of BRIGHT was to study variability in health behaviors among HTx recipients internationally, to assess risk-factors for non-adherence at different levels in the healthcare system and to describe and compare practice patterns of chronic illness management. Detailed information on the study methods and procedures has previously been published [1, 26]. In summary, multi-staged sampling of HTx recipients occurred in 11 countries and 36 HTx centers. At least two transplant centers per country were included across four continents: Europe: N = 19 (Belgium, n = 2: France, n = 3; Germany, n = 2; Italy, n = 2; Spain, n = 5; Switzerland, n = 2; UK, n = 3); North America: N = 12 (Canada, n = 4; United States, n = 8); Australia, N = 2; South America, N = 3 (Brazil). Further inclusion criteria for the HTx centers were: a) having performed ≥50 HTx in the 12–60 months

TABLE 1 | Sample characteristics.

	Overall	BE[a]	FR[a]	DE[a]	IT[a]	ES[a]	CH[a]	GB[a]	CA[a]	US[a]	AU[a]	BR[a]
Gender, N	1,366	74	159	64	111	224	46	98	106	334	51	99
Female, n (%)	375 (27.5)	24 (32.4)	39 (24.5)	15 (23.4)	18 (16.2)	53 (23.7)	14 (30.4)	22 (22.4)	32 (30.2)	106 (31.7)	20 (39.2)	32 (32.3)
Age in years, N	1,349	74	159	65	107	224	46	98	117	331	49	99
mean (SD)	53.2 (±13.2)	52.7 (±12.6)	49.7 (±13)	54.8 (±10.3)	56.5 (±12.5)	55.9 (±11.8)	49.5 (±14.7)	48.8 (±14.8)	54.4 (±13.3)	55.7 (±12.8)	50 (±13.6)	46.3 (±13.3)
Ethnicity, N	1,367	74	158	64	111	221	46	99	115	333	47	99
Caucasian, n (%)	1,176 (86)	73 (98.6)	142 (89.8)	64 (100)	110 (99.1)	202 (91.3)	42 (91.3)	93 (94)	103 (89.6)	250 (75.1)	33 (70.2)	64 (64.6)
Asian	26 (1.9)	1 (1.4)	-	-	-	1 (.5)	4 (8.7)	3 (3)	5 (4.3)	9 (2.7)	3 (6.4)	-
African American	79 (5.8)	-	2 (1.3)	-	1 (.9)	-	-	-	4 (3.5)	55 (16.5)	-	17 (17.2)
Hispanic	28 (2.1)	-	2 (1.3)	-	-	15 (6.8)	-	-	1 (.9)	9 (2.7)	-	1 (1)
Other	58 (4.2)	-	12 (7.6)	-	-	3 (1.4)	-	3 (3)	2 (1.7)	10 (3)	11 (23.4)	17 (17.2)
Marital status, N	1,373	74	158	64	110	224	46	97	116	334	51	99
Single, n (%)	238 (17.3)	8 (10.8)	35 (22.2)	7 (10.9)	14 (12.7)	26 (11.6)	8 (17.4)	26 (26.8)	19 (16.4)	58 (17.4)	13 (25.5)	24 (24.2)
Married/living with partner	948 (69.1)	56 (75.7)	103 (65.2)	49 (76.6)	83 (75.5)	156 (69.6)	31 (67.4)	59 (60.8)	79 (68.1)	234 (70)	34 (66.7)	64 (64.7)
Divorced/separated	146 (10.6)	8 (10.8)	19 (12)	6 (9.4)	11 (10)	32 (14.3)	6 (13)	10 (10.3)	10 (8.6)	29 (8.7)	4 (7.8)	11 (11.1)
Widowed	41 (3)	2 (2.7)	1 (.6)	2 (3.1)	2 (1.8)	10 (4.5)	1.(2.1)	2 (2.1)	8 (6.9)	13 (3.9)	-	-
Educational level, N	1,370	73	157	64	111	222	46	99	115	336	50	97
Primary school, n (%)	185 (13.5)	3 (4.1)	10 (6.4)	7 (10.9)	37 (33.3)	93 (41.9)	4 (8.7)	-	3 (2.6)	3 (.9)	-	25 (25.7)
Secondary school	423 (31)	42 (57.5)	53 (33.8)	6 (9.4)	51 (45.9)	60 (27)	3 (6.5)	45 (45.5)	33 (28.7)	70 (20.8)	9 (18)	51 (52.6)
Post secondary school	755 (55.1)	28 (38.4)	94 (59.8)	51 (79.7)	23 (20.7)	64 (28.8)	39 (84.8)	54 (54.4)	79 (68.7)	263 (78.3)	41 (82)	19 (19.6)
No scholar education	7 (.4)	-	-	-	-	5 (2.3)	-	-	-	-	-	2 (2.1)
Employment status, N	1,377	74	159	64	111	223	46	99	115	336	51	99
Employed, n (%)	410 (29.8)	18 (24.3)	58 (36.5)	17 (26.6)	33 (29.7)	27 (12.1)	20 (43.5)	37 (37.4)	36 (31.3)	117 (34.8)	25 (49)	22 (22.2)
Years post-transplant, N	1,349	74	159	65	107	224	47	98	110	331	49	99
mean (SD)	3.4 (±1.4)	3.4 (±1.2)	3.7 (±1.4)	3.4 (±1.4)	3.2 (±1.3)	3.6 (±1.4)	3.5 (±1.2)	3.5 (±1.2)	3.7 (±1.5)	3 (±1.3)	4.2 (±1.5)	2.8 (±1.5)
Frequency IS intake/day, N									120	337	51	100
1 time, n (%)									1	3	-	-
2 times									109	330	49	98
3 times									10	4	2	2
Number of IS/day, N									119	335	50	100
Median (Q1-Q3)									9 (6–12)	8 (6–10)	9 (7–11)	7 (6–9)
Barriers[b]												
Number of barriers Mean (SD)	3.01 (±3.98)	3.34 (±3.82)	3.12 (±3.77)	2.69 (±4.51)	1.53 (±2.97)	2.49 (±3.93)	3.61 (±3.88)	3.26 (±3.28)	4.23 (±4.76)	3.20 (±4.04)	5.10 (±4.91)	1.88 (±3.05)
Median (IQR)	1 (0–5)	2 (0–5)	2 (0–5)	1 (0–3)	0 (0–2)	1 (0–3)	2 (0–7)	2 (0–5)	2 (0–8)	2 (0–5)	4 (1–9)	0 (0–3)

[a]*Participating countries: Belgium (BE), France (FR), Germany (DE), Italy (IT), Spain (ES), Switzerland (CH), United Kingdom (GB), Canada (CA), United States of America (US), Australia (AU), Brazil (BR).*

[b]*Barrier not present (score: never)/barrier present (score: rarely; sometimes; often; always).*

Abbreviation: immunosuppressive medication (IS).

TABLE 2 | Prevalence and ranking of barriers overall and top 12 per country.

Barriers[a]	Overall N% (rank)	BE[b] n% (rank[c])	FR[b] n% (rank[c])	DE[b] n% (rank[c])	IT[b] n% (rank[c])	ES[b] n% (rank[c])	CH[b] n% (rank[c])	GB[b] n% (rank[c])	CA[b] n% (rank[c])	US[b] n% (rank[c])	AU[b] n% (rank[c])	BR[b] n% (rank[c])
Falling asleep/ oversleeping	1,379 27.1 (1)	74 27 (3)	158 25.9 (4)	64 21.9 (1)	111 14.4 (1)	224 26.8 (1)	46 28.3 (3)	99 24.2 (5)	117 39.3 (2)	336 31.5 (1)	51 31.4 (6)	99 18.2 (2)
Being away from home	1,380 25.2 (2)	74 23 (4)	158 27.8 (3)	65 15.4 (8)	111 11.7 (3)	223 16.1 (3)	46 30.4 (2)	99 33.3 (2)	117 43.6 (1)	328 27.9 (3)	51 49 (1)	99 11 (6)
Forgetfulness	1,380 24.5 (3)	74 31.1 (2)	158 20.3 (6)	64 17.2 (5)	111 9.9 (4)	224 16.1 (3)	46 23.9 (5)	99 30.3 (4)	117 35.9 (3)	337 31.5 (1)	51 39.2 (2)	99 16.2 (3)
Interruptions to daily routine	1,378 23.6 (4)	32.4 (1)	28.8 (1)	20 (2)	8.1 (6)	17.9 (2)	37 (1)	36.7 (1)	30.8 (5)	22.3 (5)	33.3 (5)	13.1 (5)
Being busy	1,379 22.8 (5)	20.6 (6)	28.5 (2)	17.2 (5)	8.1 (6)	13.4 (7)	28.3 (3)	32.3 (3)	31.6 (4)	26.4 (4)	39.2 (2)	14.1 (4)
Remembering intake of IS	1,378 18.5 (6)	21.6 (5)	22.2 (5)	7.9	12.6 (2)	15.2 (5)	15.2 (10)	20.4 (7)	29.1 (6)	16.9 (8)	27.5 (7)	19.2 (1)
Feeling too sick	1,376 15.7 (7)	17.6 (8)	10.9 (11)	10.9 (9)	5.4	11.7 (9)	8.7	22.2 (6)	22.2 (9)	21.4 (6)	35.3 (4)	5.1
No reminder support	1,376 14.2 (8)	17.6 (8)	17.2 (8)	7.9	6.3 (12)	13.9 (6)	10.9 (12)	17.2 (8)	18.8 (10)	14 (9)	23.5 (9)	10.1 (7)
Holidays or weekend	1,376 13.6 (9)	16.2 (12)	17.3 (7)	17.2 (5)	4.5	11.2 (10)	23.9 (5)	15.3 (9)	23.9 (7)	11	25.5 (8)	3.1
Sticking IS into daily routine	1,377 12.3 (10)	20.3 (7)	11.5 (10)	9.4	7.2 (10)	8.9	10.9 (12)	12.2 (11)	23.9 (7)	11.3 (12)	21.6 (11)	9.1 (8)
Side-effects	1,375 11.5 (11)	17.6 (8)	9.6	17.5 (3)	6.4 (11)	8.9	23.9 (5)	8.2	13.8	11.9 (10)	21.6 (11)	6
Getting IS refill on time	1,378 11.1 (12)	2.7	8.3	6.3	0.9	10.8 (11)	8.7	15.2 (10)	5.1	19.3 (7)	23.5 (9)	7.1 (10)
Inconvenient intake times	1,377 9.9 (13)		14.7 (9)			9.8 (12)	17.4 (8)					
IS intake several times a day	1,377 8.7 (14)						10.9 (12)			11.6 (11)	21.6 (11)	
Going away from home	1,375 8.6 (15)								15.5 (11)			7.1 (10)
Many IS at the same time	1,378 7.8 (16)			10.9 (9)	6.3 (12)				14.5 (12)			7.1 (10)
Difficulties to swallow IS	1,377 7.8 (16)			10.9 (9)	9 (5)		17.4 (8)					7.1 (10)
Intake of IS is noticed by others[d]	1,280 6.8 (18)			10.9 (9)	6.3 (12)							[d]---
Non-understanding of instructions on package	1,373 6.7 (19)	17.6 (8)		17.5 (3)	7.3 (9)	12.9 (8)	11.1 (11)					
Feeling sad or depressed	1,377 6.2 (20)											
Removing IS from package	1,378 6 (21)		10.2 (12)					9.1 (12)				
Bad taste of IS	1,378 4.9 (22)				8.1 (6)		10.9 (12)					8.1 (9)
Costs for IS	1,372 3.6 (23)	1.4	0.6	1.6	0	4	2.2	1	1.7	6.5	9.8	7.1 (10)
Feeling good	1,378 1.3 (24)											
Uncertainty about how to take IS	1,379 1.2 (25)											
No beneficial feeling	1,373 0.9 (26)											
Non-understanding of intake times	1,376 0.8 (27)											
Non-understanding of IS effect	1,377 0.6 (28)											

[a]*Barrier not present (score: never)/barrier present (score: rarely; sometimes; often; always).*

[b]*Participating countries: Belgium (BE), France (FR), Germany (DE), Italy (IT), Spain (ES), Switzerland (CH), United Kingdom (GB), Canada (CA), United States of America (US), Australia (AU), Brazil (BR).*

[c]*Ranking per country.*

[d]*The Brazilian questionnaires did not provide this item.*

Abbreviation: immunosuppressive medication (IS).

prior to inclusion and procuring a formal support letter from the HTx center's transplant director. HTx recipients were recruited using a proportional random sampling method based on size of transplant center using ISHLT criteria as a basis (i.e., small center: 50–74 HTx/last 5 years; medium center: 75–100 HTx/last 5 years; large center: >100 HTx/last 5 years) [1, 31]. Inclusion criteria of HTx recipients were a) being a ≥18-year-old HTx recipient at inclusion time; b) first single-organ transplant; c) being between one and 5 years post-transplant; and d) managing the taking of medication independently (i.e., without any professional support). All patients gave written informed consent for participation in the study, and approval for the BRIGHT study was obtained by all local ethical committees [1].

Variables and Measurement

Measurement of variables collected in this study was done using established or investigator-developed instruments by self-report, structured patient interviews as well as medical chart reviews (completed by a nurse or a clinician) [1, 26]. The questionnaires and instruments were pilot tested in diverse settings and translated into the study languages using established protocols.

Sociodemographic and clinical variables were age in years, sex, marital status, ethnicity, educational level, employment status, years post-transplant, daily frequency of IS and number of IS per day (see **Table 1** for answer categories).

Barriers to IS adherence were assessed by written self-report using the 28-item Identifying Medication Adherence Barriers (IMAB) self-report questionnaire [32]. The IMAB was specifically designed for the transplant population, the item generation was based on a systematic review of existing instruments, investigating barriers to medication adherence, published in the chronic illness literature (e.g., forgetfulness; poor health literacy; frequency, number, taste, or shape of IS; costs of IS; see **Table 2**). To enhance understandability by the patients, IMAB items were slightly adapted by changing the term "anti-rejection medication" into "immunosuppressant medications." The content validity of IMAB was tested during the Transplant360 project [32], and its internal consistency as part of this study [26].

Patients rated each of the 28 barrier items on a five point scale (never = 1/rarely = 2/sometimes = 3/often = 4/always = 5). Since answer patterns showed a skewed distribution in favor of the lower frequencies, scores were dichotomized into absence of the barrier (never) versus presence of the barriers (rarely, sometimes, often or always). Next to analyzing the barriers individually, we also calculated the total number of barriers per patient.

Data Analysis

Analyses were of descriptive nature, using the appropriate measures given measurement levels and distributions of the respective variables. Calculation of the intracluster correlation indicated the percentages of variability of the number of barriers per patient, that could be attributed to the different healthcare system levels (i.e., country, center, patient). Analyses were executed in SAS 9.4 (SAS Institute, Cary, NC).

RESULTS

Sample Characteristics

Of the 1,397 HTx recipients recruited in BRIGHT study (from an eligible 1,677), 15 (1.1%) did not provide any barrier data and were thus excluded from further analysis for this study (see **Figure 1**). The remaining 1,382 participants had a mean age of 53.2 years (SD ±13.2) and were, on average, 3.4 years (SD ± 1.4) post-transplant. The majority were male (72.5%), Caucasian (86%), educated at least post-secondary level (55.1%) and married or living with a partner (69.1%). Detailed information on the sample composition is provided in **Table 1**.

Number of Barriers Per Patient

The median number of reported barriers was 1 (mean 3.0; SD ± 4.0), with an interquartile range of 5, and ranging from zero (37% patients) to 22 barriers (0.1% of patients). The number of mentioned barriers per participant was diverging too, ranging from an average of 1.5 barriers in Italy to 5.1 barriers in Australia.

Variability of Barrier Prevalence Between Countries

Calculation of the intracluster correlation showed that 4% of variability of the total number of reported barriers was situated at the level of the country, 1.2% at the level of the centers nested within countries, while the remainder (94.8%) was intra-patient variability.

Prevalence of Individual Barriers

The prevalence of individual barriers ranged from 0.6% (i.e., non-understanding of IS effects) to 27.1% (i.e., falling asleep/oversleeping). Twelve of the 28 barriers were reported by more than 10% of all participants (**Table 2**). Five barriers were mentioned by more than 20% of the participants, i.e., falling asleep/oversleeping (27.1%), being away from home (25.2%), forgetfulness (24.5%), interruptions to the daily routine (23.6%) and being busy (22.8%). The percentage of patients who reported at least one of these top five barriers was 50.5%, while 5.3% reported them all at once.

Differences of Individual Barrier Prevalence Between Countries

Within the different countries, the ranking of individual barriers is similar to the prevalence ranking of barriers overall. The top-12 of barriers differed between countries, with Brazil having the lowest (all 12 barriers <20%) and Australia having the highest prevalence (all 12 barriers >20%). The overall most frequent barrier of falling asleep/oversleeping, appears in the top 6 of all of the countries. The barrier of being away from home, the 2nd most frequently mentioned overall, is equally ranked in the top 6 of barriers in the different countries, except for Germany (where it appeared as rank number 8). Forgetfulness, ranked as 3rd most prevalent barrier overall, is in all countries again in the 6 most prominent barriers. Some barriers were not very prevalent,

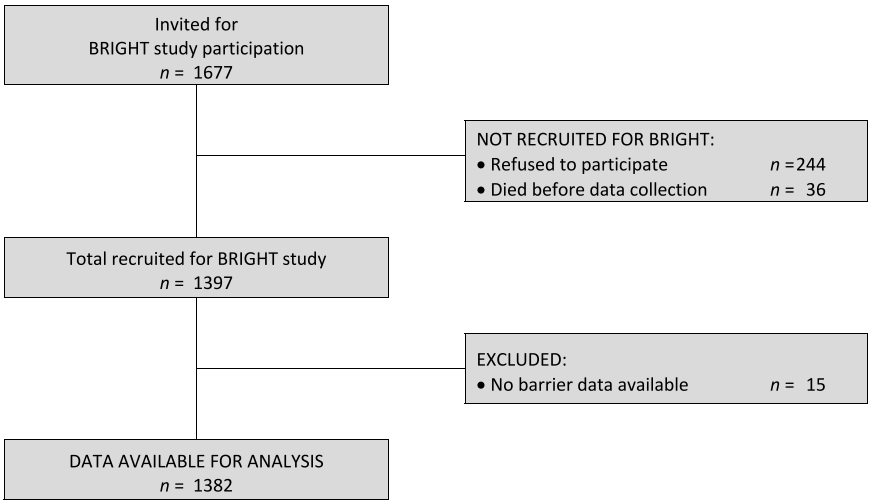


FIGURE 1 | Participant recruitment flow diagram.

generally with consistency across countries. One of those lesser reported barriers reflected cost as a barrier, ranked 23rd overall, with a prevalence of 3.6%, the highest being in Australia (9.8%), followed by Brazil (7.1%) and the US (6.5%). Although such a barrier reflects differences in countries' healthcare systems, the intracluster correlation of this particular barrier only showed 1.2% of the variability to be situated at the country-level (1.2%), the rest being patient-level variability (98.8%).

Sensitivity Analysis

A sensitivity analysis compared the current ranking of barriers, obtained using frequencies of the dichotomized items (as presented in **Table 1**) with a ranking based on patients' mean score, calculated from their responses on the scale from 1 to 5. The Spearman correlation between the two ranking systems was r = .99, indicating that their results were almost identical, thereby validating our dichotomization of item scores.

DISCUSSION

This study assessed an extensive set of barriers to immunosuppressives intake among a worldwide sample of HTx recipients and found an average of three reported barriers per recipient, with some recipients reporting no barriers, while others up to twenty-two. The five most frequently mentioned barriers were sleeping during a prescribed intake time, being away from home, forgetfulness, interruptions to daily routine and being busy. Half of the sample reported at least one of these five, and one-fifth reported all five to be present simultaneously. These most frequent barriers can be grouped into three themes, which have been mentioned in the literature before:

- *Sleeping* through an intended intake moment, the most frequently mentioned barrier and among the top-3 of barriers in eight of the eleven countries, has been mentioned among renal transplant [33] and chronic heart failure [34] patients, in studies linking daytime sleepiness to poor medication adherence.
- The two barriers *interruptions to daily routine* and being *away from home*, and a third related barrier of *inconvenient intake times*, appeared in more than half of our participating countries and in over ten percent of the participants in six countries. These were previously reported in liver or kidney transplant recipients [14, 16, 17, 23], indicating that stringent intake times of IS can be a challenge at times when the normal schedule is disrupted.
- One of most frequently reported barriers within the transplant literature is *forgetfulness.* [12, 14, 16, 17, 20, 21] Although not ranked first within our sample, this barrier ties together with barriers referring to *difficulties to remember* intake of IS, or of *lacking reminder support,* making this theme one of the important barriers, probably not entirely independent from the previous theme of routine disruptions. As to factors that could explain forgetfulness, is linked with being busy among younger peopl, or to a decline in cognitive abilities among the aged [35]. A person's personality type also seems to make a difference, since having a more compulsive or anxious personality type support adherence [36]. The meaning of forgetfulness seems to vary somewhat between high and low adherers: qualitative studies have shown that for the former group, forgetting refers to an occasional lapse, whereas for the latter, forgetfulness normalizes a consistent behavioral pattern [37–39].

Despite there being considerable differences between the top-ranked barriers among countries, most of the variability in number of reported barriers was still situated at the recipients level, as shown by the yet small intracluster correlations at the level of countries.

Even the barrier related to the healthcare system – concerning the cost of the IS, had most of its variability situated at the

recipient level, despite it being largely determined by policies of healthcare coverage. In European countries, where the healthcare system covers largely the costs of organ transplants and its related expenses (e.g., IS) [40], the prevalence of the cost barrier was expectedly low; while the highest frequencies were recorded in Australia, where almost ten percent of the participants reported cost of IS as a barrier, followed by Brazil and the US. The relatively high frequency of this barrier in Australia and the USA is in line with the findings of a study that showed that their chronically ill patients reported high out-of-pocket costs for healthcare [28], a cause of financial stress [23, 28] and a source of cost-related non-adherence [41]. Unexpectedly, Brazilian recipients also reported a relatively high perception of perceived unaffordability, in spite of the fact that financial coverage for IS also applies to Brazil [40, 42], and that cost-related nonadherence was among the lowest in the Brazilian subsample [41].

Study Limitations

We investigated barriers to adherence only using the 28 IMAB items, which admittedly primarily focused on patient level barriers. Having the focus primarily on patient level is a limitation in our study. The IMAB could be expanded with additional barriers identified through quantitative and/or qualitative research. Especially barriers at the meso level pointing to barriers in the clinical work flow and organization in transplant centers such as limited time for patient education, not addressing adherence issues during an outpatient clinic visit or lack of trust in or access to healthcare providers might also be considered to be included in a barriers instrument [24]. Another limitation is that although large and with a diverse sample, the Bright study was only cross-sectional, hence, variability and changes in barrier experience over the course of a heart transplantation could not be well documented.

Implications for Practice and Research

HTx recipients face multiple barriers to adherence to IS. Barriers are proximal determinants of health behaviors and can guide the development of adherence enhancing or remediating interventions. With regard to adherence-enhancing, the advised approach is to first assess adherence and important determinants, such as barriers, in order to identify the patients at risk and deliver a multicomponent behavioral change intervention using shared decision making. Given the impactful nature of poor adherence to IS on clinical outcomes and economic costs [2], health professionals can assess actual and potential barriers a person with a transplant is faced with as this information provides direction in choosing tailored medication adherence interventions. Assessment of barriers in a research study is different from assessing barriers in daily clinical practice. Implementing regular barriers assessment in clinical practice, optimally combined with the assessment of medication adherence as a 5th vital sign (see COMMIT guidelines) [43], calls for careful consideration of context in view of clinical work flow to support the successful implementation in clinical practice (e.g., eHealth tools available for ePROM assessment). Moreover, the information collected needs to enrich clinical decision making. Decision tools integrated in the electronic medical record provide guidance how specific barriers can be linked to adherence interventions. Ribaut et al. have mapped components that can be used [44]. Well-designed interventions also prepare the transplant team and the organization for adherence management [45]. The implementation can be facilitated by dedicated education of transplant clinicians, not only providing the necessary knowledge but primarily with (communication) skills and organizing transplant care based on principles of chronic illness management, so that time and resources are specifically invested in patient's self management support throughout the transplant journey [2]. An intervention program that successfully implemented all of these principles in a cost-effective way is published by Hooper et al. [46].

As mentioned earlier, barriers instruments can be continuously enriched with multi-level barriers generated from the literature and/or also from clinical observation. The IMAB is a good starting point, however, could be further extended.

Conclusion

We found limited international variability in primarily person-level barriers in our study. Understanding of barriers in variable contexts guides intervention development to support adherence to the immunosuppressive regimen in real-world settings. Implementation of barriers assessment in daily clinical practice needs specific considerations to guide successful implementation.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving humans were approved by the University Hospitals of Leuven (Belgium) ethics committee. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

KD, LB, FD, CR, and SD were involved in the study design. KD, GB, and SD participated in the manuscript writing. KD and GB analysed the data. All authors contributed to the article and approved the submitted version.

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CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Prevalence and Patient-Level Correlates of Intentional Non-Adherence to Immunosuppressive Medication After Heart-Transplantation—Findings From the International BRIGHT Study

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After heart transplantation (HTx), non-adherence to immunosuppressants (IS) is associated with poor outcomes; however, intentional non-adherence (INA) is poorly understood regarding its international variability in prevalence, contributing factors and impact on outcomes. We investigated (1) the prevalence and international variability of INA, (2) patient-level correlates of INA, and (3) relation of INA with clinical outcomes. Secondary analysis of data from the BRIGHT study—an international multi-center, cross-sectional survey examining multi-level factors of adherence in 1,397 adult HTx recipients. INA during the implementation phase, i.e., drug holiday and dose alteration, was measured using the Basel Assessment of Adherence to Immunosuppressive Medications Scale© (BAASIS©). Descriptive and inferential analysis was performed with data retrieved through patient interview, patient self-report and in clinical records. INA prevalence was 3.3% (n = 46/1,397)—drug holidays: 1.7% (n = 24); dose alteration: 1.4% (n = 20); both: 0.1% (n = 2). University-level education (OR = 2.46, CI = 1.04–5.83), insurance not covering IS costs (OR = 2.21, CI = 1.01–4.87) and barriers (OR = 4.90, CI = 2.73–8.80) were significantly associated with INA; however, clinical outcomes were not. Compared to other single-center studies, this sample's INA prevalence was low. More than accessibility or financial concerns, our analyses identified patient-level barriers as INA drivers. Addressing patients' IS-related barriers, should decrease INA.

Keywords: immunosuppression, heart transplantation, medication non-adherence, intentional non-adherence, correlates

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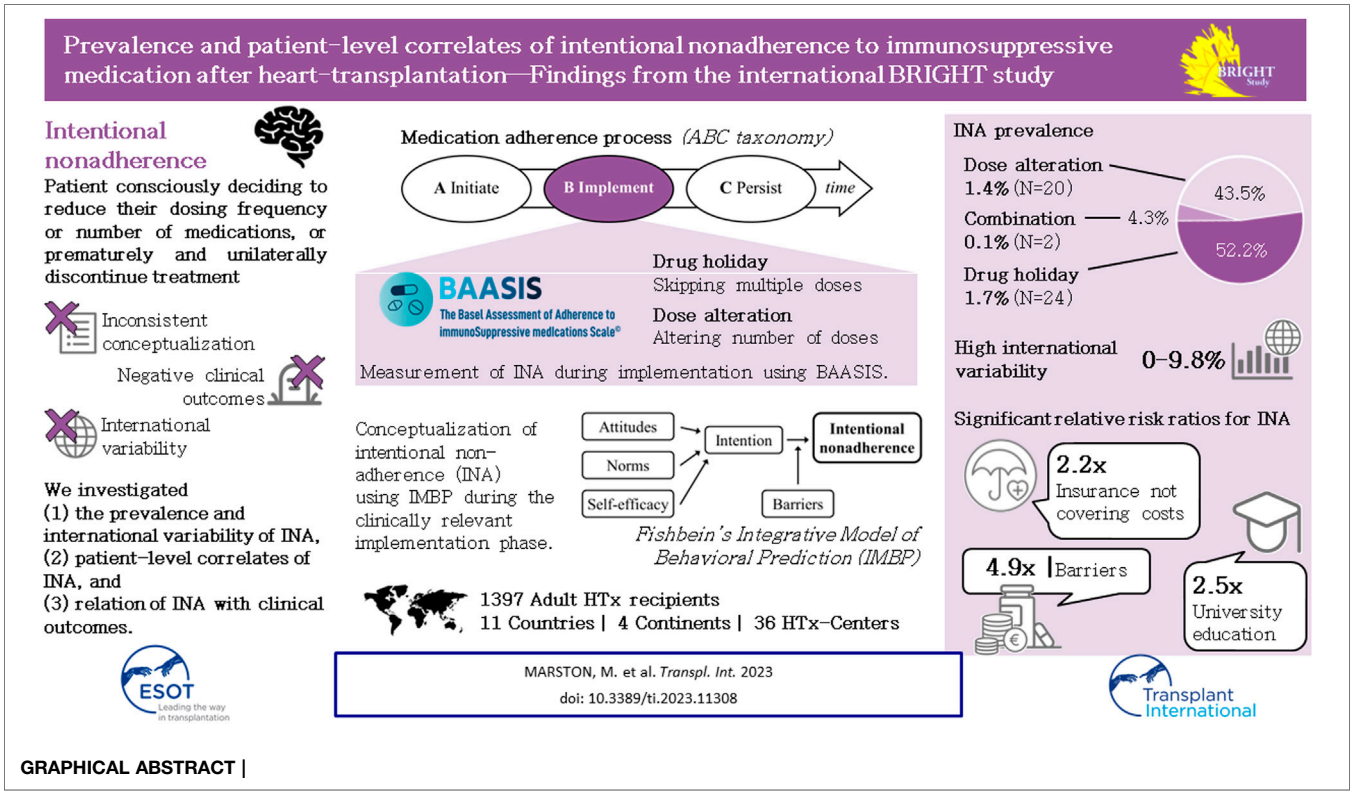
Abbreviations: HTx, Heart transplantation; INA, Intentional nonadherence; IS, Immunosuppressive medication.



GRAPHICAL ABSTRACT |

INTRODUCTION

After heart transplantation (HTx), patients need to adhere to a life-long immunosuppressive medication (IS) regimen [1]. Poor adherence to IS has been linked to poor clinical and economic outcomes [2].

Following the Ascertaining Barriers to Compliance (ABC) taxonomy definition, medication adherence is the process by which a patient follows a medication regimen as prescribed. It has 3 phases: initiation, implementation, and persistence (**Figure 1**) [3]. While non-adherence can occur during any of these phases, after HTx, initiation of IS takes place under clinical supervision and therefore medication non-adherence (NA) is most common during the implementation and persistence phases [3]. Medication NA can be discerned as either intentional or unintentional [4, 5]. Intentional non-adherence (INA) refers to a rational decision-making process and the ability of a person to act on a behavior [6, 7]. This is opposed to unintentional non-adherence, a passive and intermittent process that results from forgetfulness, a lack of capacity, skills, and/or resources [6–11].

Rational decision-making is related to the ability to formulate and carry out a behavior. Within the context of INA, patients decide to reduce their dosing frequency or number of medications, or even to prematurely and unilaterally discontinue treatment (i.e., non-persistence) [9, 12]. This also includes consciously deciding to skip several consecutive doses (i.e., a drug holiday) or to alter the dose of medication (i.e., dose alteration) [13, 14]. The objective is often to avoid disturbing side-effects, to circumvent a restrictive schedule or taking constraints (e.g., having to take food simultaneously), or to generate a feeling of control [9]. Doses may also be omitted or reduced to make a prescription last longer [15].

To date, though, INA to IS (which we will refer to simply as INA) has received only limited attention in the HTx populations and has not been well-substantiated due to inconsistent definition and measurement and large international variability. INA has not been directly studied, and estimated prevalence of drug holidays or non-persistence to IS vary widely, respectively 0%–7.1% and 0.6%–3.1% [16–18].

Deviations from prescribed medication regimen may adversely influence its effect and put the patient at risk of negative clinical outcomes—acute rejection episodes, graft loss, and death [19, 20]. It is unclear how INA influences this risk and how prevalent it is [2, 21, 22].

The limited evidence on correlates of INA focuses on patient-level barriers: beliefs [11, 23], disruption of daily routine [23, 24], and knowledge gaps [5, 25, 26]. System-level correlates: financial barriers related to a lack of health insurance coverage or other sources of increased out-of-pocket monthly expenses [27–29], vary between healthcare systems and show high international variability in relation to INA.

The aims of this study were to 1) assess the prevalence and variability of INA in adult HTx internationally, 2) investigate patient-level correlates of INA, and 3) assess INA's associations with clinical outcomes in adult HTx recipients.

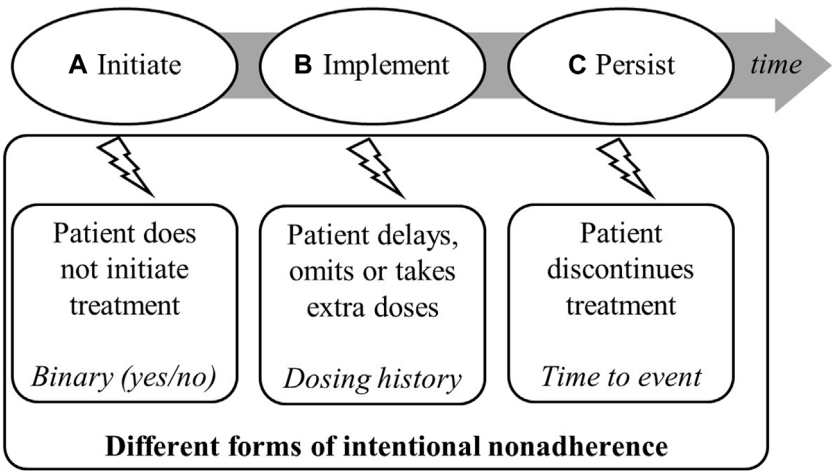


FIGURE 1 | Process of medication adherence illustrating phases in which intentional non-adherence and intentional implementation non-adherence (i.e., drug holiday and dose alteration) may appear [3].

PATIENTS AND METHODS

Design and Sample

This is a secondary data analysis of the "Building research initiative group: chronic illness management and adherence in transplantation" (BRIGHT) study [30], an international, multi-center, cross-sectional survey examining multi-level factors related to IS adherence in HTx recipients. Detailed information on the BRIGHT study has been reported elsewhere [27, 30]. In a multi-stage sampling approach, a convenience sample including 11 countries, 36 HTx centers, and a random sample of HTx recipients was selected. Transplant recipients were included using seven criteria [30]: 1) ≥18 years old at time of inclusion; 2) transplanted and followed-up for routine care in participating centers; 3) first transplant; 4) single-organ transplant; 5) 1–5 years post-transplant; 6) could read in the languages spoken in the country of the participating center; and 7) could provide written informed consent. Exclusion criteria were: 1) had participated in an adherence intervention study within the past 6 months; or 2) were receiving professional support in taking medication at the time of this study.

Variables and Measurement

We based our analyses on data collected using the BRIGHT questionnaires (i.e., BRIGHT patient interview, BRIGHT patient self-report questionnaire) and on the BRIGHT data—including those relating to patient outcomes—collected from clinical files [27, 30]. Intentional NA—drug holidays and dose alterations—patient-level correlates and center location were assessed through patient interview transcripts and patients' written self-reports [30].

Socio-Demographic Data

The following demographic data were assessed (see **Table 1** for answer options) [30]: age (in years), gender, marital status, living situation, employment status, educational level (using a standardized categorization across countries), ethnicity and center location/country.

Intentional Non-Adherence

Intentional NA was assessed using 2 items from the 5-item Basel Assessment of Adherence to immunoSuppressive medIcation Scale (BAASIS© https://baasis.nursing.unibas.ch/) [32]. The first item, *drug holiday*, was operationalized for patients indicating they had skipped two or more consecutive doses of medication. The second, *dose alteration*, was operationalized for patients indicating that they had altered their prescribed IS dosage (i.e., they had taken more or fewer pills per dose than prescribed) over the last 4 weeks [27]. Intentional NA was operationalized as a positive answer to either of these two items.

IMBP Correlates of Intentional Non-Adherence

Fishbein's Integrative Model of Behavioral Prediction (IMBP; **Figure 2**) [33] posits that *Intention to perform* is the most proximal determinant of health behavior. Intention to perform has three determinants: *attitudes*, *norms* and *self-efficacy*. An attitude is defined as a positive or negative feeling towards performing the behavior [34]. Subjective norms are defined as the beliefs an individual or a group has regarding whether or not to perform a given behavior [34]. Self-efficacy refers to the person's beliefs regarding performing a recommended behavior, despite circumstances or barriers making it difficult [34]. Fishbein's model acknowledged that the presence of personal or environmental barriers may hinder patients from acting upon their intentions and keep them from executing the recommended behavior (**Figure 2**) [34]. The next paragraphs describe the instruments to measure these five concepts. Information on the instruments' psychometric properties can be found elsewhere [27].

Intention

Intention was operationalized as the cognitive representation of a person's readiness to perform a given behavior [27]. As an

TABLE 1 | Socio-demographic characteristics and clinical outcomes for total group and patients showing intentional non-adherence.

Variables	Values/scoring	Total sample	Intentional non-adherence	
		N; mean ± SD | N (%)	N; mean ± SD | N (%)	OR[a] (95% CI)
		N = 1,397	N = 46	
Socio-demographic characteristics				
Age	Years	1,363; 53.7 ± 13.2	45; 49.8 ± 14.3	**0.98* (0.96–0.99)**
	Missing	34 (2.4%)	1 (2.2%)	
Gender	Female	379 (27.1%)	13 (28.3)	1.05 (0.55–2.02)
	Missing	7 (0.5%)	0	
Ethnicity	Caucasian	1,186 (84.9%)	35 (76.1%)	Reference
	Afro-American	80 (5.7%)	3 (6.5%)	1.27 (0.38–4.23)
	Asian	27 (1.9%)	3 (6.5%)	**4.10* (1.17–14.19)**
	Hispanic	29 (2.1%)	0	n.a.
	North-African	28 (2.0%)	1 (2.2%)	1.25 (0.17–9.51)
	Other	31 (2.2%)	4 (8.7%)	**5.02** (1.66–15.16)**
	Missing	16 (1.1%)	0	
Marital status	Married/living with partner	955 (68.4%)	26 (56.5%)	Reference
	Single	242 (17.3%)	11 (23.9%)	1.71 (0.83–3.52)
	Separated/divorced	149 (10.7%)	6 (13.0%)	1.52 (0.62–3.77)
	Widowed	41 (2.9%)	3 (6.5%)	2.81 (0.81–9.68)
	Missing	10 (0.7%)	0	
Living alone	Yes	265 (19.0%)	7 (15.2%)	1.32 (0.58–2.99)
	Missing	15 (1.1%)	0	
Education	< Secondary	370 (26.5%)	8 (17.4%)	Reference
	Completed secondary	328 (23.5%)	9 (19.6%)	1.27 (0.48–3.32)
	Further education	382 (27.3%)	13 (28.3%)	1.58 (0.65–3.85)
	University	308 (22.0%)	16 (34.8%)	**2.46* (1.04–5.83)**
	Missing	9 (0.6%)	0	
Employment	(Self-)employed (1)	366 (26.2%)	11 (23.9%)	Reference
	Looking for job 2)	40 (2.9%)	3 (6.5%)	2.58 (0.69–9.69)
	(Temp.) unable (5)	404 (28.9%)	18 (39.1%)	1.50 (0.70–3.22)
	Retired (4)	466 (33.4%)	12 (26.1%)	0.85 (0.37–1.94)
	Other (3)	97 (6.9%)	1 (2.2%)	0.34 (0.04–2.63)
	Missing	24 (1.7%)	1 (2.2%)	
Clinical outcomes				
Time since Tx	Years	1,378; 3.4 ± 1.4	45; 3.1 ± 1.4	0.84 (0.67–1.05)
	Missing	19 (1.4%)	1 (2.2%)	
Treated rejections in follow-up	N events per year	1,391; 0.9 ± 1.5	45; 1.2 ± 1.7	1.16 (0.99–1.37)
	Missing	6 (0.4%)	1 (2.2%)	
	No event[b]	840 (60.1%)	23 (50.0%)	Reference
	≥1 event	551 (39.4%)	22 (47.8%)	1.48 (0.82–2.68)

OR, odds ratio; CI, confidence interval. *p < *0.05*, **p < *0.01*, ***p < *0.001*.

[a]*Logistic regression for bivariate analysis [31], bold when significant.*

[b]*Dichotomisation, comparison of patients with no treated rejections and patients with one or more treated rejections for bivariate analysis [31].*

indicator of the capacity of a person to take actions necessary to attain a target [36], it was assessed using 3 investigator-developed items (e.g., "I always intend to take my IS on time") rated on a unidimensional 5-point Likert-type scale ranging from 1 (strongly disagree) to 5 (strongly agree) [27]. Intention was scored by calculating a mean across the 3 items. This subscale's Cronbach's *alpha* was 0.81 [27].

Attitudes

Attitudes were operationalized to reflect how favorably—such as important to avoid organ rejection—or unfavorably—such as poison—each patient considered IS. Attitudes are related to a patient's degree of belief that a given behavior will lead to a favorable or unfavorable outcome [36]. Attitudes were assessed using a 21-item investigator-developed instrument asking patients' to rate their concerns/worries (12 items, e.g., "Immunosuppressive medications are addictive") as well as how necessary they considered their IS (9 items, e.g., "Immunosuppressive medications protect my heart") [27, 30, 35]. Items were rated on a 5-point Likert-type scale ranging from 1 (strongly disagree) to 5 (strongly agree). Total scores for the *positive attitudes*—favorable—and *worries*—unfavorable—dimensions were calculated as the mean score over each item's rating. The dimensions' Cronbach's *alphas* were, respectively 0.77 and 0.66 [27].

Norms

Regarding norms, the operational definition used here relates to patients' perceptions of social pressure or relevant others' beliefs that may influence their decision-making about medication taking [27]. Important influences may include others' approval or disapproval of a behavior or the knowledge that some behaviors cannot be performed without assistance [36]. An

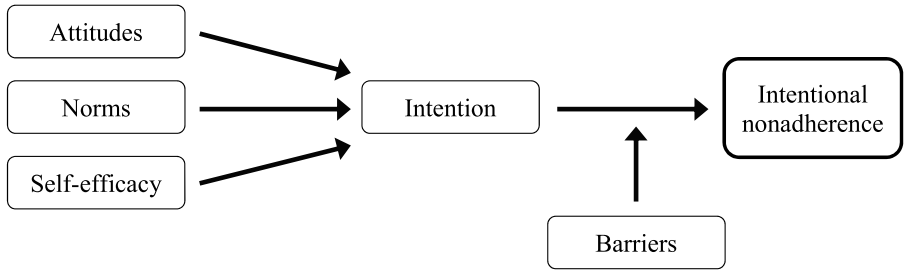


FIGURE 2 | Modified integrative model of behavioral prediction [34, 35].

11-item investigator-developed instrument based on previous work [24, 37–41] was used to measure normative beliefs about IS (e.g., "Some of my family members disapprove that I have to take immunosuppressive medications") [24, 27, 30]. Patients were asked to rate items on a 5-point Likert-type scale ranging from 1 (strongly disagree) to 5 (strongly agree). As psychometric analysis confirmed the instrument's unidimensionality, a mean score was calculated across all items. This instrument's Cronbach's *alpha* was 0.94 [27].

Self-Efficacy

Self-efficacy was defined as the patients' confidence in their ability to take their IS in a given situation [27]. This confidence depends on perceived skills and possibly the expected cooperation of others [36]. Regarding IS, self-efficacy behavior was assessed using the 23-item Long-Term Medication Behavior Self-Efficacy Scale [42]. Items were rated on a 5-point Likert-type scale ranging from 1 (not at all confident) to 5 (totally confident). As psychometric analysis showed that this scale is unidimensional, an overall mean score was calculated for self-efficacy. Cronbach's alpha was 0.98 [42].

Barriers

Barriers were operationalized as personal circumstances or environmental constraints that might either prevent a patient from enacting an intended behavior or limit their capacity to perform desired actions [12]. The 19-item IS Medication Adherence Barriers instrument represents barriers identified by patients attempting to follow IS regimens [30]. Items (e.g., "I find it hard to swallow my IS medication", "I find it hard to take my IS medication because I experience side-effects," or "I find it hard to go away from home and plan the day because I have to take my IS medication") are rated on a unidimensional 5-point Likert scale ranging from 1 (never) to 5 (always). A mean score across the 19 items is then calculated. This instrument was developed by the Transplant360 Task Force [43]. Its Cronbach's alpha was 0.89.

Financial Barriers

Financial barriers—healthcare system-level factors—, are cost-related difficulties that hinder a patient from enacting a behavior [36]. Those affecting IS taking are often related to health insurance not or only partially covering the medication costs, necessitating high monthly expenditures [15]. Financial barriers were assessed using six investigator-developed items, which were dichotomized for the purpose of this study: Health insurance covering costs of IS (no versus yes partly, yes fully); Out-of-pocket monthly cost of IS (0–$20, $20.01–$60, $60.01–$110 versus >110$); Feeling that one has enough money to pay for IS (not enough versus mostly enough, enough, more than enough); Prescription for IS not filled because it was too expensive (never versus once, twice, 3–4x, 5–6x, ≥7x); Skipping a dose to make prescription for IS last longer due to lack of money (no never versus yes sometimes, yes often); and Reducing dose to make prescription for IS last longer due to lack of money (no never versus yes sometimes, yes often).

Clinical Outcomes

Two clinical outcomes were assessed (see **Table 1**): time since transplantation (in years); and number of treated rejections experienced per year in follow-up.

Data Collection

The BRIGHT study's data collection has been described previously [27, 30]. Data were collected from early 2012–early 2017 [27].

Data Analysis

We used descriptive statistics as appropriate based on measurement levels and data distributions. Hierarchical inferential statistics, i.e., multilevel logistic regression analysis, was used to assess associations between INA (i.e., drug holiday and dose alteration), IMBP correlates (**Figure 2**) and clinical outcomes, while controlling for international variability. Socio-demographic characteristics, financial barriers and clinical outcomes that initial analyses suggested were significantly associated with INA were included in the model. Financial barrier-related data were dichotomized before inclusion. Generalized linear regression with random effects was used in the multilevel analysis of international variability. However, the small INA sample size did not allow for moderator analysis with significant or otherwise meaningful results.

Missing data analysis was performed, including a visual analysis with *Amelia II* [44] (multiple imputation software). Analysis of distribution did not reveal any substantial

differences between the 20 patients (1.4%) who provided insufficient information relative to BAASIS© to assess adherence [32]. For further analysis, the authors proceeded with list-wise deletion.

The software package used for statistical analysis was R, version 4.0.2, 2020-06-22. [45] Statistical significance was set at $p<.05$.

RESULTS

Sample Characteristics

This analysis included 1,397 patients (details provided elsewhere) [27]. Participants' mean age was 53.7 (±13.2) years; 27.1% were female; 84.9% were of Caucasian origin. At time of interview, most (68.4%) were married or living with partners; 19.0% were living alone. The majority (72.8%) had completed secondary school or higher, with 22.0% holding University degrees; 26.2% were employed or self-employed; 28.9% were temporarily or fully unable to work; and 33.4% were retired. Financial barriers such as health insurance not covering IS costs and high monthly out-of-pocket IS expenses were reported respectively by 9.2% and 9.5% of patients. A more detailed overview of patient-level characteristics can be found in the **Tables 1**, **2**.

Intentional Non-Adherence

Prevalence

Intentional NA was observed in 46 of 1,397 patients (3.3%). Drug holidays were reported by 24 (1.7%), dose alteration by 20 (1.4%). Two (0.1%) reported a combination of drug holiday and dose alteration.

International Variability

International variability was high, with INA prevalence spanning from 0% in Germany to 9.8% in Australia (**Figure 3**). Drug holidays ranged from 0% in Germany to 4.3% in Switzerland, and dose alteration from 0% in Germany to 7.8% in Australia.

Correlates of Intentional Non-Adherence

In univariable analyses, lower age (OR = 0.98, CI = 0.96–0.99), being of Asian or *other* origin (OR = 4.10, CI = 1.17–14.19 and OR = 5.02, CI = 1.66–15.16), and university education were associated with higher INA (OR = 2.46, CI = 1.04–5.83). Lack of insurance coverage for IS was the only financial barrier significantly related to a higher risk of INA (OR = 2.21, CI = 1.01–4.87). Low intention was strongly related to INA (OR = 0.54, CI = 0.38–0.77). High worries (OR = 1.81, CI = 1.15–2.85), low self-efficacy (OR = 0.59, CI = 0.44–0.80) and high barriers (OR = 4.90, CI = 2.73–8.80) also significantly increased the odds for INA (**Table 3**).

The multivariate analysis of demographic correlates showed that having a university degree was significantly related to INA (OR = 2.95, CI = 1.05–8.29). Intentional NA was strongly associated with the IMBP correlate barriers (OR = 4.81, CI = 2.17–10.65) and insurance not covering IS costs (OR = 2.32, CI = 1.02–5.25).

When controlling for differences between countries (as a random effect), being of Asian origin (b = 0.076, p = 0.036), being a widow (b = 0.077, p = 0.012), not living alone (b = 0.032, p = 0.035) and having a university degree (b = 0.035, p = 0.035) correlated with a higher risk of INA. Barriers remained the only IMBP that is associated with a higher risk of INA (b = 0.11, $p <$ 0.001).

Clinical Outcomes

On average, patients had been transplanted 3.4 years (±1.4) and had experienced 0.9 (±1.5) treated rejections per year in follow-up. The proportion of patients who had experienced at least one rejection episode during follow-up was not significantly higher in those reporting INA (n = 22/46, 47.8%) than in the overall sample (n = 551/1,397, 39.4%; OR = 1.48, CI = 0.82–2.68).

DISCUSSION

To our knowledge, this is the first study to investigate the prevalence and correlates of INA to immunosuppressive medication after HTx internationally. Its major strengths are its international multisite sample and the use of a theoretical model to guide the exploration of correlates of intentional non-adherence [3, 19, 46, 47].

Intentional Non-Adherence

Our sample's overall INA rate, 3.3% (n = 46/1,397), was lower than those reported in comparable clinical populations [32]. Few studies have been published distinguishing drug holiday and dose alterations of IS after HTx using the BAASIS©; [32, 48–51]. BAASIS©, as a self-report method, is embedded in the ABC taxonomy, assessing phases of medication adherence and providing bases for operationalization and assessment of INA (i.e., drug holidays or dose alterations) [46, 52, 53]. Respectively, three and four studies have reported higher prevalence either of drug holidays (8.3%–11.0%) [49–51] or of dose alterations (5.6%–12.1%) [48–51]. Skipping multiple doses—drug holiday—represents a higher risk for negative clinical consequences and is especially concerning [17, 40, 54]. Despite similar medication regimens described, i.e., drug type and twice-daily dosing, patients included in these studies had longer times—4.8 and 7.5 years—since transplantation [48, 49]; and non-adherence has been shown, although inconsistently, to increase over time [55–57]. Compared to non-adherence rates for other types of medication (e.g., adjuvant endocrine therapy in breast cancer: 7%–14%; anti-retroviral therapy in HIV: 17.8%; tyrosine kinase inhibitors in chronic myeloid leukemia: 27%), the rates reported for post-HTx INA to immunosuppressants are among the lowest in literature [52, 58–63]. This may be explained by immunosuppressants' low forgiveness—the need for extremely close adherence to maintain their effects [64–66]—which focusses patients' attention very closely on their regimens [67–69]. Compared to recipients of other solid organs—such as lung, liver, and kidney—[17, 25, 54, 70] heart recipients' low INA rates may also reflect the limited therapeutic options available in

TABLE 2 | Financial barriers for total group and patients showing intentional non-adherence.

Variables	Values/scoring	Total sample	Intentional non-adherence	
		N (%)	N (%)	OR[a] (95% CI)
		N = 1,397	N = 46	
Health insurance covering costs of IS medication	**No[b]**	128 (9.2%)	8 (17.4%)	**2.21* (1.01–4.87)**
	Yes, partly	502 (35.9%)	17 (37.0%)	Reference
	Yes, fully	743 (53.2%)	19 (41.3%)	
	Missing	24 (1.7%)	2 (4.3%)	
Out-of-pocket monthly cost of IS medication	**>110$[b,c]**	133 (9.5%)	8 (17.4%)	2.04 (0.93–4.48)
	60.01–110$	129 (9.2%)	5 (10.9%)	
	20.01–60$	241 (17.3%)	7 (15.2%)	Reference
	0–20$	850 (60.8%)	25 (54.3%)	
	Missing	44 (3.1%)	1 (2.2%)	
Feeling having enough money to pay for IS medication	**Not enough[b]**	243 (17.4%)	9 (19.6%)	1.27 (0.60–2.70)
	Mostly enough	244 (17.5%)	8 (17.4%)	
	Enough	615 (44.0%)	21 (45.7%)	Reference
	More than enough	222 (15.9%)	3 (6.5%)	
	Missing	73 (5.2%)	5 (10.9%)	
Prescription for IS medication not filled because it was too expensive	**Never[b]**	1,349 (96.6%)	44 (95.7%)	1.54 (0.20–11.80)
	Once	7 (0.5%)	0	
	Twice	8 (0.6%)	0	
	3–4x	4 (0.3%)	1 (2.2%)	Reference
	5–6x	0	0	
	≥7x	1 (0.1%)	0	
	Missing	28 (2.0%)	1 (2.2%)	
Skipping a dose to make prescription for IS medication last longer due to lack of money	**No, never[b]**	1,344 (96.2%)	44 (95.7%)	1.08 (0.14–8.15)
	Yes, sometimes	21 (1.5%)	1 (2.2%)	Reference
	Yes, often	8 (0.6%)	0	
	Missing	24 (1.7%)	1 (2.2%)	
Reducing dose to make prescription for IS medication last longer due to lack of money	**No, never[b]**	1,349 (96.6%)	43 (93.5%)	3.16 (0.71–14.01)
	Yes, sometimes	17 (1.2%)	2 (4.3%)	Reference
	Yes, often	4 (0.3%)	0	
	Missing	27 (1.9%)	1 (2.2%)	

*OR, odds ratio; CI, confidence interval; IS, immunosuppressive. *p < 0.05, **p < 0.01, ***p < 0.001.*

[a]*Logistic regression for bivariate analysis [31], bold when significant.*

[b]*Dichotomisation, comparison of bold value against others for bivariate analysis [31].*

[c]*According to currency, the cut-off values were set as follows, US$ = 20, 60, 110/£ = 13, 29, 53/€ = 15, 45, 83/CA$ = 19, 57, 104.*

case of graft rejection, dysfunction or loss [20, 71]. While kidney recipients have the option, for example, of dialysis or renal transplantation from living donors, a heart transplant is usually a one in a life-time gift [51, 72–75].

International Variations and Financial Barriers

Our findings show that INA prevalence varies internationally, the highest rates being observed in Australia (9.8%), Brazil (6.0%) and Canada (5.0%). A range of country-level correlates (e.g., insurance coverage, financial barriers, access to medication) have been offered as explanations [76–78]. Measurable moderating variables, such as low insurance coverage for IS in Australia, the USA and Canada [76], or the perceived financial burden of high monthly out-of-pocket expenses in Switzerland [29] may help explain some disparities. Low accessibility, such as greater distance to the transplant center, does not seem to favor INA. [29, 77] When referring to delayed access to a specialist or higher waiting times for appointments, e.g., Canada and oppositely Germany, low accessibility appears to match higher INA rates. [29] This implies that better organized services help compensate low accessibility and prevent INA. [77].

Correlates of Intentional Non-Adherence

Belonging to an ethnic minority—more specifically, being of Asian or of other origin—increased the odds of INA. This may result from lower levels of support within these populations [79–81] or variations in social desirability across ethnic groups regarding organ transplantation [80]. Social norms may also increase the tendency to underreport INA in favor of other forms of NA, such as forgetfulness [82]. In line with previous research, having a university degree was significantly related to higher rates of INA [71, 83]. It may be assumed that higher-educated persons feel they have the skills to recognize and weigh IS-related benefits and risks [72]. It also strongly suggests that INA does not arise from a lack of understanding [84] or health literacy [58, 70, 85–87]. Instead, it suggests that INA is more closely related to the decision-making process outlined by

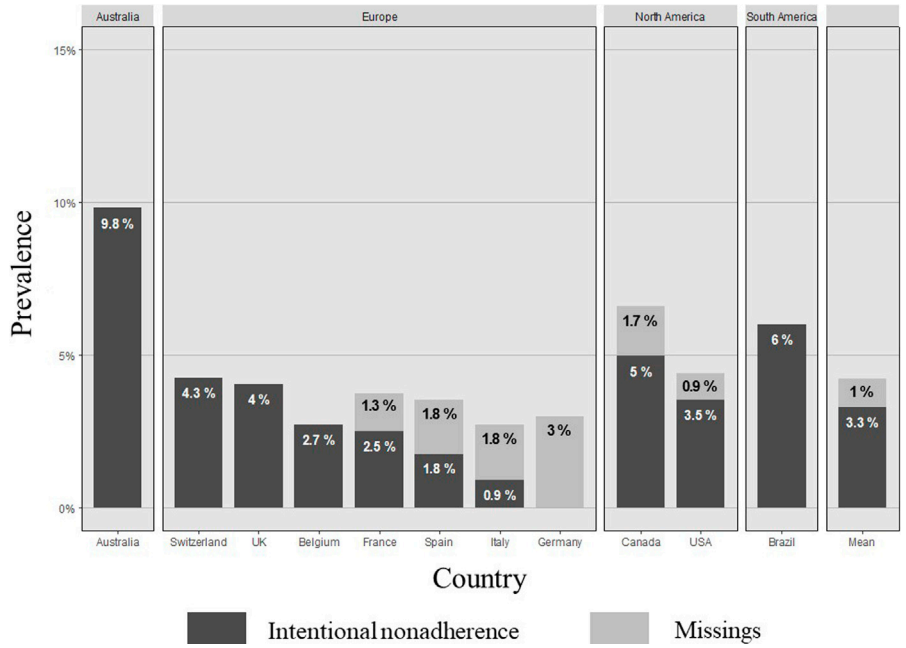


FIGURE 3 | Prevalence of intentional non-adherence internationally. Sample, N (%): Australia, 51 (3.7); Switzerland, 47 (3.4); UK, 99 (7.1); Belgium, 74 (5.3); France, 158 (11.5); Spain, 223 (16.2); Italy, 109 (7.9); Germany, 65 (4.8); Canada, 119 (8.7); USA, 337 (24.3); Brazil, 100 (7.2). Missings: France, 1.3%; Spain, 1.8%; Italy, 1.8%; Germany, 3.0%; Canada, 1.7%; USA, 0.9%; Mean, 1.0%.

the theory of planned behavior [88] and how the patient balances the benefits of following the IS regimen against the risks and barriers, e.g., side-effects, taking constraints or disruption of their normal routines [5, 17, 81, 89].

IMBP Correlates of Intentional Non-Adherence

Worries (i.e., negative feelings) towards following the IS regimen as prescribed were particularly strongly related to INA. This supports the idea that intentional behavior, even regarding the weighing-out of necessities and concerns, is tipped more by patients' fears and worries (e.g., "IS medication is toxic for my body" or "doctors place too much trust in IS medication") than by clinicians' assurances that IS is necessary and beneficial [25, 75, 88]. Therefore, a slightly heightened sense of worry could greatly increase a patient's risk of attempting to modulate the IS' side-effects (e.g., "When I suffer from uncomfortable side effects, it is best if I reduce the dosage of my IS medication a little") [90] or to increase their compatibility with daily routines (e.g., "Taking IS medication disrupts my daily life") [5, 88].

Self-efficacy correlated strongly with *lower* rates of INA. Our results show lower levels of self-efficacy in patients indicating INA than in the overall sample (3.95 ± 0.89 vs. 4.36 ± 0.81, $p < .01$). Self-efficacy relates to patients' beliefs in their ability to affect a situation. It is demonstrated by patients being confident about taking IS in a given situation [27, 91]. Patients experiencing IS constraints may be tempted to cut back on or briefly halt their IS to limit their side-effects, test their effectiveness or increase their sense of control over their disease and its treatment [92]. When such INA behaviors occur, they reflect low self-efficacy, but foster a false sense of control [5]. This, in turn, leads to intentional and fully conscious non-adherence [91, 93].

Despite the intention to adhere to IS regimen, multiple barriers may hinder a patient from performing the necessary behaviors, such as taking multiple pills at once, taking IS whilst busy with other matters, taking them despite side-effects or having to follow an inconvenient schedule. Consequently, barriers were the strongest predictor of INA. Indeed, even when behaviors are intended, certain barriers can prevent patients from enacting them. This tendency supports the hypothesis that regimen-related constraints, especially difficulties taking IS, are more critical than the suspicion that IS is harmful [58].

Recent findings focusing on cost-related medication non-adherence also show that some financial barriers may relate to patient-level factors rather than healthcare system-level factors, i.e., whether "health insurance covers the cost of IS" or "monthly out-of-pocket expenses for IS [are manageable]" [51, 76, 94]. Examples of patient-level factors include attempts to "make prescriptions last longer" or "delay IS medication refills," and relate closely to how patients prefer to allocate funds [15, 76]. Regarding INA, these results emphasize the importance of addressing financial barriers at the patient level [76].

Limitations

The reliability of patient self-report is strongly dependent on the data collection techniques used, e.g., patient interview, and on how the patient understands collected information will be used. Both the wording of questions and the interviewer's attitude may influence the accuracy of the responses, as patients may believe it

TABLE 3 | Correlates of intentional non-adherence and bivariate analysis.

Variables	Values/scoring	Total sample	Intentional non-adherence	
		N; mean ± SD N (%)	N; mean ± SD N (%)	OR[a] (95% CI)
		N = 1,397	N = 46	
Predictors of the IMPB model				
Intention to adhere to the immunosuppressants regimen	1 (strongly disagree) to 5 (strongly agree)	1,376; 4.69 ± 0.53	45; 4.41 ± 0.68	**0.54*** (0.38–0.77)**
	Missing	21 (1.50)	1 (2.17)	
Barriers to take immunosuppressants as prescribed	1 (never) to 5 (always)	1,378; 1.19 ± 0.30	45; 1.47 ± 0.54	**4.90*** (2.73–8.80)**
	Missing	19 (1.36)	1 (2.17)	
Attitudes towards taking immunosuppressants (dimension positive attitudes/looking towards the future)	1 (strongly disagree) to 5 (strongly agree)	1,375; 4.46 ± 0.46	45; 4.46 ± 0.40	0.99 (0.51–1.89)
	Missing	22 (1.57)	1 (2.17)	
Attitudes towards taking immunosuppressants (dimension worries)	1 (strongly disagree) to 5 (strongly agree)	1,370; 1.91 ± 0.57	45; 2.12 ± 0.60	**1.81* (1.15–2.85)**
	Missing	27 (1.93)	1 (2.17)	
Perceived norms related to immunosuppressants	1 (strongly disagree) to 5 (strongly agree)	1,241; 1.30 ± 0.60	42; 1.43 ± 0.61	1.36 (0.89–2.08)
	Missing	156 (11.17)	4 (8.70)	
Self-efficacy with taking immunosuppressants	1 (not at all confident) to 5 (completely confident)	1,362; 4.36 ± 0.81	45; 3.95 ± 0.89	**0.59*** (0.44–0.80)**
	Missing	35 (2.51)	1 (2.17)	

*OR, odds ratio; CI, confidence interval. *p < 0.05, **p < 0.01, ***p < 0.001.*
[a]*Logistic regression for bivariate analysis [31], bold when significant.*

is more acceptable to have forgotten a dose than to have intentionally/purposely not taken it, i.e., social desirability bias. And if non-adherent patients refuse to participate because they consider their behaviors unacceptable, this will skew prevalence estimates for those behaviors downwards [52, 95–97]. At the same time, self-report helps gain a deeper insight into how IS is taken (i.e., number of pills taken per dose, doses taken) and why (i.e., open question on adherence) [96, 98]. Because our analyses of patients' behaviors rely quite heavily on those patients' underlying intentions, we assume our findings offer a firm basis for future research on targeted interventions [46, 96].

Although our operational definition implied a link between non-persistence and rational decision making, we did not approach non-persistence as INA. This sample's IS non-persistence rate (i.e., discontinuation of the regimen) was very low ($N = 7$, 0.5%). This finding echoed those of other studies, all of which reported very small prevalence (0.6%–3.1%) of medication non-persistence [17, 18, 49]. In all cases, including cases with a high relative rate of missing information on INA—e.g., Spain, Italy, Germany—, the number of cases involved were too low to allow in-depth analyses. Still, considering the clinical impact of non-persistence; [20, 65, 99, 100], further insight is needed to determine, for example, whether this measurement arises from a misunderstanding of the question. For example, there needs to be a clear distinction between interruptions in IS use that arise from regimen changes versus those where, contrary to their clinicians' advice, patients simply abandon their IS regimens for prolonged periods; [101–103]. The former represents a therapeutic adjustment, the latter a potentially life-threatening behavior based on a conscious but misguided (and hopefully preventable) decision [67, 83].

Also, as this was a cross-sectional study, no longitudinal data were collected. Therefore, it is not possible to draw inferences regarding INA's development or evolution. Patients were asked about their non-adherence over the last month. This cannot cover possible life-cycles of INA behaviors (i.e., it is not possible to say whether patients go through phases during which the type and level of non-adherence behaviors change) [92, 104]. While current findings suggest that non-adherence increases over time, [52, 57, 66, 70], applying these findings to INA will require data on intentionality and negative perceptions (worries) collected across multiple time points. In short, capturing INA's dynamic underlying nature will require further longitudinal research [105].

Conclusion

Based on a validated measurement (i.e., the BAASIS©) of intentional non-adherence to immunosuppressive medication (INA) [32], and referring to Fishbein's Integrative Model of Behavioral Prediction to further understand INA-relevant behavior, this large multi-center study assessed the prevalence of INA on an international level. INA occurs when patients intentionally alter their medication regimens against medical advice, i.e., via drug holidays and/or dose alteration. Our analyses indicated that the correlates most strongly associated with INA were having a university-level education, belonging to an ethnic minority, or lacking health insurance that covered IS costs. As reasons, patients commonly cite worries (e.g., burdensome side-effects) or barriers (e.g., constraints related to their medication regimens), or a desire to regain a sense of control over their lives. In addition to highlighting the

importance of patient-level factors associated specifically with INA, these findings support the development and use of individually-tailored interventions to decrease INA.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusion of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

Ethical approval was obtained from the participating centers' ethical boards or commissions prior to data collection. Informed written consent was obtained from all included patients, in line with guidelines of the Declaration of Helsinki [106]. Anonymity and confidentiality of data and patient information were assured during the study and the secondary analysis [27, 30].

AUTHOR CONTRIBUTIONS

SG, FD, and CR are BRIGHT study's principal and co-investigators. For the current study, MM, LB, and SG analyzed the data and wrote and critically revised the manuscript. All authors contributed to the article and approved the submitted version.

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CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Employment Status Following Heart Transplantation: Data From the Danish Nationwide Social Service Payment Register During 20 years

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Most studies on vocational rehabilitation after heart transplantation (HTX) are based on self-reported data. Danish registries include weekly longitudinal information on all public transfer payments. We intended to describe 20-year trends in employment status for the Danish heart-transplant recipients, and examine the influence of multimorbidity and socioeconomic position (SEP). Linking registry and Scandiatransplant data (1994–2018), we conducted a study in recipients of working age (19–63 years). The cohort contained 492 recipients (79% males) and the median (IQR) age was 52 years (43–57 years). Five years after HTX, 30% of the survived recipients participated on the labor market; 9% were in a flexible job with reduced health-related working capacity. Moreover, 60% were retired and 10% eligible for labor market participation were unemployed. Recipients with multimorbidity had a higher age and a lower prevalence of employment. Five years after HTX, characteristics of recipients with labor market participation were: living alone (27%) versus cohabitation (73%); low (36%) versus medium-high (64%) educational level; low (13%) or medium-high (87%) income group. Heart-transplant recipients with multimorbidity have a higher age and a lower prevalence of employment. Socioeconomically disadvantaged recipients had a lower prevalence of labor market participation, despite being younger compared with the socioeconomically advantaged.

Keywords: heart transplantation, labor market participation, socioeconomic position, multimorbidity, public transfer payments

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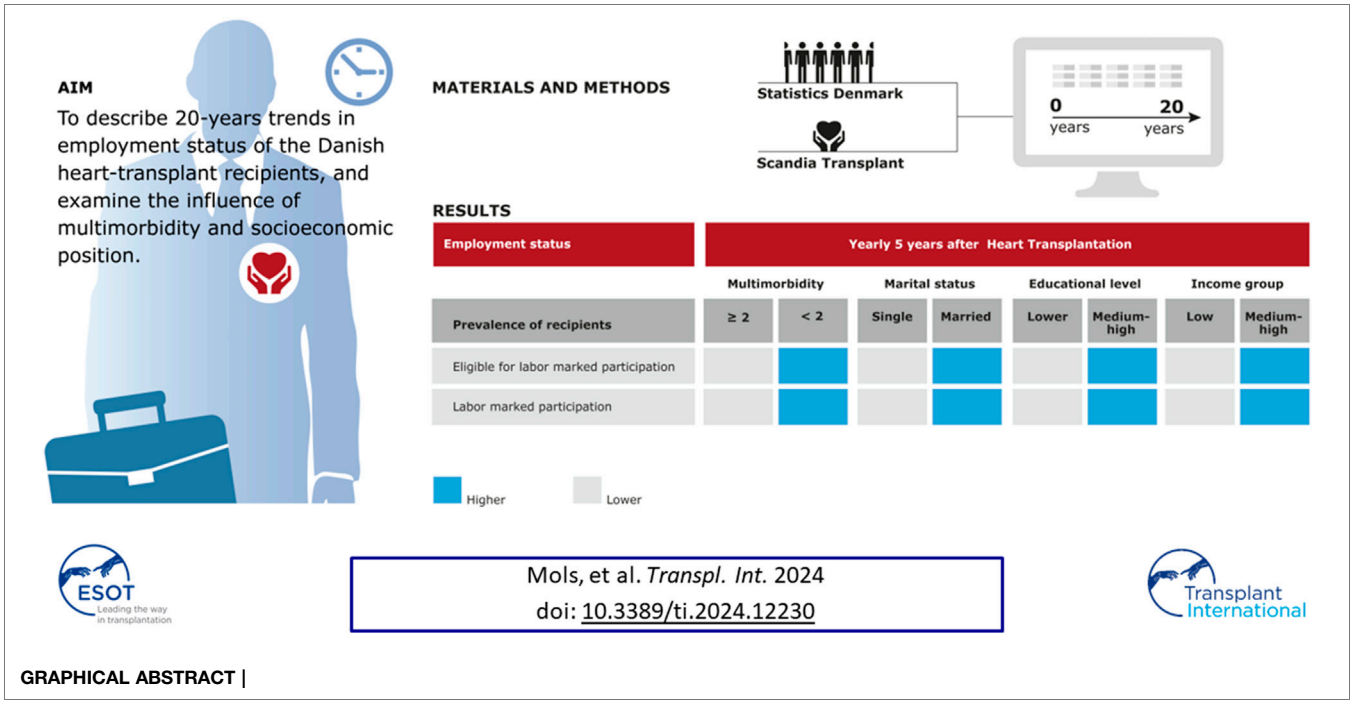
Abbreviations: ATC, Anatomical Therapeutic Chemical Classification system.; CRS, The Danish Civil Registrations System; DNPR, The Danish National Patient Registry; NPR, The Danish National Prescription Registry; DREAM, The Danish Rational Economic Agent Model Database; HF, Heart Failure; HTX, Heart transplantation; ICD, International Classification of Diseases; IQR, Interquartile Range; PCRR, The Psychiatric Central Research Register; SEP, Socioeconomic Position; STD, Scandia-transplant Database.



GRAPHICAL ABSTRACT |

INTRODUCTION

Heart transplantation (HTX) has become the definitive treatment influencing survival rates and quality of life in patients with end-stage heart failure (HF) [1, 2]. Worldwide, the median survival of adult heart-transplant recipients is 12 to 13 years and the 1-year survival rate is 91% [3]. During the last 30 years, advances in surgical techniques, perioperative management, and immunosuppressive therapies directed at acute graft rejection have improved life expectancy in heart-transplant recipients [3–5]. The improved prognosis has facilitated more attention to employment status post-HTX [2, 6, 7]. Employment is known to be essential for social identity, self-esteem, self-confidence, as well as mental and physical health in patients with HF [8, 9]. Moreover, labor market contribution carries economic advantages for both patients and society [8, 9].

Previous studies have reported a wide variation in the prevalence of return to work (31%–71%) in heart-transplant survivors [10–13]. Yet, studies on employment status after HTX have generally been based on questionnaires or other self-reported data. In Denmark, it is possible to make robust descriptions of labor market dynamics following HTX due to well-established and highly complete population-based registers and weekly longitudinal information on all public transfer payments from Danish authorities [14, 15]. A nationwide study in Denmark of patients with HF suggested that multimorbidity is associated with reduced chance of return to work within 1-year after first-time hospitalization [8]. Moreover, socioeconomic deprivation is known to be more likely in individuals with multimorbidity [16–19]. Improved insights into the influence of multimorbidity and socioeconomic position (SEP) on labor market participation in heart-transplant recipients may contribute to strategies to strengthen social recovery. Therefore, in this setting, we sought to describe 20-year trends in employment status for the Danish heart-transplant recipients, and examine the influence of multimorbidity and SEP.

MATERIALS AND METHODS

Setting and Data Sources

Denmark has a primarily tax-financed universal healthcare system with free access to healthcare for all residents regardless of employment status [15]. Moreover, public welfare benefits and other social services are obtainable for all residents. Denmark has a rich infrastructure of nationwide administrative and clinical registers of high quality [15]. All residents are assigned a permanent and unique 10-digit identifier that allows for both accurate linkage at individual level and complete long-term follow-up [20].

In the present study, we used data from the following nationwide registers:

- Scandiatransplant Database (STD), which collects clinical data on all Danish heart-transplant recipients since 1983 [21]. It is mandatory for hospitals to report to this database.
- The Danish Rational Economic Agent Model (DREAM) Database, integrated data on social service payment transfers. DREAM contains weekly information on

residents receiving any kind of public welfare payments since 1991 [14].

- The Danish National Patient Registry (DNPR) [22] containing information on discharges from somatic hospitals since 1977 and from outpatient and emergency room visits since 1995. Records include dates of admission and discharge, discharge diagnosis according the International Classification of Diseases (ICD-8 and since 1994 ICD-10 codes), along with codes for diagnostic and surgical procedures.
- The Psychiatric Central Research Register (PCRR) [23] containing information on all inpatient psychiatric diagnoses since 1969 and outpatient diagnoses since 1995.
- The Danish National Prescription Registry (NPR) [24], established in 1995 and containing data on all prescriptions reimbursed at Danish community pharmacies. Prescribed pharmacotherapies are coded according to the Anatomical Therapeutic Chemical [ATC] Classification system.
- Statistics Denmark's [25] education and income registers, which contain information on highest level of completed education and income.
- The Danish Civil Registrations System (CRS) [20] contains data on vital status, date of birth, gender as well as cohabitation and marital status with daily update.

Study Cohort and Definitions

Denmark has two transplant centers—at the University Hospital of Copenhagen and at Aarhus University Hospital. We identified a national cohort of Danish recipients who underwent first-time HTX between 1 January 1994, and 31 December 2018 by the STD. The index date was defined as the date of the first HTX in the STD. We retrieved data on age, gender, and civil status from the CRS [20]. We restricted the cohort to recipients in working age (19–63 years) at index date and alive on discharge date. This upper age limit was chosen to identify those with a labor market expectation of at least 1-year before retirement, typically at the age of 65 years. Recipients who were not recorded in the DREAM register (n = 9) were excluded. The number of heart-transplant recipients alive at end of follow-up was counted. In accordance with a national Danish HF study [8], age at index date was divided into three categories (19–40, 41–50, and +51 years). Time since HTX was defined as 0–1, >1–10, and >10 years.

We identified non-psychiatric and psychiatric conditions by ICD codes registered in the DNPR [15] 10 years before index date (primary and secondary diagnoses) (**Supplementary Table S1**). Treatment with pharmacotherapies was defined as ≥1 redeemed prescription 6 months before index date according to the NPR [15]. The number of cardiovascular pharmacotherapies was summarized, and polypharmacy was defined as redeeming at least one prescription for ≥5 different cardiovascular agents [15] (**Supplementary Table S2**).

Consistent with prior definitions of multimorbidity in Danish studies [26, 27], we calculated the number of non-psychiatric and psychiatric conditions 10 years before index date based on data obtained from the DNPR [15, 22] and the PCRR [15, 23]. The used algorithm estimated multimorbidity as the co-occurrence of two or more chronic conditions included in 11 comprehensive chronic disease groups. We summarized the number of multimorbidity based on the count of chronic disease groups, excluding all cardiovascular diseases (**Supplementary Table S1**).

We retrieved individual-level SEP data from the CRS and Statistics Denmark the year before index date [20, 25]. The SEP compiled information on cohabitation status, marital status, educational level, and personal income group. Cohabitation status was defined as living alone or cohabitation (living with other individuals) and marital status as married (registered partnership) or single (including never or not yet married, divorced, or widowed). Based on international standard classification, highest educational level was divided into three groups: primary and lower education (low); upper secondary education and academy profession (medium); bachelor and above (high). To account for inflation and salary changes over time, we determined personal income (pre-tax total) based on the annual percentiles in the Danish population. We classified personal income into percentiles and used the 25th percentile as cut-off point for low (≤25th percentile) and medium-high (>25th percentile) income (**Supplementary Table S3**). Average 5-year household income was not included since data on household income statistics was only available after 2004 in Danish registers.

Labor Market Participation

We complied information from the DREAM register on labor market participation [14]. For each week starting 1 year before the index date (week −52) and continuing for up to 5 years, we grouped patients into six categories of employment status according to the type of social transfer benefits received: regular employment (i.e., employed or receiving parental leave payments, benefits due to sick child, or vacation payments); flexible job (a job for those with reduced health-related working capacity); health-related work absenteeism (i.e., sick leave, unemployed awaiting flexible job, rehabilitation, or work ability clarification); unemployment, not health related (i.e., unemployment benefit or social assistance, not health related); retirement (early retirement pensions, post-employment retirement, retirement); censoring or death. The lengths of work disability periods financed by the employer (not recorded in DREAM) have varied between 14 and 30 days during the 20-year period-analyzed (**Supplementary Table S4**). Baseline employment status was identified by the week before the week of HTX (week −1).

Statistical Analysis

Continuous baseline characteristics were presented as median values with 25th–75th interquartile range (IQR) because the observed skewedness in the data. Categorical variables were presented as numbers and percentages. Recipients were followed until 1 January 2019, death, or emigration, whichever came first.

To describe the weekly changes in employment status 1 year before (week −52) and 2 years after (week 104) index date, we graphically illustrated prevalence of each of the following categories for each week: regular employment; flexible job;

TABLE 1 | Classification of labor marked participation.

Categorization	Weekly employment status	Sankey diagram	Employment status by multimorbidity and SEP	
Education	Unemployed, not health related	-	-	-
Regular employment	Regular employment	Regular employment	Labor marked participation	Eligible for labor marked participation
Flexible job	Flexible job	Reduced workability		
Unemployed, not health related	Unemployed, not health related	-	-	
Health-related work absenteeism	Health-related work absenteeism	Reduced workability	-	
Retirement	Retirement	Retirement	-	-
Emigrated	Censored or Death	-	-	-
End of study				

SEP, socioeconomic position.

health-related work absenteeism; unemployment, not health related; retirement; censoring or death (**Table 1**) (**Supplementary Table S4**). We have followed the Statistics Denmark's rules on sensitive and personal data and therefore we do not report aggregated results based on less than five observations or numbers below five. Thus, the "education" category was merged together with the category "unemployed, not health related." Moreover, we hided the categories of "censored" or "death" until there were at least five patients in each of them.

Sankey flow illustration is a technique for data visualizations that emphasizes movement or flow from one state to another [28]. We used the Sankey graphical illustrations to display the movements between heart-transplant recipients in regular employment, with reduced work ability, and retired 1 year before (week −52) to 1 year (week 52) after index date. We defined reduced work ability by recipients in flexible job or at health-related work absenteeism because recipients in these social payment groups are unable or have limited ability to work due to illness. However, they do not receive permanent retirement benefits and thus have the possibility for increased vocational rehabilitation (**Table 1**) (**Supplementary Table S4**).

To examine the influence of multimorbidity and SEP on employment status and to identify the most vulnerable heart-transplant recipients presumably susceptible to reduced labor market participation, we stratified the analyses by all the variables of multimorbidity and SEP: degree of multimorbidity (0-1 versus 2+); cohabitation status (living alone versus cohabitation); marital status (single versus married); educational level (low versus medium-high [medium or high]); income group (low versus medium-high). To specifically describe the pattern of labor market participation 1 year before (year-1) HTX and annually within 5 years of follow-up (year 1, year 2, year 3, year 4, and year 5), we graphically displayed the prevalence of heart-transplant recipients by labor market participation, within the group of recipients eligible for labor market participation, overall as well as by the stratifying variables of multimorbidity and SEP. Heart-transplant recipients defined as ineligible for labor market participation included: education; retirement; emigrated; end of study; deaths. Heart-transplant recipients identified with labor market participation included individuals with regular employment or flexible jobs (**Table 1**) (**Supplementary Table S4**).

Analyses were conducted using the SAS Statistical Software version 9.4 (SAS Institute, Cary, NC) and R version 4.1.0 (2021-05-18).

RESULTS

A total of 649 heart-transplant recipients were identified during the study period. Of these, 492 were of working age (19–63 years) at the time of surgery, registered in the DREAM database and alive at discharge. The cohort contained 390 males (79%) and the median (IQR) age was 52 years (43–57 years). The three most prevalent non-psychiatric conditions before index-date in the HTX cohort were HF (87%) followed by cardiomyopathy (67%) and cardiac arrhythmias (48%). Psychiatric conditions were observed in less than 1% of recipients. The median (IQR) number of both non-psychiatric (excluding cardiovascular diseases) and psychiatric conditions was 1 (1-2) (**Table 2**).

Figure 1 displays the dynamic patterns in weekly changes in employment 1 year before and up to 2 years after HTX. The prevalence of regular employment 1 year before index date was 38%, decreasing to 12% at surgery, and increasing to 21% 2 years after index date. Recipients in a flexible job showed a stable pattern with approximately 6% having reduced health-related working capacity during the study period. The prevalence of heart-transplant recipients with health-related work absenteeism was highest at index date (35%), whereas the prevalence was 9% 2 years after surgery. Eight percent of the recipients were unemployed, not health related, 1 year before HTX versus 2% after 2 years. The prevalence of recipients on retirement increased the year up to HTX, while the prevalence was steady and approximately 50% 2 years after surgery. Four weeks before HTX, the prevalences were approximately: regular employment (18%); flexible job (6%); health-related work absenteeism (29%); unemployment, not health related (4%); retirement (43%).

TABLE 2 | Baseline characteristics of heart-transplant recipients.

	Total
	***N* = 492**
Gender	
Male	390 (79)
Female	102 (21)
Age	
Median (IQR)	52 (43–57)
Age groups	
19–40	114 (23)
41–50	342 (70)
+51	36 (7)
Follow-up time in years	
0–1	33 (7)
1–5	115 (23)
5–10	122 (25)
10+	222 (45)
Alive at end of follow-up	306 (62)
Non-psychiatric conditions (10 years prior to the index date)	
Cardiovascular disease	
Myocardial infarction	182 (37)
Angina Pectoris	216 (45)
Heart failure	429 (87)
Heart valve diseases	58 (12)
Cardiac arrhythmias	237 (48)
Congenital heart disease	34 (7)
Cardiomyopathy	328 (67)
Cardiac inflammation	48 (10)
Aortic disease	NA
Peripheral arterial disease	10 (2)
Cerebrovascular disease	42 (9)
Cardiogenic shock and pulmonary edema	48 (10)
Hypertension	62 (13)
Diabetes	64 (13)
Chronic obstructive pulmonary disease	49 (10)
Cancer	19 (4)
Chronic neurological disease	8 (2)
Chronic arthritis	NA
Chronic bowel disease	7 (1)
Chronic liver disease	11 (2)
Chronic kidney disease	24 (5)
Psychiatric conditions (10 years prior to the index date)	NA
Multimorbidity (10 years prior to the index date)	
Number of chronic diseases, median (IQR)	1 (1–2)
Cardiovascular polypharmacy (6 months prior to the index date) [a]	
Prescribed medications ≥5	276 (56)
Cohabitation status	
Living alone	141 (29)
Cohabitation	351 (71)
Marital status	
Single	191 (39)
Married	301 (61)
Highest obtained educational degree	
Low (primary and lower secondary education)	151 (31)
Medium (upper secondary education and academy profession degree)	234 (48)
High (bachelor and above)	95 (19)
Missing	12 (2)
Personal income group	
Low income (≤25th percentile)	57 (12)
Medium-high income (>25th percentile)	435 (88)
Employment status	
Regular employment	77 (16)
Flexible job	28 (6)
Unemployment, not health related	17 (3)
Health-related work absenteeism	152 (31)
Retirement	218 (44)

Values are n *(%).*

NA, not available due to data protection.

[a]*Data available since 1995 in the Danish National Prescription Registry.*

Through the Sankey flow diagram in **Figure 2**, movements from 1 year before to 1 year after index date were observed between the groups of heart-transplant recipients in regular employment, with reduced work ability, or on retirement. Twenty-one percent of recipients with regular employment as well as 34% with reduced work ability moved to the retirement group. Within the group of recipients with regular employment, 27% moved to the group with reduced workability from 1 year before to 1 year after HTX. The movement from reduced work ability to regular employment was observed in 15% of the heart-transplant recipients.

Prevalence estimates of labor market participation within the group of recipients eligible for labor market participation at 1 year before HTX to 5 years after as well as prevalence by the stratified variables of multimorbidity and SEP are depicted in **Figure 3**. One year after HTX, 26% of the recipients participated in the labor market, increasing to 30% after 5 years (9% in a flexible job; 21% in a regular job). In the time between 2–5 years after index date, approximately 10% eligible for labor market participation did not participate on the labor market. Those recipients within the lowest age interval (19–40 years) compared to the highest age interval (51–63 years), presented higher prevalence with labor market participation (**Figure 4**). In recipients with at least two chronic diseases, the prevalence of both recipients eligible for and with labor market participation was lower compared with recipients with no more than one chronic disease (**Figure 3**). Of notice, we found no indication of differences in age between recipients with 0-1 versus 2+ chronic diseases (**Supplementary Figure S1**). We observed a socioeconomic influence in labor market participation. In heart-transplant recipients living alone, being single, with low educational level, or in the lowest income group, the prevalence of labor marked participation was lower during the study period, though less pronounced in recipients living alone (**Figure 3**). Except for educational level, the most socioeconomically disadvantaged heart-transplant recipients were younger (**Supplementary Figure S1**). Five years after HTX, characteristics of recipients with labor market participation were: living alone (27%) versus cohabitation (73%); single (35%) versus married (65%); low (36%) or medium-high (64%) educational level; low (13%) or medium-high (87%) income group.

DISCUSSION

Our nationwide study in heart-transplant recipients is the first to describe long-term employment dynamics with a high weekly accuracy. We had several novel findings: i) 5 years after HTX, 30% of the recipients participated on the labor market, 9% of those were in a flexible job; ii): sixty percent of survived recipients were retired as well as 10% of recipients eligible for labor market participation was unemployed 5 years after HTX; iii) recipients with multimorbidity had a higher age and a lower prevalence of employment; iv) socioeconomically disadvantaged heart-transplant recipients had a lower prevalence of labor market

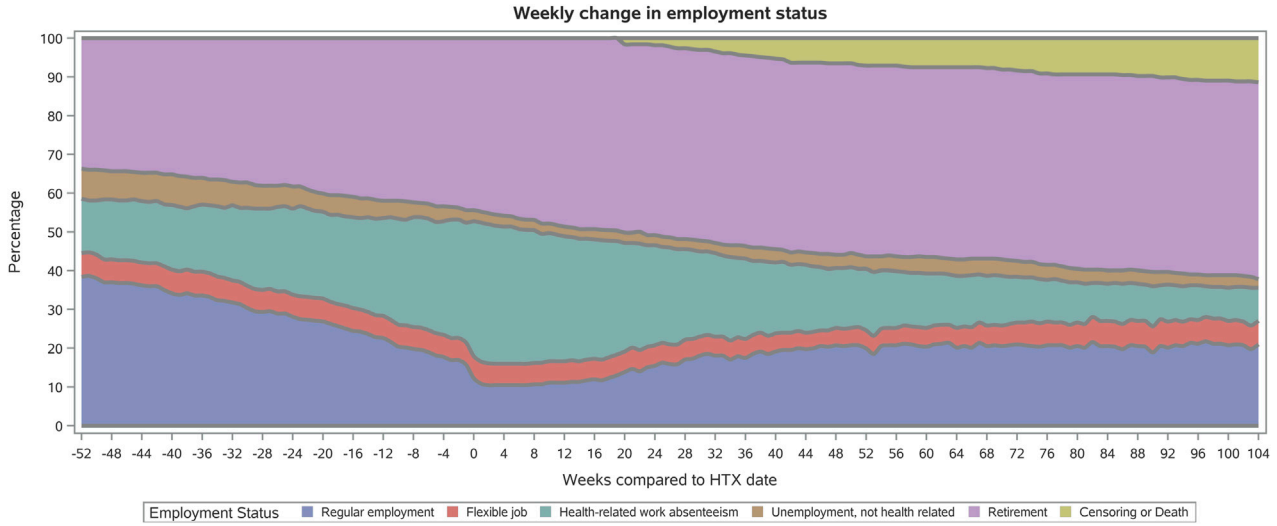


FIGURE 1 | Weekly employment status in heart-transplant recipients from 1 year before to 1 year after surgery. HTX, heart transplantation.

participation, despite being younger than the socioeconomically advantaged.

Previous studies have reported return to work following HTX [10–12, 29]. However, these studies did not describe detailed labor market participation by public transfer payments from authorities. White-Williams et al. performed [13] a questionnaire survey study in 237 heart-transplant recipients from the University Medical Centers in the United States (US). Pre-transplant (listed for HTX date), 17% of recipients were active on the labor market, increasing to 26% 1 year after surgery. Only, 45% of the recipients working 1-year post-transplant had also been working pre-transplant [13]. Kristen et al. (2009) [10] forwarded a questionnaire to 150 heart-transplant recipients 8.5 ± 0.4 years after surgery at a German university hospital. Thirty-six percent of recipients were of working age (<65 years) and employed after 12.6 ± 1.9 months [10]. A single-center study (2019) [11] included survived recipients attending a Scottish heart-transplant clinic (n = 154). One year before HTX, 61% (n = 47) of recipients were working. Of those, 83% (n = 39) returned to work and 21% had reduced working hours [11]. In the newly presented UNOS (United Network for Organ Sharing) database study, they addressed the prevalence of employment following HTX in the US [12]. The study included 10,132 recipients who survived at least 1-year (75% were males). Median (IQR) age in the non-working group was 51 years (42–56) versus 49 years (39–55 years) in the working group. Twenty-two percent of survived recipients were employed 1 year after surgery and employment prevalence of 2-year survivors increased to 32.9%. Within the group of recipients with employment 1-year after HTX, 62.8% were not working at listing or surgery date. Moreover, 16.1% who were not working at listing or surgery date obtained a working position afterwards [12]. Likewise, a newly published systematic review [30] on employment following thoracic transplantation reported that employment ranged from 19.7% to 69.4% for heart-transplant recipients [30]. The findings from the review and individual studies varied considerably. Discrepancies between these results may be explained by a variety of reasons, including inclusion criteria (e.g., working age interval; labor market participation status at index data), measures of labor market participation (e.g., questionnaire-based data; other self-reported data; question-asking technique at clinical visits), and national government set-up (e.g., universal public welfare benefits; other social services or more selective welfare stats).

Our register-based approach allowed us to illustrate the movements in labor market participation dynamically 1 year before and up to 5 years after HTX. Our findings confirm the results based on the UNOS database with higher accuracy and prolonged long-term follow-up. Thus, approximately 30% of the survived heart-transplant recipients were employed long-term after surgery (21% in a regular job as well as 9% in flexible job). Additionally, we observed that only 5% of recipients moved from reduced workability to regular employment within the first year after HTX and the prevalence of retired recipients increased from 35% to 60%. These observations support the idea that with vocational rehabilitation, many heart-transplant recipients are able to participate on the labor market [2]. However, as shown in our data, 10%–12% of the recipients eligible for work are unemployed in the period 2–5 years after HTX, which could reflect missed facilitation of social recovery.

Several factors have been identified to influence labor market participation. The UNOS database study [12] found that independent predictors of obtaining employment after HTX were age, gender, employment status at time of listing or transplant, education, insurance status, ethnicity, and postoperative complications. However, the most influential predictor was reported to be the preoperative employment status [12]. Similarly, the review regarding thoracic transplantation reported that the most positively associated factors with employment post-

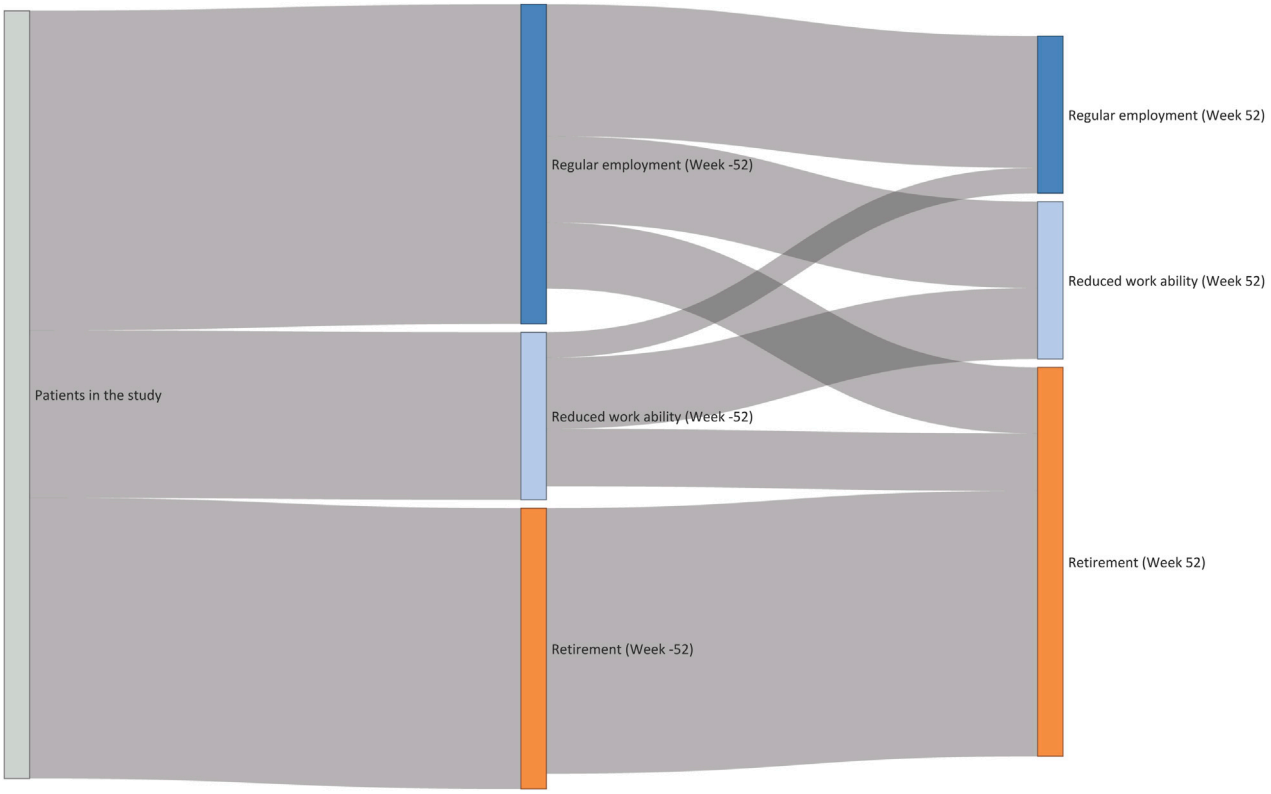


FIGURE 2 | Movements from 1 year before to 1 year after surgery within the groups of heart-transplant recipients in regular employment, with reduced work ability, or on retirement.

surgery were younger age, higher educational level, and pre-surgery employment, whereas the most negatively associated were longer duration of unemployment before transplant and Medicaid coverage [30]. Unlike these studies, we described the impact of multimorbidity and SEP on labor market participation. Our study showed that multimorbidity reduced both the prevalence of recipients eligible for labor market participation and the number of recipients with labor market participation during a period of 5 years after HTX. The Danish nationwide register-based cohort study [8] among first-time hospitalized patients with HF patients (n = 21,455) reported that comorbidities such as stroke (OR 0.55; 95% CI 0.45–0.69), chronic kidney disease (OR 0.46; 95% CI 0.36–0.59), and diabetes mellitus (OR 0.76; 95% CI 0.68–0.85) were all associated with a reduced likelihood of return to work [8]. Another Danish study [31] including 5,365 patients hospitalized with cardiac disease (mean [SD] age 50 years [11]; 70% males) reported that poor self-reported physical and mental health and high symptom burden were associated with detachment from the workforce within 1-year after discharge [31]. Along with our results, these studies support that heart-transplant recipients with the ability to work may have a better physical function, less limitation in their activities, lower age, and male gender.

Our results could indicate socioeconomic differences in workability following HTX. In accordance with the previous UNOS study [12], we found that in recipients with a lower level of education or income, the prevalence of both eligibility and participation on the labor market was lower. A possible explanation could be that individuals employed and having a low SEP are known to be more predisposed to unfavorable psychosocial working conditions and more likely face mental and social problems outside the workplace compared with those employed with a high SEP [32]. Thus, they might experience additional barriers to labor market participation. Accordingly, employment-related barriers for workability, such as less physically demanding jobs in individuals with a high educational level, is reported to facilitate more successful reintegration into the labor market [9, 12, 30, 32]. The slightly lower prevalence of both eligibility and labor market participation in heart-transplant recipients living alone or unmarried reflects that social support from a partner might result in improved self-management and physical recovery in heart-transplant recipients. This was supported by a recent Danish study [27] in heart-transplant recipients (n = 649; 78% males, 59% in age interval 41–60 years) suggesting a higher risk of first-time MACE (Major Adverse Cardiovascular Event) within 1–10 years after surgery (HR 1.46, 95% CI 0.98–2.17). In addition, the study illustrated that low educational level (adjusted HR 1.66, 95% CI 1.14–2.43) and low income (adjusted HR 1.81, 95% CI 1.02–3.22) were associated with a first-time MACE [27]. In agreement with our findings, these observations indicate a higher illness burden in socioeconomically disadvantaged heart-transplant recipients, thus leading to reduced workability.

In agreement with previous studies, our observations underline the call for more special attention to address employment status in the target group of socioeconomically

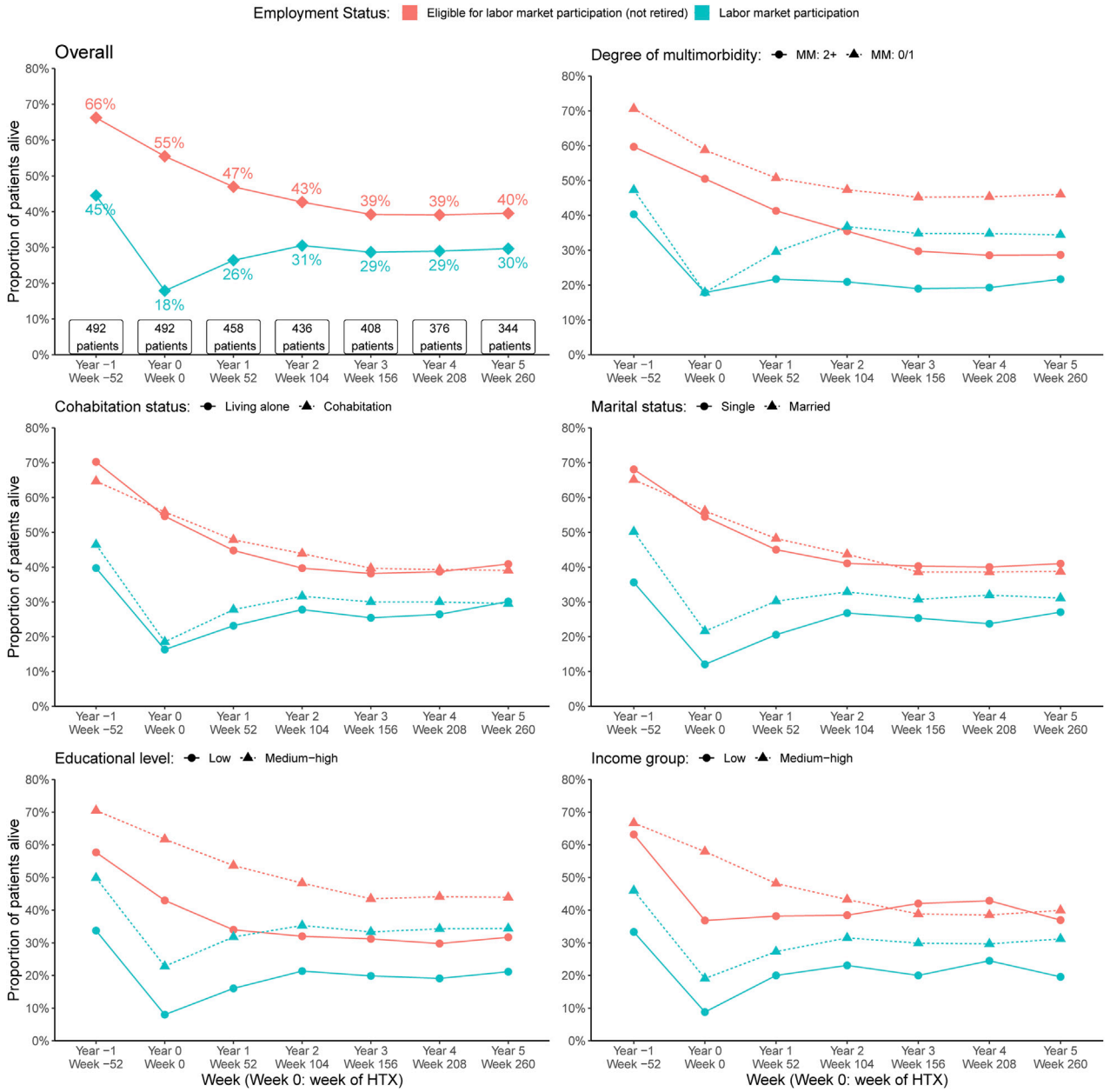


FIGURE 3 | Prevalence estimates of labor market participation within the group of recipients eligible for labor market participation at 1 year before HTX to 5 years after. The prevalences are depicted overall and by the stratifying variables of multimorbidity, cohabitation status, marital status, educational level, and income group. HTX, heart transplantation; MM, Multimorbidity.

disadvantaged heart-transplant recipients with multimorbidity. However, more research is needed into strategies to support workforce reintegration continuously and long-term after HTX. Systematic screening of heart-transplant recipients at follow-up visits for self-reported psychical, social, and mental factors associated with reduced labor market participation may be beneficial.

The major strengths is the use of nationwide administrative and clinical registries with complete and unselected information. These registries made it possible to present weekly, detailed and updated data on labor market participation with complete and long-term follow-up during 1994–2018. This strengths is essential compared to the UNOS-STAR database study (part of the International Society for Heart & Lung Transplantation), where employment status is documented by systematic questions at the time of post-transplant follow-up visits.

Our study also has some limitations. Given the reliance on the DREAM register, visibility into health-related disability payments

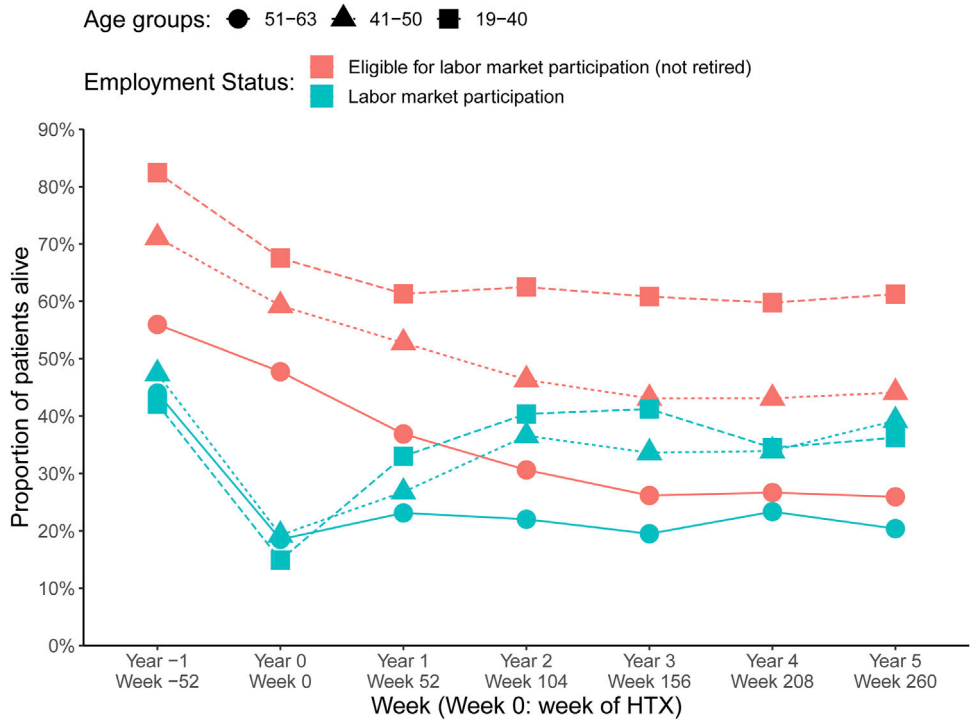


FIGURE 4 | Labor market participation by age groups HTX, heart transplantation.

was reduced to governmental expenses with no information pertaining to employer disability. Moreover, the first 2 weeks of any social transfer are not recorded in the DREAM register as the employer covers costs. This limits a complete understanding of labor market dynamics, but likely only for those who are disabled for a very short period, as those disabled for longer periods would typically receive governmental benefits. Consequently, this is unlikely to impact the study findings. Another limitation is that this study is observational and has a small sample size. We have a descriptive study design and as such, we could not assess any confounding effects. Thus, descriptions and illustrations may not be interpreted as associations or causations. Finally, the transferability of our findings may only be relevant to other European countries with a social structure and a public welfare system similar to Denmark.

Five years after HTX, 30% of recipients participated on the labor market, whereas 10% of recipients eligible for labor market participation were unemployed. Recipients with multimorbidity have a higher age and a lower prevalence of employment. Socioeconomically disadvantaged heart-transplant recipients displayed a lower prevalence of labor market participation, despite being younger compared with the socioeconomically advantaged.

DATA AVAILABILITY STATEMENT

Study data, statistical plan, and log-files can be made available through proposal to the Project Database (ID: 707738) at Statistics Denmark. Requests to access the datasets should be directed to https://www.dst.dk/en/TilSalg/Forskningsservice.

ETHICS STATEMENT

No institutional review permission or informed consent was obtained, as it is not required for register based studies in Denmark. This study was approved by the Danish Data Protection Agency (no: 1-16-02- 656-18) and the Danish Patient Safety Authority, authorizing access to medical records (no: 3-3013- 188 3173/1).

AUTHOR CONTRIBUTIONS

RM, HE, and BL designed the study. RM collected the data. RM, HE, and BL directed data management and analysis, carried out by IB and EH-P. All authors participated in the discussion and interpretation of results. RM, HE, and BL organized the writing and RM wrote the initial draft. All authors contributed to the article and approved the submitted version.

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CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontierspartnerships.org/articles/10.3389/ti.2024.12230/full#supplementary-material

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ORIGINAL RESEARCH
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Kidney Transplantation Improves Health-Related Quality of Life in Older Recipients

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Kidney transplantation is the best treatment for kidney failure in older patients. However, little is known regarding changes in health-related quality of life (HRQoL) from before to after transplantation and determinants of HRQoL in older kidney transplant recipients (KTR). We studied both, using data of older (≥65 years) patients waitlisted for kidney transplantation and older KTR 1 year after transplantation from the TransplantLines Biobank and Cohort Study. HRQoL was assessed using the SF-36 questionnaire. We included 145 older waitlisted patients (68% male, age 70 ± 4 years) and 115 older KTR at 1 year after transplantation (73% male, age 70 ± 4 years). Both mental (48.5 ± 8.4 versus 51.2 ± 7.7, $p = 0.009$) and physical (47.4 ± 8.5 versus 52.1 ± 7.2, $p < 0.001$) HRQoL were higher among included KTR, compared to the waitlisted patients. In paired analyses among 46 patients with HRQoL-data both before and after transplantation, there was a trend towards increased mental HRQoL (49.1 ± 8.4 to 51.6 ± 7.5, $p = 0.054$), and significantly increased physical HRQoL (48.1 ± 8.0 to 52.4 ± 6.7, $p = 0.001$) after transplantation. Among all assessed factors, the number of patient-reported immunosuppressive drug-related side effects was most strongly negatively associated with both mental and physical HRQoL. In conclusion, HRQoL is significantly higher among older KTR after kidney transplantation compared to older waitlisted patients.

Keywords: elderly, health-related quality of life, kidney transplantation, immunosuppression, patient reported outcome measures, side-effects

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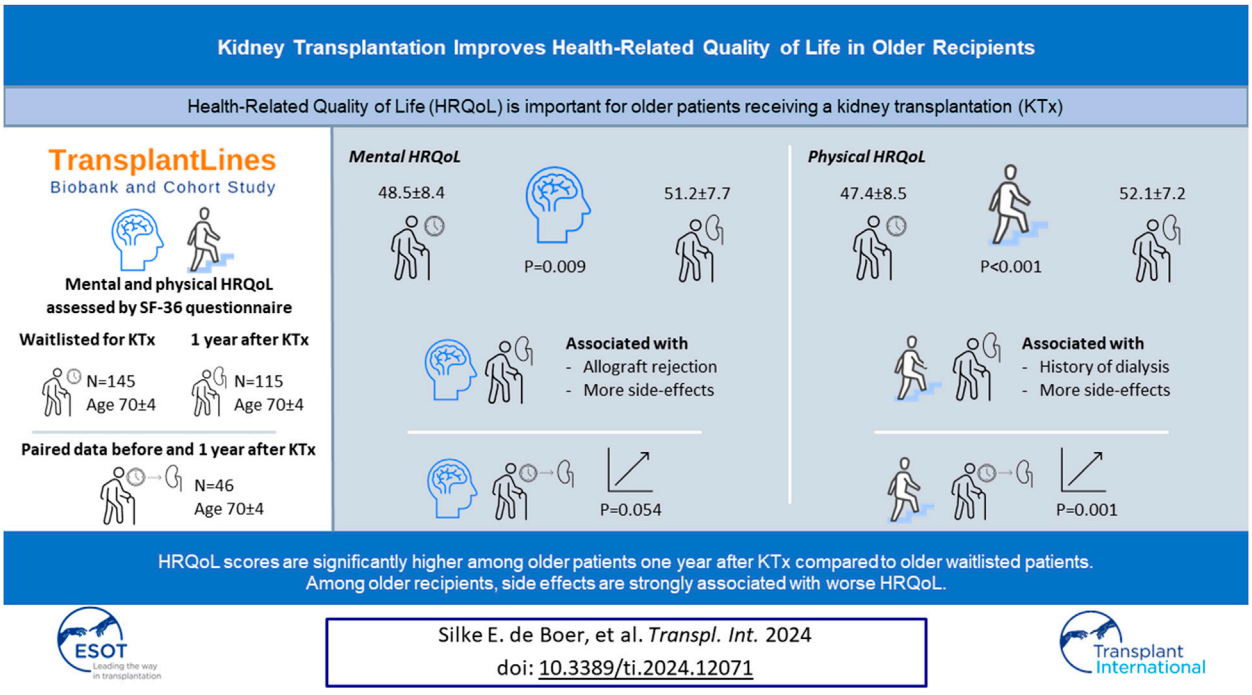
INTRODUCTION

Kidney transplantation is the preferred treatment for patients with end-stage kidney disease. It improves quality of life and offers survival benefit in comparison with other forms of kidney replacement therapy [1]. Older patients are an important and growing part of the kidney transplant population. In 2019, 30% of the newly transplanted kidney transplant recipients (KTR) in the Netherlands were above 65 years of age, compared to ~15% in 2005 [2]. Most studies show at least some survival benefit for older KTR in comparison with patients that remain on the waiting list [3–6], while some other studies show no survival benefit [7–10]. Importantly, several studies indicate that the mortality risk for older KTR is up to 3 times higher in the first 3–12 months after kidney transplantation, in comparison with waitlisted patients [4, 7, 11].



GRAPHICAL ABSTRACT

Kidney transplantation, however, is also associated with improvement in health-related quality of life (HRQoL) [1]. Because the survival gain is limited among older patients, any improvement in HRQoL may be an important reason to consider a kidney transplantation in this population. Unfortunately, data on HRQoL of older KTR are scarce and most previous studies only report data from small cohorts (<55 patients) [12, 13]. In addition, a comparison of HRQoL before and after transplantation was studied in only one population of older KTR thus far [14, 15]. Consequently, factors associated with HRQoL in older KTR remain largely unknown, even though these may help to identify patients that could benefit most from transplantation.

The aim of this study was to fill the important knowledge gaps that now exist regarding HRQoL before and after kidney transplantation of the growing and distinct group of older patients. Such information is crucial for providing proper counselling to older patients for renal replacement therapy. To do so, we compared HRQoL of older (≥65 years) patients waitlisted for kidney transplantation with HRQoL of older KTR 1 year after transplantation. In addition, we aimed to identify potential determinants of HRQoL after kidney transplantation.

PATIENTS AND METHODS

Study Design

We used data from the ongoing, prospective, TransplantLines Biobank and Cohort study (ClinicalTrials.gov identifier: NCT03272841) [16]. From June 2015, all (potential) solid organ transplant patients and donors (aged ≥18 years) of the University Medical Centre Groningen (UMCG, Netherlands) were invited to participate. All participants gave written informed consent on enrolment. The study protocol was approved by the local Institutional Review Board (METc 2014/077), adheres to the UMCG Biobank Regulation, and is in accordance with the WMA Declarations of Helsinki. The clinical and research activities being reported are consistent with the Principles of the Declaration of Istanbul as outlined in the "Declaration of Istanbul on Organ Trafficking and Transplant Tourism."

Study Population

The participation rate of the TransplantLines Biobank and Cohort study was 81%. We included HRQoL data of 145 older (≥65 years at the time of evaluation) patients waitlisted for kidney transplantation. HRQoL was assessed after transplant evaluation and approval, but before transplantation. In addition, HRQoL data of 115 older (≥65 years at the time of transplantation) KTR 1 year after transplantation were included. Of note, within these groups, 46 patients had available HRQoL both before and after transplantation, and were therefore included in both groups. A flow diagram is presented in **Figure 1**. As can be depicted from **Figure 1**, there is a group of older patients without HRQoL data while waitlisted. The main reason therefore is that they were included in the Transplantlines Biobank and Cohort study shortly after transplantation. Furthermore, it is important to denote that all KTR were in close medical follow-up after transplantation, also the ones that did not complete the SF-36 1 year after transplantation.

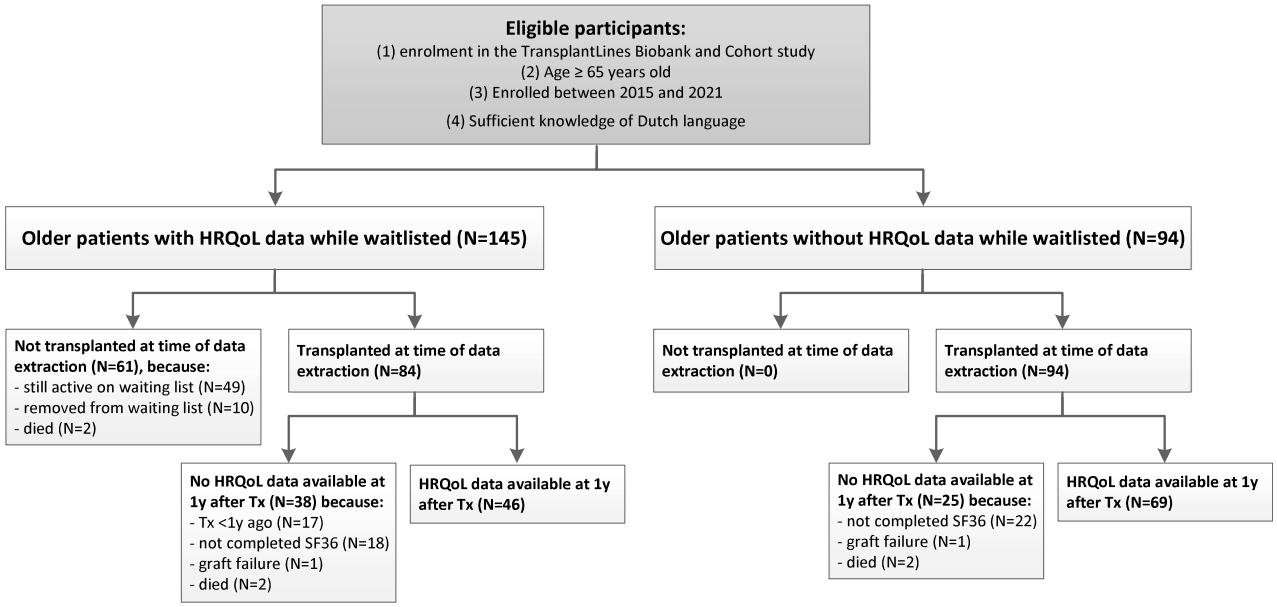


FIGURE 1 | Patient flow diagram. Abbreviations: HRQoL, health-related quality of life; KTR, kidney transplant recipients; Tx, transplantation.

Assessment of HRQoL

HRQoL was assessed using a Dutch translation of the 36-item Short Form-36 (SF-36) Health Survey [17]. Higher scores reflect better HRQoL [17]. Using reference values of the Dutch population [17], aged 65–75 years, a standardized mental component score (MCS) and physical component score (PCS) were calculated [18]. By definition, this implies that if a participant has the same HRQoL score as the presented reference value, their score is 50. Generally, scores between 45–55 are considered to be average, and scores <40 are indicative of significantly impaired HRQoL [19].

Assessment of Covariables

Demographic and clinical data—including participation in the Eurotransplant Senior Program—were retrieved from the medical files. The Eurotransplant Senior Program allocates kidneys within a geographic area from donors aged ≥65 years to recipients ≥65 years regardless of HLA match, thereby minimizing cold ischemia time [20]. Medical comorbidities at time of evaluation or transplantation were indexed using the Charlson Comorbidity Index [21]. Because all older patients received 2 points for the presence of their kidney disease, a Charlson Comorbidity Index score of 2 means that there are no other indexed comorbidities. Delayed graft function was defined as the need for dialysis in the first week after transplantation, and a rejection episode as a treated biopsy-proven acute rejection. Participants were defined as having post-transplant diabetes mellitus when they did not meet the diabetes mellitus criteria set by American Diabetes Association before transplantation, but did meet these criteria at 1 year after transplantation [22, 23]. Malnutrition was defined according to the criteria set by the Global Leadership Initiative on Malnutrition, considering that all KTR meet the etiologic criteria for disease burden/inflammation [24]. Data regarding partner status, children, education and financial situation were obtained from questionnaires. Number of immunosuppressive-drug related side effects was assessed using the Modified Transplant Symptom Occurrence and Symptom Distress Scale-59R at 1 year after transplantation [25]. Side-effects were considered as present if the symptom occurred regularly, almost always or always. Covariables that were selected had previously been found to be associated with HRQoL [26–32].

Statistical Analyses

Normally distributed data are presented as mean ± standard deviation (SD), non-normally distributed data as median [interquartile range [IQR]] and categorical data as numbers (valid percentages). Statistical difference between two groups were assessed using one-sample T-tests, independent sample T-tests, Mann-Whitney U tests, and Fisher's exact test or Pearson Chi-Square tests for categorical variables. Additionally, differences in HRQoL scores of older patients waitlisted for kidney transplantation and older KTR 1 year after transplantation were assessed using Cohen's D effect size. This effect size was calculated by dividing the difference between the pre- and posttransplant score by the (pooled—for independence groups) SD of this difference. Effect sizes of 0.2, 0.5 and 0.8 are considered as small, medium and large, respectively [33].

Among KTR with data both before and 1 year after transplantation, differences in HRQoL scores were assessed using paired sample T-tests. Furthermore, within this

TABLE 1 | Characteristics of older patients waitlisted for kidney transplantation and of older KTR one year after transplantation.

Patient demographics	Older patients waitlisted for KTx (*N* = 145)	Older KTR (*N* = 115)
Male sex, *n* (%)	98 (68)	83 (73)
Age at time of HRQoL assessment/Tx	70 ± 4	70 ± 4
White patients, *n* (%)	140 (97)	110 (96)
BMI, kg/m^2	27 ± 4	27 ± 4
Partner at time of HRQoL assessment/Tx, *n* (%)	122 (84)	95 (83)
Children, *n* (%)	130 (90)	104 (90)
Education level, *n* (%)		
Low	70 (49)	43 (40)
Intermediate	32 (22)	30 (28)
High	42 (29)	35 (32)
Financial situation, *n* (%)		
(Some) shortage of money	5 (4)	3 (3)
Just right	32 (22)	27 (28)
(Some) money left	84 (59)	66 (69)
Does not want to tell	22 (15)	4 (4)
Medical history		
Dialysis before HRQoL assessment/Tx	65 (45)	69 (60)
Hemodialysis	55 (38)	46 (40)
Time on hemodialysis, weeks	86 ± 76	109 ± 63
Peritoneal dialysis	10 (7)	23 (20)
Time on peritoneal dialysis, weeks	76 ± 62	96 ± 50
None	80 (55)	46 (40)
Diabetes mellitus at time HRQoL assessment/Tx	45 (31)	17 (15)
Charlson Comorbidity Index score	3 [2–4]	3 [2-3]
Primary kidney disease, *n* (%)		
Glomerulonephritis	20 (14)	19 (17)
Interstitial nephritis	10 (7)	8 (7)
Cystic kidney disease	23 (16)	17 (15)
Other congenital/hereditary disease	4 (3)	1 (1)
Renal vascular disease, excluding vasculitis	35 (24)	26 (23)
Diabetic nephropathy	19 (13)	7 (6)
Other multisystem diseases	9 (6)	8 (7)
Other	4 (3)	7 (6)
Unknown	21 (15)	22 (19)
Transplant-specific characteristics		
First kidney Tx, *n* (%)	140 (97)	106 (93)
Other organ Tx before kidney Tx, *n* (%)	1 (1)	2 (2)
Donor type, *n* (%)		
Donation after cardiac death	n/a	20 (17)
Donation after brain death	n/a	41 (36)
Living donor	n/a	54 (47)
Eurotransplant Senior Program donor, *n* (%)	n/a	42 (37)
ABO-incompatible transplantation, *n* (%)	n/a	7 (6)
Donor sex, *n* males (%)	n/a	64 (56)
Donor age, years	n/a	66 [62–70]
Induction therapy, *n* (%)		
Basiliximab	n/a	108 (94)
Antithymocyte globulin	n/a	2 (2)
Alemtuzumab	n/a	2 (2)
Rituximab	n/a	7 (6)
None	n/a	3 (3)
Immunosuppressive starting regimen, *n* (%)		
TAC/MMF/prednisolone	n/a	108 (94)
Cyclosporine/MMF/prednisolone	n/a	2 (2)
TAC/EVR/prednisolone	n/a	4 (4)
Iscalimab (CFZ-533)/MMF/prednisolone	n/a	1 (1)

Data regarding educational level and financial situation were missing in, 1 and 2 older patient(s) waitlisted for KTx and in 7 and 15 older KTR, respectively. Other variables were complete. Normal distributed variables are presented as mean ± SD, not-normally distributed variables as median [IQR] and categorical data as number (valid %).
Abbreviations: EVR, everolimus; HRQoL, Health related quality of life; KTR, kidney transplant recipients; (K)Tx, (kidney)transplantation; MMF, mycophenolic acid; TAC, tacrolimus.

subgroup, we compared the characteristics of older KTR with a MCS or PCS below the median score before transplantation with those of older KTR with a MCS or PCS above the median score before transplantation. Finally, we assessed which factors are associated with HRQoL of older KTR at 1 year after transplantation using univariable and multivariable linear

TABLE 2 | Clinical outcomes one year after transplantation for 115 older KTR with available data on HRQoL one year after transplantation.

Clinical course	Older KTR (*N* = 115)
eGFR at one year after Tx, mL/min/1.73 m^2	48 ± 16
eGFR <30 mL/min/1.73 m^2 at one year after Tx, *n* (%)	15 (13)
Hemoglobin, g/dL	13.2 ± 1.6
Delayed graft function, *n* (%)	26 (23)
Rejection in the first year after Tx, *n* (%)	9 (8)
Methylprednisolone	7 (6)
Antithymocyte globulin	4 (3)
Alemtuzumab	1 (1)
Malnourished at one year after Tx, *n* (%)	42 (43)
Development of PTDM during the first year after Tx, *n* (%)	20 (17)
Malignancy during the first year after Tx, *n* (%)	7 (6)
BCC and/or SCC (single or multiple)	4
Other (colorectal, prostate, breast, bladder)	3[a]
Cardiovascular event during the first year after Tx, *n* (%)	3 (3)
Number of hospitalizations in the first year after Tx per older KTR, *n* (%)	
No hospitalization	59 (51)
1 hospitalization	30 (26)
2 hospitalizations	19 (17)
≥ 3 hospitalizations	7 (6)
Number of infections in the first year after Tx per older KTR[b], *n* (%)	
No infection	47 (41)
1 infection	30 (26)
2 infections	18 (16)
≥ 3 infections	20 (17)
CMV-primo infection in the first year after Tx, *n* (%)	7 (6)
BK viraemia in the first year after Tx, *n* (%)	25 (22)

Data regarding malnourishment were missing in 17 older KTR. Other variables were complete.
Normal distributed variables are presented as mean ± SD, not-normally distributed variables as median [IQR] and categorical data as number (valid %).
Abbreviations: BCC, Basal cell carcinoma; eGFR, estimated glomerular filtration rate; KTR, kidney transplant recipient; SCC, Squamous cell carcinoma.
[a]*One patient had a SCC and other cancer.*
[b]*Excluding CMV and BK viraemia.*

regression analyses adjusted for age, sex and pre-emptive transplantation with the MCS and PCS as dependent variables. The variance inflation factor was measured for each variable in the multivariable regression analysis and was <1.7 in all analyses [34].

Data were analyzed using SPSS software version 23.0 and R version 4.1.1. In all analyses, a two-sided *p*-value <0.05 was considered as statistically significant.

RESULTS

Baseline Characteristics

In total, 145 patients waitlisted for kidney transplantation (age 70 ± 4 year; 68% males) were included in the study, among whom 65 patients (45%) were on dialysis at the time of HRQoL assessment. The median Charlson Comorbidity Index in this population was 3 [IQR 2–4].

In addition, 115 older KTR (age at time of transplantation 70 ± 4 year; 72% males) with available data on HRQoL 1 year after transplantation were included, among whom 46 (40%) were pre-emptively transplanted. Notably, half of the older KTR had a Charlson Comorbidity Index of 2 at the time of the transplantation, indicating no other indexed comorbidities besides end-stage kidney disease. More extensive baseline characteristics of both populations are shown in **Table 1**. Clinical characteristics of older waitlisted patients and older KTR were comparable (**Table 1**).

Course of the First Year After Transplantation

Among the 115 older KTR with available data on HRQoL 1 year after transplantation, mean eGFR 1 year after transplantation was 48 ± 16 mL/min/1.73 m^2. Fifteen older KTR (13%) had an eGFR ≤30 mL/min/1.73 m^2. Nine older KTR (8%) suffered from rejection in the first year. Forty-two (37%) older KTR were malnourished and 20 (17%) developed post-transplant diabetes mellitus (PTDM) 1 year after transplantation.

During the first year, 49% of patients were hospitalized at least once in addition to the admission for transplantation. Main reasons for the total of 100 hospitalizations were infections (*N* = 47), elective surgeries (*N* = 15) and hemorrhage (*N* = 8). In addition, we observed 9 hospitalizations for (analysis of) kidney function decline, including rejection.

A detailed overview of clinical outcomes and events among older KTR in the first year after transplantation is presented in **Table 2**.

The baseline characteristics of the 40 patients without HRQoL data at 1 year after transplantation were comparable to the 115 patients included in analyses, with the exception for the prevalence of diabetes, which was higher among patients without HRQoL data at 1 year after transplantation. Notably, there was no significant difference in either mental or physical HRQoL prior to transplantation between both groups (**Supplementary Tables S1, S2**).

Reported Side Effects of Immunosuppressive Drugs One Year After Transplantation

Self-reported immunosuppressive-drug related side effects at 1 year after transplantation were common; the median number of side effects was 4 [IQR: 2–9] per KTR. Notably, 10 (9%) older KTR reported no side-effects. The most reported side-effects were erectile dysfunction (46% of males), bruises (36%), tremor (30%), dry skin (26%), reduced interest in sex (25%), increased urge to urinate (22%) and lack of energy (23%).

HRQoL of 145 Older Patients Waitlisted for Kidney Transplantation

Mean mental (standardized MCS 48.5 ± 8.4) and physical HRQoL (standardized PCS 47.4 ± 8.5) scores of 145 older waitlisted patients were lower than the age-matched general population (p = 0.037 and p < 0.001,

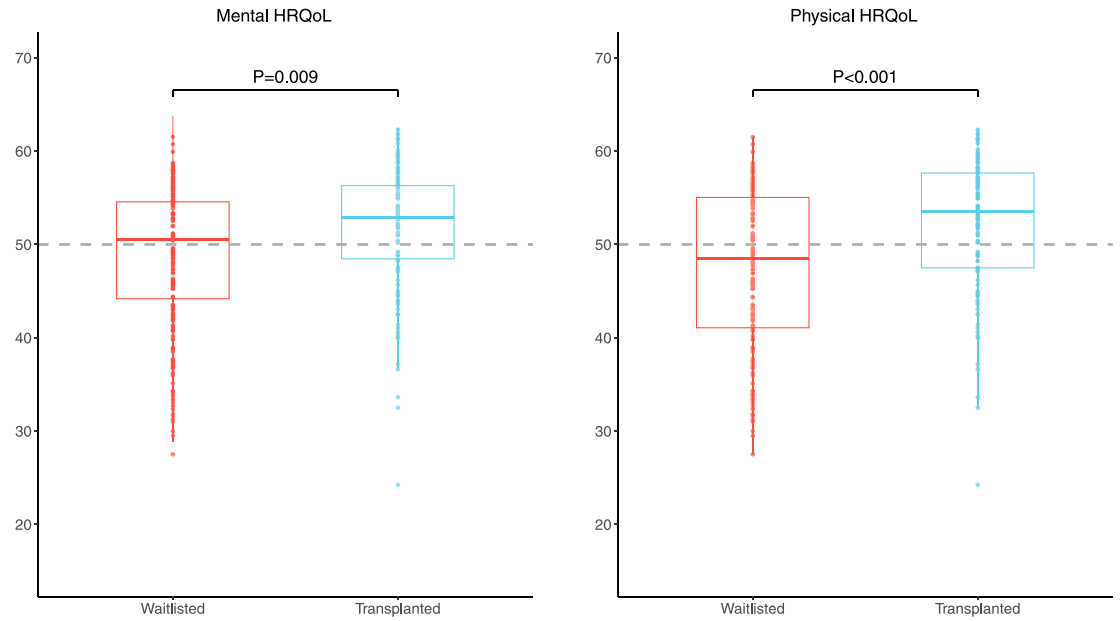


FIGURE 2 | Boxplot of standardized MCS and PCS of 145 older patients waitlisted for kidney transplantation and 115 older KTR 1 year after transplantation. The dotted grey line represents the age-matched general population, which by definition has standardized PCS and MCS scores of 50.0.

respectively), of which the mean score is by definition 50.0 ± 10.0 (**Figure 2**).

Among the HRQoL subdomains, the score on the mental health subdomain of the waitlisted patients was higher in comparison with the age-matched general population (78.9 ± 13.5 versus 75.9 ± 17.3; $p = 0.009$). The score on the physical functioning subdomain did not differ between waitlisted patients and the age-matched general population ($p = 0.33$). Scores on all other 6 subdomains were significantly lower among waitlisted patients compared to the scores of the age-matched general population ($p < 0.05$ for all, **Supplementary Table S3**).

Mean mental and physical HRQoL scores of the 12 waitlisted patients that did not receive a transplantation (because they were delisted or died on the waiting list) did not differ from those of the 84 patients that got a transplantation (standardized MCS 52.3 (±7.7) versus 48.2 (±8.3, P for difference 0.107), standardized PCS 44.3 (±11.1) versus 46.6 (±8.4, P for difference 0.502).

HRQoL of 115 Older Patients After Kidney Transplantation

Mean mental HRQoL of 115 older KTR at 1 year after transplantation was comparable to the age-matched general population (standardized MCS: 51.2 ± 7 versus 50.0 ± 10.0 $p = 0.10$), while mean physical HRQoL was significantly higher (standardized PCS: 52.1 ± 7.2 versus 50.0 ± 10.0, $p = 0.003$) (**Figure 2**). Older KTR at 1 year after transplantation had better scores on the HRQoL subdomains "mental health" ($p < 0.001$), "vitality" ($p = 0.035$), "bodily pain" ($p < 0.001$) and "physical functioning" ($p < 0.001$) compared to the age-matched general population. Other subdomain scores were comparable ($p > 0.05$, **Supplementary Table S3**).

Comparison of HRQoL of 145 Older Patients Waitlisted for Kidney Transplantation and 115 Older Patients After Kidney Transplantation

Both mental and physical HRQoL scores were significantly higher among 115 older KTR at 1 year after transplantation compared to 145 older waitlisted patients (standardized MCS: 51.2 ± 7.7 versus 48.5 ± 8.4, $p = 0.009$, Cohen's D 0.32 and standardized PCS: 52.1 ± 7.2 versus 47.4 ± 8.5, $p < 0.001$, Cohen's D 0.59), as presented in **Figure 2**. In addition, all HRQoL subdomain scores, except the subdomain "mental health," were significantly higher among older KTR at 1 year after transplantation compared with older waitlisted patients ($p < 0.02$ for all) (**Figure 3**; **Supplementary Table S4**).

Mental and physical HRQoL among patients waitlisted for transplantation was not different for patients <70 or ≥70 years old. Similarly, 1 year post-transplantation, there was no difference in HRQoL among between these two age categories (data not shown).

Comparison of HRQoL Before and After Transplantation Among 46 Patients With Repeated HRQoL Measurements

In paired analyses among 46 older KTR with HRQoL data both from the waitlist period and at 1 year after kidney transplantation, mental HRQoL scores after transplantation were numerically higher, but not statistically different (standardized MCS: 49.1 ± 8.4 versus 51.6 ± 7.5, $p = 0.05$, Cohen's D 0.29), as presented in **Supplementary Table S5**. Physical HRQoL scores were significantly higher after transplantation compared to before transplantation (standardized PCS: 48.1 ± 8.0 versus 52.4 ± 6.7,

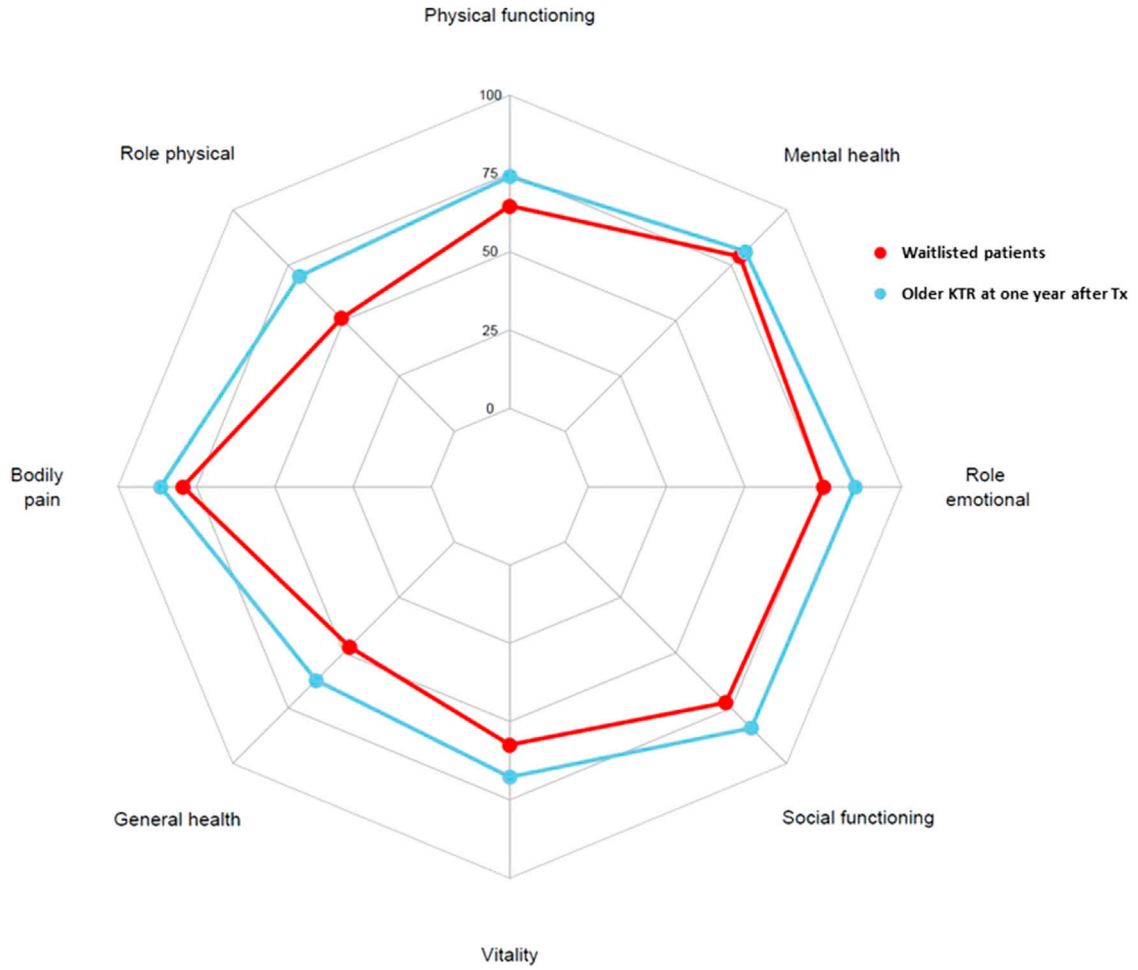


FIGURE 3 | Comparison of HRQoL subdomain scores of 145 older patients waitlisted for kidney transplantation (blue) with HRQoL subdomain scores of 115 older KTR at 1 year after transplantation (red). All HRQoL subdomain scores were higher among older KTR 1 year after transplantation compared to older patients waitlisted for transplantation ($p < 0.02$ for all), with the exception for the mental health subdomain, which was not statistically different.

$p = 0.001$, Cohen's D 0.52). Results of subdomain scores were generally comparable to the unpaired analyses.

Notably, the largest HRQoL improvements were observed in patients with a HRQoL lower than median HRQoL score before transplantation (difference in standardized MCS for patients below and above median: +7.6 ± 7.0 and −2.6 ± 6.7, $p < 0.001$, respectively). This difference was more pronounced regarding the physical HRQoL score (difference in standardized PCS for patients below and above median: +9.5 ± 6.8 and −1.0 ± 6.0, $p < 0.001$, respectively), as presented in **Figure 4**; **Supplementary Table S6**. Characteristics of KTR with HRQoL scores before transplantation below or above the median were not statistically different.

Factors Associated With HRQoL of Older KTR at One Year After Transplantation

In linear regression analyses, after adjustment for age, sex and pre-emptive transplantation, number of patient-reported immunosuppressive-drug related side effects was strongly associated with a lower mental HRQoL at 1 year after transplantation (St. β −0.36, 95% CI −0.55 to–0.18). Other associated factors with mental HRQoL were rejection in the first year (St. β −0.33, 95% CI −0.51 to −0.15) and hospitalization in the first year after transplantation [**Table 3**; **Supplementary Table S7** (for crude values)].

Number of patient-reported immunosuppressive-drug related side effects was also strongly associated with lower physical HRQoL at 1 year after transplantation, after adjustment for age, sex and pre-emptive transplantation (St. β −0.55, 95% CI −0.72 to −0.38). Pre-emptive transplantation (St. β 0.25, 95% CI 0.06–0.43) was also positively associated. The mean physical HRQoL score of pre-emptive patients was significantly higher compared to patients with a dialysis vintage (standardized PCS: 54.2 ± 7.2 versus 50.6 ± 7.0, $p = 0.011$. Higher monthly income (St. β −0.24, 95% CI −0.46 to −0.03) and post-transplant diabetes mellitus (St. β −0.22. 95% CI −0.40 to–0.04) were negatively associated with physical HRQoL at 1 year after

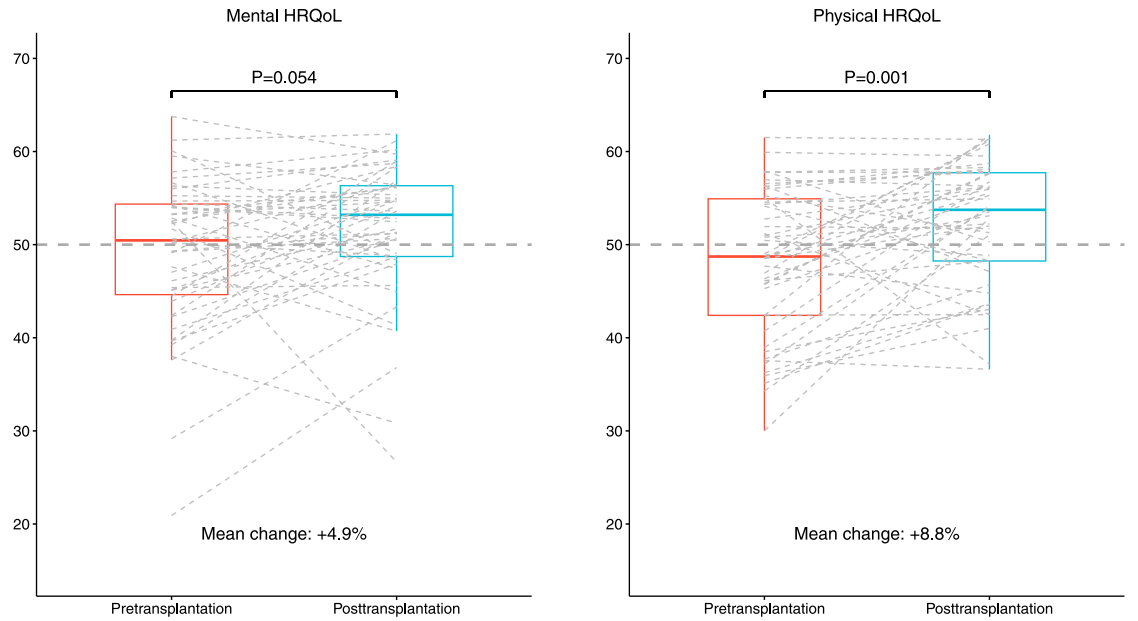


FIGURE 4 | Boxplot of standardized MCS and PCS of 46 older KTR with HRQoL data both before and after transplantation. The dotted grey line represents the age-matched general population, which by definition has standardized PCS and MCS scores of 50.0.

transplantation [**Table 3**; **Supplementary Table S7** (for crude values)].

DISCUSSION

Our results show the beneficial effect of kidney transplantation on the health-related quality of life of older recipients. HRQoL at 1 year after transplantation of older KTR was higher compared to HRQoL of older patients waitlisted for kidney transplantation in both unpaired and paired analyses, and HRQoL of older KTR was equal or even better in comparison with the age-matched general population. Moreover, participants with the lowest HRQoL scores before transplantation showed the largest improvement of these scores after transplantation. Among all assessed factors, the number of patient-reported immunosuppressive-drug related side effects was the most important factor associated with both a lower mental and physical HRQoL, followed by an episode of allograft rejection for mental HRQoL and a history of dialysis for physical HRQoL.

A within-participant comparison of HRQoL before and after kidney transplantation among older patients has been previously performed in only one study population [14, 15]. Also in this population, a moderate to large HRQoL improvement at 1 year after transplantation compared to before transplantation was observed. This HRQoL improvement was already present at 2 months after transplantation [14], and persisted up to 3 years afterwards [14, 15]. Our findings are also in line with a previous study comparing HRQoL of older KTR with (non-waitlisted) hemodialysis patients [35]. Notably, we also confirmed that (general physical) HRQoL of older KTR is comparable to the age-matched population as previously reported [12, 36]. This might sound surprising, given the fact that a substantial part of the KTR had to deal with hospitalizations, infections and malnourishment in the first year after transplantation. It therefore is important to realize that HRQoL is a very subjective parameter.

Of note, as mentioned in the methods section, we used reference values from the Dutch population aged 65–75 years [17] to calculate the standardized MCS and PCS. This was chosen as it represents the most comparable population for our sample consisting of older Dutch patients. Since most other studies use reference values from the general U.S. population [18], the results of the MCS and PCS cannot readily be compared with those found in other studies.

Older KTR reported to experience a median of four side effects of immunosuppressive therapy, and the number of side effects was strongly associated with a lower HRQoL. This is in accordance with the findings of the BENEFIT (EXT) trial. This randomized-controlled trial showed that KTR treated with belatacept, which has generally less side-effects, had better HRQoL compared to calcineurin inhibitors-treated controls at several timepoints after transplantation [31]. We therefore hypothesize that alterations in the immunosuppressive regimen of older KTR may help to further improve their HRQoL, and this will be assessed in the ongoing OPTIMIZE-trial [37].

A history of treated biopsy proven acute rejection was also associated with a lower mental HRQoL. Although this association was not found among older KTR before [28], it has been

TABLE 3 | Factors associated with mental and physical HRQoL at one year after transplantation among older KTR.

Variables	Linear regression analyses with standardized MCS as dependent variable			Linear regression analyses with standardized PCS as dependent variable		
	Model 1			Model 1		
	St. β	95% CI	P	St. β	95% CI	P
Patient demographics						
Female sex	–0.18	–0.36 to 0.01	0.07	–0.02	–0.20 to 0.17	0.85
Age	0.05	–0.14 to 0.24	0.59	-0.03	–0.22 to 0.15	0.73
BMI	0.12	–0.07 to 0.30	0.20	0.04	–0.14 to 0.23	0.66
Partner	0.13	–0.06 to 0.32	0.18	–0.06	–0.26 to 0.13	0.54
Children	–0.03	–0.21 to 0.16	0.79	0.01	–0.17 to 0.19	0.92
Education level						
Low	–0.18	–0.42 to 0.06	0.15	0.02	–0.23 to 0.27	0.88
Intermediate		reference			reference	
High	–0.12	–0.35 to 0.11	0.31	–0.01	–0.25 to 0.23	0.94
Financial situation						
(Some) shortage of money	0.02	–0.21 to 0.24	0.88	–0.03	–0.26 to 0.18	0.75
Just right		reference			reference	
(Some) money left	–0.09	–0.31 to 0.12	0.40	-0.24	**–0.46 to –0.03**	**0.027**
Medical history						
Pre-emptively transplanted	0.01	–0.18 to 0.19	0.92	0.25	**0.06 to 0.43**	**0.008**
Diabetes mellitus pre-KTx	0.06	–0.12 to 0.25	0.50	0.08	–0.11 to 0.26	0.40
CCI pre-KTx	–0.12	–0.31 to 0.06	0.20	-0.06	–0.25 to 0.12	0.50
CCI 3 or higher pre-Tx	–0.18	–0.37 to 0.00	0.06	–0.11	–0.30 to 0.07	0.23
Kidney transplant characteristics						
Living donor	0.01	–0.22 to 0.24	0.94	–0.18	–0.40 to 0.05	0.122
Clinical course of the first year after Tx						
eGFR	0.15	–0.03 to 0.34	0.10	–0.06	–0.24 to 0.13	0.57
eGFR <30 ml/min/1.73m^2	–0.17	–0.35 to 0.01	0.07	–0.07	–0.25 to 0.11	0.45
Hemoglobin	0.14	–0.05 to 0.33	0.15	0.17	–0.02 to 0.35	0.083
Delayed graft function	–0.17	–0.38 to 0.03	0.09	–0.01	–0.21 to 0.20	0.95
Rejection in the first year after Tx	–0.33	**–0.51 to –0.15**	**<0.001**	–0.02	–0.20 to 0.17	0.87
Malnourished at one year after Tx	0.08	–0.12 to 0.27	0.48	–0.19	–0.39 to 0.01	0.07
Development of PTDM during the first year after Tx	–0.13	–0.31 to 0.06	0.18	–0.22	**–0.40 to –0.04**	**0.016**
Number of hospitalizations in the first year after Tx per older KTR	–0.21	**–0.40 to –0.02**	**0.030**	–0.12	–0.31 to 0.06	0.19
Any hospitalization in the first year after Tx	–0.24	**–0.42 to –0.05**	**0.014**	–0.14	–0.33 to 0.05	0.14
Number of infections in the first year after Tx per older KTR	–0.13	–0.32 to 0.05	0.15	–0.15	–0.33 to 0.03	0.09
Any infection in the first year after Tx	–0.09	–0.27 to 0.10	0.34	–0.12	–0.30 to 0.06	0.19
Number of side effects in the first year after Tx per older KTR	–0.36	**–0.55 to –0.18**	**<0.001**	-0.55	**–0.72 to –0.38**	**<0.001**

Model 1: All adjusted for age, sex, and pre-emptive tranplantation, except the variable age, sex and pre-emptive transplantation. Data regarding educational level was missing in 7 older KTR; 19 older KTR had missing data regarding financial situation or did not want to tell their financial situation. Abbreviations: MCS, mental component score of the SF-36 health-related quality of life questionnaire; PCS, physical component score of the SF-36 health-related quality of life questionnaire; CCI, Charlson Comorbidity Index; eGFR, estimated glomerular filtration rate; PTDM, post-transplant diabetes mellitus; Tx, transplantation.

Bold values represent statistically significant associations (p < 0.05).

previously described among younger KTR [28, 38]. We hypothesize that a rejection may reduce confidence in the transplant function and expectations for the future. Together with the accompanying hospital admission—a factor which was also associated with lower HRQoL in our study—there might be an increased perception of illness, leading to a diminished feeling of control over their disease. This could make KTR feel more like patients and heighten their awareness of their illness, factors that has been previously associated with lower mental HRQoL [39–41].

Therefore, it is very important that clinicians are aware of the relationship between the above mentioned determinants and low mental HRQoL, so any physical and mental health issues can be openly discussed and both medical and psychosocial support can be provided if necessary. This needs to be emphasized, because in particular mental health problems, like anxiety and depression, often go unrecognized and untreated in patients on renal replacement therapy [42, 43].

A history of dialysis was also associated with a lower physical HRQoL among older KTR. Although this is in contrast with findings in other studies amongst KTR [44, 45], a negative association between time on dialysis and post-transplant HRQoL has been described before [32]. This negative association might be—besides better patient and graft survival [46]—an additional reason to aim for pre-emptive kidney transplantation. The association of PTDM with reduced physical HRQoL has not been described in KTR before, but a negative impact of diabetes mellitus on HRQoL has been well documented in the general population [47]. It underscores the

importance of interventions aimed at preventing and treating PTDM [48].

The finding that participants with a HRQoL score below the median before transplantation showed a greater increase in HRQoL after transplantation, while participants with a HRQoL score above the median HRQoL showed no difference in HRQoL after transplantation, might indicate that older KTR with a poor HRQoL benefit the most from a kidney transplantation regarding HRQoL. It is unlikely that this result is simply a reflection of regression to the mean, given the huge difference between pre- and posttransplant scores. Also, HRQoL of older KTR with scores above the median before transplantation does not decline; there is no significant change after transplantation.

These results can contribute to the discussion of the pros and cons of kidney transplantation in the older, shared-decision making and expectation management.

Strengths of this study are the availability of a broad variety of characteristics of both older patients waitlisted for kidney transplantation and older KTR, which allowed us to compare both groups extensively and to provide an overview of factors associated with HRQoL at 1 year after transplantation of older KTR. In addition, we were able to compare paired HRQoL scores of before and after transplantation in a subgroup of older KTR. Furthermore, given the high study participation rate of 81%, our study sample is likely representative for the older KTR population. Despite the lack of HRQoL data 1 year post-transplantation for 40 older, living, KTR with functioning grafts—who were consequently excluded from analyses—we believe these missing data had minimal impact on our overall findings. Although we found some minor differences between both groups, the differences that were found (such as a different prevalence of diabetes at baseline), were not independently associated with lower HRQoL 1 year after transplantation. Moreover, HRQoL prior to transplantation was comparable between both groups. Therefore, the absence of these data probably does not influence our results importantly.

However, we cannot exclude the possibility of selection bias. We only included older KTR with HRQoL data at 1 year after transplantation, excluding patients who died ($N = 4$) or suffered from graft failure ($N = 2$) within the first year after transplantation, although these numbers were quite small. A few other factors that may limit the external validity of our study need to be mentioned. The first one is the observational, single-center study design. Groups of waitlisted and transplanted patients were not completely equal or comparable as a result of this design, and our findings for the comparison of HRQoL among these groups should therefore be interpreted with caution. Secondly, a relatively limited number of patients—especially those with repeated HRQoL measurements—were included. Nevertheless, even with this sample size, we identified significant differences in HRQoL and statistically significant associated factors. Third, the median Charlson comorbidity index of our study population was relatively low. Although we did not observe an association between this index and HRQoL, it does mean that our findings may have limited generalizability to populations with more severe comorbidity. Fourth, our sample consisted of a relatively high percentage of KTR that was pre-emptively transplanted or had a living donor.

Furthermore, due to logistical reasons, we did not perform repeated measurements of HRQoL of the waitlisted patients, even though such assessments might have provided additional information. Ideally, results should be established in larger populations and re-evaluated at later time points.

In conclusion, our study shows the advantage of kidney transplantation among older KTR, with a significantly higher HRQoL 1 year after transplantation compared to before transplantation. KTR with the lowest HRQoL scores before transplantation showed the largest improvement of these scores after transplantation. The number of patient-reported immunosuppressive drug-related side effects was strongly associated with lower HRQoL of older KTR.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because Public sharing of individual participant data was not included in the informed consent of the TransplantLines Biobank and cohort study, but data can be made available to interested researchers upon reasonable request by mailing to the data manager of the TransplantLines Biobank and Cohort study. Requests to access the datasets should be directed to datarequest.transplantlines@umcg.nl.

ETHICS STATEMENT

The studies involving humans were approved by the local Institutional Review Board (METC) of the UMCG. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SdB, TK, DK, SBe, and JS were responsible for conceptualization. SdB, TK, and DK were responsible for original draft preparation, visualization and methodology. BvM, GN-M, RP, SBa, SBe, and JS contributed to writing, reviewing and editing. All authors contributed to the article and approved the submitted version.

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CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontierspartnerships.org/articles/10.3389/ti.2024.12071/full#supplementary-material

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REVIEW
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Physical Exercise After Solid Organ Transplantation: A Cautionary Tale

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An increasing body of randomized controlled trials suggests the safety of engaging in moderate to vigorous intensity exercise training following solid organ transplantation. Fueled by emerging sport events designed for transplant recipients and the ever-growing body of research highlighting the diverse health benefits of physical activity, transplant recipients are now increasingly participating in strenuous and occasionally competitive physical endeavors that largely surpass those evaluated in controlled research settings. This viewpoint article adopts a cautionary stance to counterbalance the prevalent one-sided optimistic perspective regarding posttransplant physical activity. While discussing methodological limitations, we explore plausible adverse impacts on the cardiovascular, immunological, and musculoskeletal systems. We also examine the physiological consequences of exercising in the heat, at high altitude, and in areas with high air pollution. Risks associated with employing performance-enhancing strategies and the conceivable psychological implications regarding physical activity as a tribute to the 'gift of life' are discussed. With a deliberate focus on the potential adverse outcomes of strenuous posttransplant physical activity, this viewpoint aims to restore a balanced dialogue on our comprehension of both beneficial and potentially detrimental outcomes of physical activity that ultimately underscores the imperative of well-informed decision-making and tailored exercise regimens in the realm of posttransplant care.

Keywords: SOT, solid organ transplant, exercise, adverse event, methodological appraisal, critical appraisal, physical activity, side effects

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CITIUS ALTIUS, FORTIUS?

Promoting moderate to vigorous-intensity physical activity is gaining traction as a strategy to address prevalent cardiovascular, metabolic, muscular, and mental comorbidities in solid organ transplant recipients (SOTRs). This is in part supported by direct evidence from controlled intervention studies [1–4] and further driven by strong indirect evidence seen in the general population, translated in the World Health Organization physical activity

Abbreviations: SOT, solid organ transplant; SOTRs, solid organ transplant recipients; RCTs, randomized controlled trials; VO_2peak, peak oxygen uptake.

recommendations [5]. In 2019, a collaborative position statement from the Canadian Society of Transplantation and CAN-RESTORE recommended SOTRs to participate in moderate to vigorous-intensity exercise 3–5 times per week [1]. The absence of sufficient evidence limited the formulation of more specific training recommendations. A surge in initiatives spearheaded by organizations like the World Transplant Games Federation, Transplant Sport, and Transplantoux is now encouraging SOTRs to participate in at times demanding and sometimes competitive physical endeavors. A survey-based investigation involving 220 athletes engaged in the British and World Transplant Games revealed that nearly one-third of respondents aspired to win national and international events, respectively [6]. Notably, over half of the respondents perceived limitations to their performance related to injury, illness, or lack of fitness. Nonetheless, the increasing ambition and potential of SOTRs is evident in successful undertakings such as 130 km cycling races, iron man triathlons, and high-altitude trekking expeditions to for instance the summit of Kilimanjaro [7–10]. Such admirable endeavours are undertaken by a select subpopulation of SOTRs often portrayed as role model. This prompts the question of whether the original Olympic motto '*citius, altius, fortius*' should be embraced within the transplant community. Without contradicting the value of appropriate individualised training programs for SOTRs [1–4] and without discrediting those who have achieved highly competitive goals, this review aims to summarise the current evidence on potential downsides of strenuous physical activity after SOT. This review explores physical activity effects on various organ systems, the influence of climatic conditions, the use of performance-enhancing drugs, and methodologic limitations of the present literature. Occasional speculative arguments will not be avoided, as they can contribute to sparking an open debate that may ultimately lead to improved informed decision-making and implementation of thoughtful, personalised physical activity interventions.

ORGAN SYSTEMS AT RISK

Although poorly researched to date, particularly in SOTRs, strenuous exercise could be postulated to adversely impact various organ systems (**Figure 1**; **Table 1**).

Musculoskeletal Injuries

While osteoporosis is common among patients awaiting transplantation, further bone loss is a typical phenomenon throughout the early posttransplant period [11]. Even patients without a pretransplant history of osteoporosis face an elevated risk of posttransplant osteoporosis and fractures [12, 13]. The incidence of fractures is four to five times higher compared to the general population [14, 15] and can be attributed, in part, to the side effects of immunosuppressive agents such as glucocorticoids, cyclosporine A, and tacrolimus [16–19]. Particularly in individuals engaging in endurance sports, an imbalance between energy expenditure and caloric intake can lead to the relative energy deficiency in sport syndrome, further reducing bone mineral density and increasing the risk for stress fractures [20, 21].

Immunosuppressive agents, together with obesity and/or type 2 diabetes, also increase the risk for tendinopathy [22, 23]. Some evidence indicates heart and kidney transplant recipients to be at elevated risk of (Achilles) tendinopathy, possibly related to fluoroquinolone therapy [24, 25]. Both undertraining and overtraining are known to set healthy athletes at risk for non-contact soft-tissue injury [26]. Tailoring a progressive training load seems essential in injury prevention, particularly in SOTRs already predisposed to injury. Training load not only relates to the volume and intensity of exercise, but also to tissue-specific mechanical stress associated with a given type of exercise. For instance, high-impact sports such as long-distance running amplify the risk of stress fractures in the lower limbs [27, 28]. Vigilance for exercise-induced overuse injuries in SOTRs seems justified. Screening practices with timely bone mineral density measurements and personalized pharmacological and training approaches may be advised. Supported by promising results in heart and lung transplant recipients, the latter may amongst

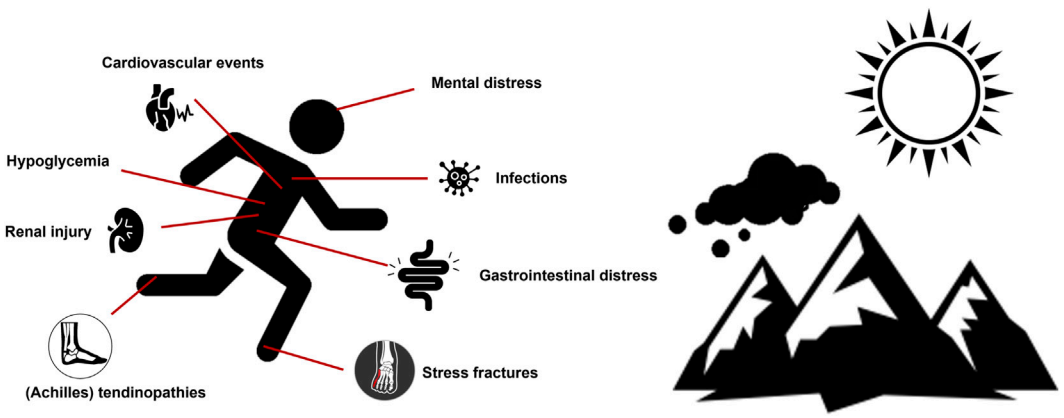

FIGURE 1 | Potential adverse outcomes of participation in posttransplant strenuous physical activity conducted in challenging environmental conditions.

TABLE 1 | Potential adverse effects of strenuous physical exercise in solid organ transplant recipients, and potential strategies to mitigate these adverse effects.

System	Potential adverse effects	Potential mitigation strategies
Musculoskeletal	- Overuse injuries: stress fractures, (Achilles) tendinopathies, and other soft-tissue injuries	- Load management: avoid over- and undertraining - Personalized, progressive increase in training volume and intensity - Implement resistance training - Implement warming-up routines - Attention to sufficient recovery (*e.g.,* soft tissue therapy, mobility exercises, active recovery (light exercise), good sleep, cryotherapy, thermotherapy, post-exercise nutrition) - Add variety in training routine and limit (the increase in) long duration repetitive movements (*e.g.*, long-distance running) - Respect tissue-specific load-capacity ratio - Avoid imbalance between energy expenditure and caloric intake - In case of overweight: weight loss - Training load can be modified by extrinsic factors, such as training surface and footwear - Be alert for early symptoms - Screen for osteoporosis. When present: calcium-vitamin D supplementation and/or bisphosphonate treatment
Immunological	- Increased risk of infection, in particular that of the upper respiratory and urinary tract	- Avoid overreaching/overtraining - Implement infection preventing strategies following strenuous exercise and during strenuous training periods (*e.g.*, hygiene practices, immunization) - Prevent dehydration and infrequent voiding - Avoid environments that house a high number of pathogens (*e.g.,* natural waters, public swimming pools) - Dynamic customization of immunosuppressive regime may be useful, but remains a topic of future research
Cardiovascular	- Cardiovascular events during acute strenuous exercise - Increased risk for development of certain cardiovascular diseases (coronary plaques, atrial fibrillation, myocardial fibrosis) in those surpassing the 'optimal dose of exercise'?	- Preparticipation cardiovascular screening (cardiopulmonary exercise test, functional imaging, coronary computed tomography scan, coronary angiography) - Personalized, progressive increase in training load - Balanced approach regarding long-term training load
Gastrointestinal	- Gastrointestinal distress (*e.g.*, diarrhea, regurgitation, nausea) - Gut microbial dysbiosis	- Avoid too strenuous exercise - Adequate hydration - Dietetic measures
Endocrine	- Acute dysregulation of blood glucose levels	- Patient education on exercise-induced modulation of blood glucose and symptom recognition - Dietetic and insulin interventions before, during, and after exercise
Renal	- Impaired kidney perfusion - Acute kidney injury - Rhabdomyolysis	- Avoid too strenuous exercise - Respect muscle load-capacity ratio; prevent excessive exercise-induced muscle damage - Maintain good hydration and electrolyte balance
Systemic, renal, cardiovascular, and respiratory systems during exposure to extreme environments	- Acute mountain sickness - Impaired kidney function and kidney injury - Cardiovascular disease - Impaired lung function - Increased mortality risk	- Avoid strenuous exercise in environments characterized by high levels of heat, humidity, altitude, or air pollution - Opt for indoor alternatives - Heat mitigation strategies: strategically choose time of day, time of year, clothing, hydration, *etc.* - Decrease exercise intensity and duration
Psychological	- Mental distress: feelings of guilt or personal failure	- Elicit intrinsic motivation rather than relying on extrinsic factors (*e.g.*, leveraging a patient's feelings of guilt toward their donor) to initiate and/or maintain a physically active lifestyle
Various	- Drug-drug interactions - Contaminated supplement use - High dietary protein intake increasing kidney workload - Incorrect use or non-adherence to medication	- Patient education on drug-drug interactions - Professional counseling regarding medication and nutrition in the context of health and exercise performance - Use of high quality batch-tested supplements only, if necessary at all

others consist of bisphosphonate treatment, well-planned aerobic weight-bearing exercise, and resistance training [29–31].

Immune Modulation

Immunosuppressive therapy has turned allotransplantation into a curative option for end-stage organ disease [32]. However, chronic immunosuppressive therapy comes at a price of heightened vulnerability to infections. Especially within the initial year and contingent upon the transplant type, patients are susceptible to common or opportunistic infections, primarily affecting the lungs, gastrointestinal system, and urinary tract [33, 34]. In the general population, engaging in mild to moderate-intensity exercise, *i.e.*, below 60% of peak oxygen uptake (VO_2peak), promotes immunovigilance and reduces infection incidence [34]. However, a contrasting effect is observed with strenuous exercise, such as prolonged exercise exceeding 60% VO_2peak [34]. Through complex interactions of transient changes in adaptive and innate immune system components, increased inflammatory responses, and metabolic factors that impair immune cell metabolic capacity, engagement in strenuous exercise leads to temporarily suppressed immune function [35]. In healthy athletes, a typical example of this phenomenon is the six-fold increased risk for upper respiratory tract infection within the first week after a marathon [36]. The interaction with immunosuppressive therapy is less clear. Blood samples from kidney transplant recipients and matched healthy controls, drawn after a strenuous 81-km bicycling trip, showed appositional gene expression upon incubation with bacterial endotoxin lipopolysaccharide [37]. Immune response genes were overrepresented in controls, whereas numerous apoptotic genes were overrepresented in kidney transplant recipients. These findings, albeit in a limited cohort of 10 transplant recipients and 10 healthy controls, suggest that SOTRs are at increased risk for infection upon contact with a pathogen in the early aftermath of strenuous exercise. Note that certain sport environments such as natural waters and public pools house a higher number of pathogens that can lead to illnesses. In addition, endurance sports may predispose individuals to urinary tract infections due to infrequent voiding and dehydration, particularly in women exercising in hot and humid weather conditions [38–40]. One should balance the benefits against potentially unfavorable immunomodulation of strenuous exercise after SOT. Whether dynamic customization of the immunosuppressive regimen is warranted in response to acute or long-term participation in moderate or strenuous exercise awaits examination in future studies.

Cardiovascular Events

Regular participation in physical activity has been established as a key factor in reducing cardiovascular morbidity and mortality across the general population [5, 41]. However, the cardiovascular advantages of physical activity exhibit a curvilinear dose-response relationship. Surpassing an 'optimal dose of exercise' in terms of duration and intensity might raise the potential for coronary plaque development [42–44], atrial fibrillation [45–47], and myocardial fibrosis [48, 49]. Furthermore, during acute high intensity exercise, cardiac workload and blood pressure increase to potentially hazardous levels which may lead to myocardial infarction and sudden cardiac death in susceptible individuals. This is translated in a >100-fold increased risk of acute myocardial infarction in sedentary individuals during participation in vigorous physical activity [50]. This heightened risk is associated with the presence of underlying coronary artery disease. Coronary artery disease is highly prevalent in SOTRs [42, 51–53]; the 5-year cumulative incidence for coronary artery disease after kidney transplant is 7.6% [51], cardiac allograft vasculopathy in heart transplant patients has a prevalence of 18% [52], coronary stenosis is present in one-third of liver transplant candidates [53], and the 5-year cumulative incidence of cardiovascular events after liver transplantation is 14% [54]. Nonetheless, to our knowledge, apart from one study [55], reports of cardiovascular events occurring during physically demanding exercise [7–10] or during controlled exercise-based rehabilitation are lacking. We speculate that this observation is consequent to profound selection bias and in-depth medical preparticipation screening. Some forms of preparticipation screening (i.e., cardiopulmonary exercise test, functional imaging, coronary CT scan and, if necessary, coronary angiography) may indeed be indicated, particularly in those with heightened cardiovascular risk profile planning to engage in moderate and/or vigorous exercise training or physically strenuous endeavors [56].

Gastrointestinal Distress

Diarrhea is a common issue among SOTRs, irrespective of exercise. Its prevalence varies, ranging from 13% after kidney transplantation to 40% after liver transplantation [57, 58] and may be of infectious origin but is very often related to side effects of immunosuppressive agents such as tacrolimus and mycophenolate [59]. Gut ischemia, together with mechanical (e.g., increasing intra-abdominal pressure) and neuroimmune endocrine factors, is believed to play an important contribution in exercise-induced diarrhea and gastrointestinal distress symptoms such as regurgitation, nausea, and, in some instances, gastrointestinal bleeding [60]. Unspecified non-infectious diarrhea has been associated with elevated risk of graft failure (e.g., dehydration with negative effects on organ perfusion and function), mortality, and gut microbial dysbiosis [61, 62]. Microbial dysbiosis is widely prevalent among transplant recipients and has been associated with mortality [63]. In contrast to moderate-intensity exercise, strenuous exercise of long-duration and/or high intensity can negatively impact intestinal health, as it reduces intestinal blood flow and increases intestinal permeability, leading to impaired gut-barrier function, depressed immune function, and increased risk for viral and bacterial infections [64, 65]. While in the general population evidence suggests that regular moderate-to-vigorous aerobic physical activity reduces the risk of gastrointestinal malignancies [66], diabetes [67], chronic kidney disease [68, 69], fatty liver disease [70], and gut microbial dysbiosis [71], little is known about the impact of strenuous physical exercise on the gastrointestinal tract in SOTRs.

Diabetes

Approximately 10–40 percent of SOTRs have some form of diabetes mellitus, mainly type 2 diabetes and posttransplant diabetes mellitus [72]. Class I level A recommendations support the increase in weekly physical activity to 150 min of moderate or 75 min of vigorous intensity activity in all patients with type 2 diabetes [73]. The beneficial glucometabolic effects of exercise in SOTRs are remarkably understudied and at least for now lack solid evidence base [74, 75]. Exercise in patients with diabetes treated with insulin or medication improving insulin secretion (e.g., sulfonylurea) requires specific attention. Exercise-induced increase in insulin sensitivity can modulate blood glucose levels till several hours after exercise cessation [76, 77]. In general, long-duration aerobic exercise increases the risk of acute hypoglycemia, but it appears that there is a great intra- and interindividual variation in blood glucose response to a given exercise stimulus [77]. A brief bout of exercise at vigorous intensity on the other hand increases plasma glucose during and briefly after exercise due to a mismatch between gluconeogenesis and muscle glucose utilization [78]. High diabetes prevalence in SOTRs highlights the importance of patient education regarding exercise-induced modulation of blood glucose, hypoglycemia symptoms recognition, blood glucose monitoring, and adequate dietary strategies before, during, and after exercise.

Renal Injury

Exercise-induced release of noradrenaline during moderate and vigorous-intensity exercise in temperate climate leads to a reduction of kidney blood flow by about 20% and 52%, respectively, [79, 80]. These physiological changes could be postulated to set kidney transplant recipients, many of whom have an estimated glomerular filtration rate below 60 mL/kg/m^2 [81], at risk for kidney injury. Of course also other transplant groups often suffer compromised kidney function [82–84]. A prospective study of 76 healthy marathon runners reported a 48% incidence of acute renal failure, mostly grade 1 [85]. Based on serum creatinine levels, earlier findings in 23 marathon runners indicated a 55% incidence of acute renal failure, while 74% of participants showed significant increases in tubular biomarkers [86]. Whether these findings truly imply significant kidney injury remains open for debate, but vigilance may be required.

Though a rare condition, muscle breakdown from strenuous exercise may lead to rhabdomyolysis and associated acute kidney failure and liver dysfunction [87]. The risk increases with excessive, high intensity, long duration, eccentric muscle contractions conducted by less trained individuals. Hot environments, electrolyte imbalance, and inadequate protein and carbohydrate intake may further increase the risk [87].

Environmental Factors

In contrast to training interventions conducted in controlled research environments, real-world settings often involve environmental stressors that were previously unconsidered. These stressors can include factors like heat, humidity, ambient hypoxia (altitude), and air pollution. Extrapolating safety data from research settings in mild environmental conditions or from observational studies involving carefully selected individuals exposed to challenging environments to the wider transplant population in real-world settings is inappropriate.

Exercise in hot and humid climates causes redistribution of cardiac output to the skin. Combined with evaporation-induced dehydration, this may result in an additional 15%–30% reduction in renal blood flow [88–90], a decrease in glomerular filtration rate, and acute tubular injury possibly resulting in acute kidney injury [88–93].

Apart from hot environments, exercise endeavors are not infrequently organized in oxygen-deprived conditions. Acute altitude sickness, ranging from mild to life threatening forms, may develop upon recent ascent to altitudes ≥2,500 m [94]. Transplant recipients have successfully summited high-altitude peaks such as Kilimanjaro (Tanzania). At its peak 5,895 m above sea level, around 80% of healthy sojourners develop acute mountain sickness [95]. The current literature indicates comparable summitting success rates in well-trained transplant recipients compared to healthy controls [8]. Normal physiological responses, including changes in oxygen saturation and heart rate, appear largely similar to those observed in healthy controls when exposed to increasing altitudes [7, 8, 96–98]. However, a higher incidence of arterial hypertension in liver transplant patients has been reported [98], and higher altitude sickness scores have been reported in lung transplant recipients [7]. In the latter, the rise in right ventricular contractility was blunted, indicating impaired cardiac adaptation to hypoxia. The underlying mechanisms behind this phenomenon could be linked to cardiac autonomic dysfunction due to surgical vagal nerve transection in lung transplantation and/or to the neurotoxic effects of immunosuppressive agents like calcineurin inhibitors. High altitude exposure could also have negative impact on the kidneys. Hypoxia can trigger the development of acute and chronic kidney failure [99, 100]. Acute hypoxia at high-altitude triggers hyperventilation with subsequent development of respiratory alkalosis, for which the kidneys need to compensate [100]. It also increases the renal excretion of sodium and water, potentially decreasing renal perfusion with subsequent reductions in glomerular filtration [100]. High altitude may also lead to high-altitude renal syndrome in which a combination of polycythemia, hyperuricemia, hypertension, and proteinuria coexist and can induce nephropathy with different histopathological features such as glomerular hypertrophy, basement membrane thickening, glomerulosclerosis, and fibrosis [101]. Hypoxia is also known to play a key role in the progression of chronic kidney disease to end stage kidney disease [100].

Young physically inactive adults residing in regions characterized by high levels of particulate matter, commonly encountered in big cities and regions with high levels of air pollution, exhibit an augmented susceptibility to cardiovascular disease upon elevating their physical activity levels to ≥1,000 MET-min/week (equivalent to approximately ≥4 h of moderate-intensity physical activity) [102]. Furthermore, engagement in vigorous but not moderate-intensity physical activity in areas with high levels of air pollution appears to escalate mortality risks among older adults [103]. These findings hold particular relevance to lung transplant candidates and recipients, as poor air quality in their living environments correlate with adverse waitlist occurrences and compromised lung function, respectively [104, 105]. Consequently, exercise recommendations must factor in

air pollution levels, emphasizing that, in areas with poor air quality, vigorous-intensity exercise should be conducted indoors or substituted with moderate-intensity alternatives.

Mental Distress—The "Gift of Life" Metaphor

Receiving solid organ transplantation and thereby the "gift of life" may induce substantial psychological distress among recipients [106]. Upon receiving a donor organ, recipients may experience a sense of obligation not only towards their donors, but also towards the medical team and transplant community [107]. It is not uncommon practice among healthcare practitioners to leverage the "gift of life" metaphor as a potent means of fostering motivation towards adopting a healthy physically active lifestyle. "It is a minimal gesture to honor your donor." Therefore, inability to commence or sustain suitable levels of posttransplant physical activity, regardless of the causes, can evoke sentiments of guilt and personal failure. Research in 134 kidney transplant patients indicated the presence of feeling of guilt in the large majority of patients, with an average guilt score of 69 on a Visual Analogue Scale from 0-100 [108]. It is important to recognize the potential unintended mental strain that patients might undergo and to persist in viewing them as individuals with distinct needs and experiences. Upholding patients' autonomy and fostering shared decision-making could offer a more ethical and sustainable strategy for interventions targeting the enhancement of patients' physical activity behavior.

PERFORMANCE ENHANCERS: CAVEATS

In situations where performance enhancement is pursued, the use of performance enhancing strategies lurks around the corner. Notably, for pain prevention or relief, a significant portion (12%–48%) of healthy participants in endurance sport events have been reported to utilize non-steroidal anti-inflammatory drugs or analgesics [109–111]. Non-steroidal anti-inflammatory drugs have been shown to exert toxicity on the kidneys and gastrointestinal tract and to promote arterial hypertension [112]. Furthermore, these drugs can potentially alter blood concentrations of immunosuppressive medications through drug-drug interactions [113–115]. The same concern exists regarding other over-the-counter drugs and dietary supplements. Supplement manufacturers are not obligated to conduct third-party testing of their product's safety, efficacy, or potential contamination by substances such as anabolic androgenic steroids or stimulants [116]. Such contamination can arise either inadvertently due to substandard manufacturing practices or deliberately with the aim of enhancing product efficacy [117]. The prevalence of supplement use within athletic populations varies widely, spanning from 11% to 100%, depending upon factors such as the definition used to call a product a supplement, the timeframe considered, and the data collection methodology in the different studies [118]. Apart from carbohydrate and protein supplements, athletes predominantly turn to minerals and vitamins in their endeavors to enhance performance, promote health, and aid recovery [118]. Nutritional supplement adoption is similarly widespread among SOTRs. A study involving liver, kidney, and combined lung-heart transplant recipients revealed that 58% of the patients consistently integrated supplements into their regimens, independent of exercise participation, encompassing vitamins, minerals, and diverse herbs asserted to possess therapeutic advantages [119]. A notable concern arises from the fact that in roughly 75% of cases, the treating physician remained uninformed about patients' supplement intake.

Transplant recipients should be cautious when mimicking the dietary habits of professional athletes. For example, the International Association of Athletics Federations recommends a daily protein intake of 1.3–1.7 g/kg for weight-stable athletes, and 1.6–2.4 g/kg for athletes aiming to attain weight loss while preserving lean body mass [120]. This stands in contrast to the existing daily dietary protein recommendations for kidney transplant recipients, which are currently established at 0.8 g/kg of body weight [121, 122]. Substantial dietary protein intake following kidney transplantation has been hypothesized to contribute to elevated blood pressure, secondary graft failure, and an increased risk of cardiovascular events [121, 123, 124].

Lastly, competitive and performance-oriented transplant recipients may be inclined to temporarily adjust their medication schedules in order to achieve performance advantages. Chronotropic incompetence induced by beta blockers can reduce VO_2peak by 5%–15%, significantly diminishing cardiorespiratory exercise performance [125]. Patients participating in challenging aerobic events could thus be tempted to temporarily decrease the dosage of these ergolytic agents. This is of course inadvisable, as this medication provides a significant survival benefit in certain conditions such as heart failure or after acute myocardial infarction [126]. A similar assumption could apply for the inappropriate increase in erythropoietin use to achieve above normal total hemoglobin mass in patients receiving erythropoietin treatment, e.g., about one in ten kidney transplant patients [127].

A CRITICAL APPRAISAL OF THE RESEARCH METHODOLOGY IN THE FIELD OF EXERCISE IN SOTRs

Various randomized controlled trials (RCTs) suggest that safety concerns are not readily apparent in posttransplant exercise-based rehabilitation [74, 75, 128]. However, RCTs and systematic reviews of RCTs are commonly misconstrued as the primary sources for assessing adverse intervention effects. Apart from the limited data the present literature enables us to make strong safety claims, other methodological concerns are present that limit statements about training intervention's effectiveness, generalization, and implementation (**Figure 2**). A recent Cochrane review that evaluated the harms and benefits of exercise interventions in liver transplant recipients corroborates our critical appraisal [4]. The authors concluded that there were very few data on adverse events outcomes, and that based on very low-certainty evidence the role of exercise training in affecting mortality, health-related quality of life, and physical function was very uncertain [4].

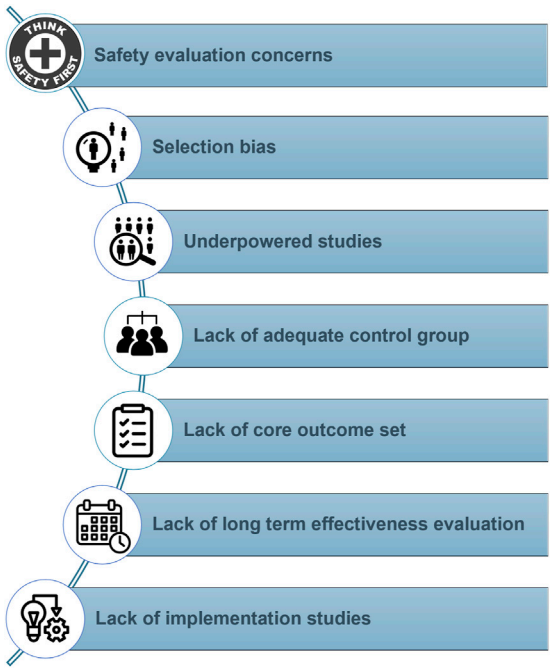

FIGURE 2 | Common methodological concerns present in the current literature regarding physical activity and exercise interventions after solid organ transplantation.

Safety Evaluation Concerns

In the realm of posttransplant exercise training, RCTs tend to prioritize intervention benefits, while the evaluation of harms is either demoted to a secondary role or omitted altogether. A recent systematic review of RCTs examining exercise training after SOT showed that adverse events were explicitly documented in merely eight out of the 21 studies encompassed [128]. Additionally, safety assessment frequently relied on retrospective self-reporting of adverse events. This approach might have resulted in the omission of harms that patients deemed insufficiently severe or significant, as well as harms that they did not perceive to be connected to the study. Although we did not perform a systematic literature search to confirm our hypothesis, it is likely that training studies in SOTRs, in line with similar studies in SOT candidates [129], not only poorly define and describe safety but also fail to inform the reader whether dropouts may have been related to adverse events. Future studies should *a priori* define adverse events, include a prospective evaluation of potential harms, and clearly describe whether dropouts could potentially have been related to the applied intervention. Safety claims based on RCTs have additional shortcomings in that most of these studies are underpowered and of insufficient duration to detect anything beyond the most common harms.

Selection Bias and Underpowered Studies

Strict eligibility criteria and substantial selection bias considerably limit the generalizability of the RCTs' conclusions on harms and benefits and lead to underpowered studies. Selection bias is a significant concern in the present research field. It results in a sample that is not representative of the transplant population in real-world settings. A recent review on RCTs showed that only 35% of the approached kidney transplant recipients were found eligible and willing to participate in exercise RCTs [74]. In liver transplant recipients, only one in three approached patients were included in the final analyses [75]. Systematic reviews in heart and lung transplant recipients have reported difficulties in evaluating selection bias due to issues with the selection procedures in a significant number of analyzed studies [2, 3]. Future literature reviews on safety of exercise after transplantation should also include other types of studies on top of RCTs, given that observational studies may be less restrictive in their eligibility criteria and achieve larger sample sizes [130, 131].

Lack of Adequate Control Group and Core Outcome Set

The absence of blinding constitutes another prevalent bias in exercise RCTs. Given the nature of the intervention, blinding participants to the exercise regimen is essentially unattainable, rendering the intervention arm susceptible to expectancy effects [132]. Consequently, to facilitate more credible between-group comparisons of intervention effects, it is recommended to employ an attention control group or a sham exercise comparator (e.g., flexibility exercise training) instead of usual care. Furthermore, the lack of a standardized set of core outcomes evaluated throughout the different studies, great heterogeneity in the applied training interventions, and other methodological limitations make it difficult to draw strong conclusions and recommendations from the existing literature.

Lack of Long-Term Behavior Change and Effectiveness Evaluation

Lack of long-term follow-up is a major shortcoming, as it is required to evaluate long-term effects on hard objective outcomes such as mortality, graft function, and the incidence of cardiovascular or other life-threatening events [1, 3, 74, 75]. While exercise interventions have demonstrated favorable outcomes concerning cardiorespiratory fitness, muscle strength, and quality of life in the short term, these advantages are transient and do not last over the long term [132–138]. Short-term exercise-based rehabilitation after transplantation may be recommended for specific patients to enhance their physical and psychological capacity for physical activity. However, continuous engagement in lifelong exercise training is likely unfeasible for the majority of the population [133]. Consequently, in our perspective, exercise interventions should consistently be preceded by tailored physical activity behavioral interventions when aiming for long-term clinical impact [139].

Lack of Implementation Studies

Despite the multifaced health benefits associated with exercise RCTs, the implementation of such interventions remains challenging. The majority of exercise studies have been

conducted under strict research conditions, often neglecting critical aspects such as stakeholder involvement throughout the whole lifespan of a research project; *i.e.*, the co-design of the intervention, public and patient involvement in the recruitment strategy, selection of relevant outcomes, interpretation, and dissemination of study results. Moreover, the local context in which the intervention is delivered, and the development of tailored implementation strategies adapted to that context have also been overlooked. In addition to evaluating the efficacy and effectiveness of exercise interventions, the study of methods that promote systematic uptake of these interventions in clinical practice may offer valuable insights with real-world impact [140]. Therefore, there is a critical need to bridge the gap between research and practice and integrate exercise and physical activity interventions into routine clinical care to promote their implementation and ultimately improve patient outcomes.

THE DIFFERENCE BETWEEN MEDICINE AND POISON LIES IN THE DOSE

In this review, we delved into the existing literature to analyse the impact of (strenuous) physical activity on SOTRs. Embracing a stance akin to the devil's advocate, we did not avoid sometimes speculative arguments hoping to stimulate dialogue within the posttransplant exercise research community. It is crucial to emphasize that while exercise can serve as a potent therapeutic intervention after transplantation and is probably underutilized in the transplant population, the line between its medicinal benefits and potential harm lies in the dosage administered. Tailoring exercise frequency, intensity, duration, and type to the unique needs of each individual as well as continuous monitoring for potential adverse events is imperative. Although past case reports suggest the feasibility of completing tremendous physical endeavours after transplantation, a one-size-fits-all approach is not viable, given the associated risks spanning various organ systems, including the transplanted organ. Appropriate precautions may sometimes be advised to mitigate potential adverse events. Lastly, we underscored frequent methodological concerns in the present research field as a call for more high-quality studies.

AUTHOR CONTRIBUTIONS

Conceived the study: SDS; Drafting of the manuscript: DS and SDS; Development of the figures: SDS; All authors contributed to the article and approved the submitted version.

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CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Nurse-Led Self-Management Support After Organ Transplantation – A Multicenter, Stepped-Wedge Randomized Controlled Trial

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In this unblinded multi-center stepped-wedge randomized controlled trial the effectiveness of the nurse-led ZENN-intervention was tested in promoting self-management skills in comparison to standard care among heart, lung and kidney transplant recipients. This intervention is based on behaviour change theories and was conducted in four sessions over 6 months at the outpatient clinic. The experimental group received standard care, plus the ZENN-intervention, while the control group received only standard care. Both groups completed questionnaires at baseline, at 6 months and 1 year follow-up. At baseline, the experimental group (n = 69) scored significantly lower than the control group (n = 106) on the primary outcome Skills and Technique Acquisition (STA). No significant between-group differences were found on the secondary outcomes self-management, self-regulation, quality of life and medication adherence at T1 and T2. There was a significant increase on the self-management scale STA between T0 and T1 in the experimental group. Therefore, participants included in the experimental group had lower self-management skills at baseline and reported significant improvement after completing the intervention. No significant intervention effect was found in the primary analysis, however, for recipients with reduced self-management skills the intervention may be beneficial.

Clinical Trial Registration: https://onderzoekmetmensen.nl/en/trial/24150, Netherlands Trial Register NL8469.

Keywords: nurse practitioners, patient participation, motivation, goal, self-efficacy

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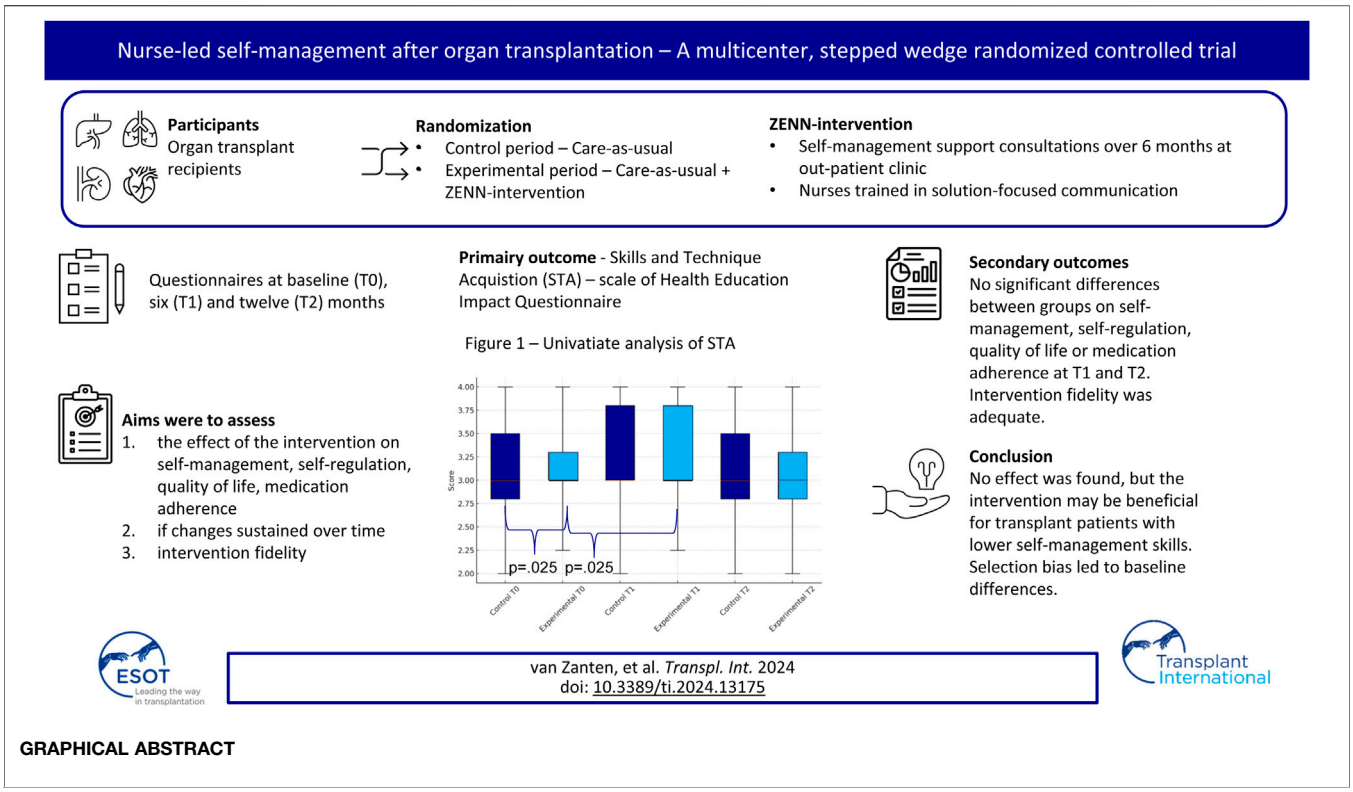
INTRODUCTION

Life after a solid-organ transplantation (SOTx) can present medical, social and emotional challenges [1–8]. Recipients need optimal self-management skills to deal with these challenges. Self-management can be defined as "the individual's ability to manage the symptoms, treatment, physical and psychosocial consequences and life style changes inherent with a chronic condition"



GRAPHICAL ABSTRACT

[9]. Previous research has shown recipients' need for holistic care after SOTx [10, 11]. According to recipients, support for medical management is sufficient, but emotional and role management support is often lacking [11, 12]. Optimal self-management can contribute to better clinical outcomes, lower healthcare costs [13] and a higher QoL [14].

Skills needed to achieve adequate self-management include awareness of possible problems, ability to solve problems, setting goals, making an action plan, executing it and being able to monitor and evaluate progress and, if necessary, adjust the goal. Many of these are self-regulation skills as defined by Self-regulation Theory [15]. Self-regulation can be defined as a "goal-guidance process, occurring in iterative phases, that requires the self-reflective implementation of various change and maintenance mechanisms that are aimed at task- and time-specific outcomes" [15]. Three phases are important here [1] goal selection, setting and representation [2]; active goal pursuit; and [3] goal attainment and maintenance or, when necessary, goal disengagement [15]. Adequate goal pursuit requires intrinsic motivation, self-efficacy, perseverance, planning and flexibility [16].

Previous research highlighted that there is a need for improved SMS in the first-year post-transplantation, but that attitudes, needs and preferences of transplant recipients regarding self-management vary per person [10, 17]. Current interventions have been criticized for not being able to provide person-centered and tailored support due to a one-size-fits-all approach. Moreover, interventions have been investigated specific patient groups with few studies addressing common self-management challenges among recipients of the various organs [18–20]. Furthermore, interventions are insufficiently guided by behavior change theories [20–22] and are time and resource intensive. To address some of the shortcomings, a SMS intervention was developed [17]. The overall aim of the ZENN-intervention (ZElfmanagement Na Niertransplantatie; Dutch acronym for self-management after kidney transplantation) is for recipients, with the guidance of nurse practitioners (NPs), to enhance their self-management skills in order to integrate their treatment and life goals. Key elements of the intervention are [1] a holistic approach [2], tailoring to patients needs and priorities [3], shared-decision making, and [4] patient empowerment. Early pilot-testing among kidney transplant recipients demonstrated feasibility and acceptability [23]. Given that self-management challenges and skills required after transplantation are comparable for recipients of kidney, liver, heart and lungs, the ZENN intervention may be beneficial for all SOTx recipients [20]. In this study, the first aim was to assess the effect of the intervention on participants' self-management and self-regulation skills, QoL, medication adherence, controlling for socio-demographic and medical characteristics. The second aim was to assess if the changes were sustained over time and the third aim was to assess adherence to the intervention protocol by NPs to test the intervention fidelity.

FIGURE 1 | Self-Management Web.

MATERIALS AND METHODS

Design

This multi-center study had an un-blinded stepped-wedge cluster randomized controlled trial (RCT) design and was performed between September 2020 and May 2022 [24]. A classical RCT with blinded group allocation was not suitable because it is not possible to expect NPs to switch between using and not using the learned communication techniques depending on group allocation. Additionally randomization was performed at the department level and not on NP level, due to the small number of NPs per department. All departments started with a control period and the start date of transition to the experimental period was randomized. The patients in both groups are different, which means that they will not cross-over from control to experimental group. Seven departments from five university medical centers in the Netherlands were included: four kidney transplant departments, one heart transplant department, one liver transplant department and one lung transplant department.

Eligibility Criteria

Potential participants were eligible if they had received a heart, kidney, liver or lung transplantation, were over 18 years old, were transplanted two to 13 months ago, had sufficient understanding of the Dutch language and had a functioning graft. Exclusion criteria were: cognitive limitations, participating in other lifestyle or self-management promoting programs which could influence the outcome and in case of kidney transplant recipients, renal replacement therapy expected to be needed within 3 months of inclusion.

Procedure

The intervention was delivered at the out-patient clinic by NPs. Immediately prior to transition from the control period to the experimental period, NPs were trained in the theoretical background and practical steps in carrying out the intervention. This training consisted of an e-learning course and a live training guided by a psychologist using a training actor to practice communication skills. The live training was conducted online due to COVID-19 restriction at the time. Participants completed a baseline (T0), a 6 months follow-up (T1) and a 12 months follow-up questionnaire (T2). Participants in the experimental group received the intervention between T0 and T1. The CONSORT Guidelines were used to guide reporting [25].

ZENN-Intervention

The ZENN-intervention [17] is a nurse-led SMS intervention primarily based on the theoretical framework of the Self-Regulation Theory. The intervention strategies are based on evidence-based techniques taken from Self-Regulation Theory [15], Solution-Focused Brief-Therapy [26, 27] and Motivational Interviewing [28].

The intervention is divided over several approximately 15-minute consultations. The intervention has four phases that

Steps	Operationalization
Phase 1: Assessment	
• Raising awareness of self-management problems and evaluate life areas using Self-Management Web • Assess motivation for change • Set goal(s) • Assess self-efficacy for change • Make an action plan	• Complete Self-Management Web & discuss green, orange and red scoring • Use VAS ruler (0-10) to explore current situation versus desired situation & motivation for change • Discuss recipients' prioritization of life areas and set a SMART goal • Use VAS ruler • Discuss concrete steps to achieving the SMART goal
Phase 2: Evaluation and concretization	
• Evaluate progress • Explore experience and attribution of successes (mastery experiences) • Make/re-assess action plan • Assess self-efficacy for change • Review Self-Management Web	• Discuss goal progress using VAS (0-10) ruler to compare current situation versus desired situation; complement successes • Discuss internal characteristics contributing to progress • Discuss steps to goal pursuit, review or adapt if necessary, include if-then plans (implementation intentions) • Use VAS ruler • Discuss potential changes in scoring of the Web and synergy with set goals
Phase 3: Monitoring	
• Monitor progress and satisfaction • Re-assess/adapt goal or action plan • Review Self-Management Web • Explore generalization of skills	• Discuss goal progress using VAS (0-10) ruler to compare current situation versus desired situation; explore and complement successes • Discuss set goal, adapt if necessary. Disengage if unachievable and replace. Discuss action plan, adapt if necessary; include if-then plans (implementation intentions) • Discuss potential changes in scoring of the Web and synergy with set goals • Discuss goal pursuit experience, learned skills, and potential application to other goals/life areas
Phase 4: Continuation and generalization	
• Evaluate progress and satisfaction • Relapse prevention • Explore generalization of skills	• Discuss goal progress using VAS (0-10) ruler to compare current situation versus desired situation; explore and complement successes • Discuss situations that are challenging, concrete actions and strategies to cope. Discuss if-then plans (implementation intentions) • Discuss goal pursuit experience, learned skills, and potential application to other goals/life areas

FIGURE 2 | Content of phases ZENN-intervention. Adapted from Beck et al. [17]. Abbreviations: VAS, Visual Analogue Scale; SMART goal, Specific, Measurable, Achievable, Relevant and Time-Bound.

must be completed, whereby the number of consultations depended on the logistical constraints of the setting and needs of the patient. Tools used during the consultations are the communication aid Self-Management Web (**Figure 1**) and a logbook in which the NP can keep track of the stages completed. For a visual overview of the steps and operationalization per phase, see **Figure 2**. The development of the ZENN-intervention and pilot testing has been extensively described elsewhere [17, 23].

Data Collection

Primary Outcome

Self-management was measured using the 40-item Dutch Version of the Health Education and Impact Questionnaire (heiQ) [29]. This instrument consists of eight domains. As there is no overall score of the heiQ, the "Skills and Technique Acquisition" (STA) subscale was chosen as primary outcome. This scale was chosen as the content was deemed nearest to the skills promoted in the intervention. The other seven subscales are described below as secondary outcomes. Response options are based on a 4-point Likert scale: "Strongly disagree" [1] to "Strongly agree" [4]. Interpretation of the heiQ is through mean scores on each domain, with subscale scores ranging between 1 and 4. Good validity and reliability have been established [29].

Secondary Outcome

The remaining subscales of the heiQ are "Health directed activity," "Positive and active engagement in life," "Emotional distress," "Self-monitoring and insight," "Constructive attitudes and approaches," "Social integration and support," and "Health service navigation" [29]. Higher values on the domain indicate higher levels of self-management, with the exception of the scale "Emotional distress," for which the interpretation is reversed.

Self-regulation was measured using the 21-item Self-regulation skills instrument in transplantation (SSIt) [30]. This instrument is divided into two scales "Setbacks" and "Successes." Response options are based on a 5-point Likert scale: (1) "Completely disagree" to (5) "Completely agree." Mean scores are calculated per subscale. A higher score on the subscale "Setbacks" indicates greater difficulties with the process of goal setting, initiating a plan to reach a goal, and dealing with setbacks. A higher score on the subscale "Successes" indicates successes in the process of goal setting, intrinsic motivation for initiating the plan, and self-efficacy. Good validity and reliability have been established [30].

Quality of life was assessed using the 26-items World Health Organization Quality of Life – Brief Version (WHOQoL-BREF) [31]. This instrument consists of five domains: "Physical health"; "Psychological"; "Social relationship"; Environment, and "Overall QoL" and "General health." Mean scores are calculated per

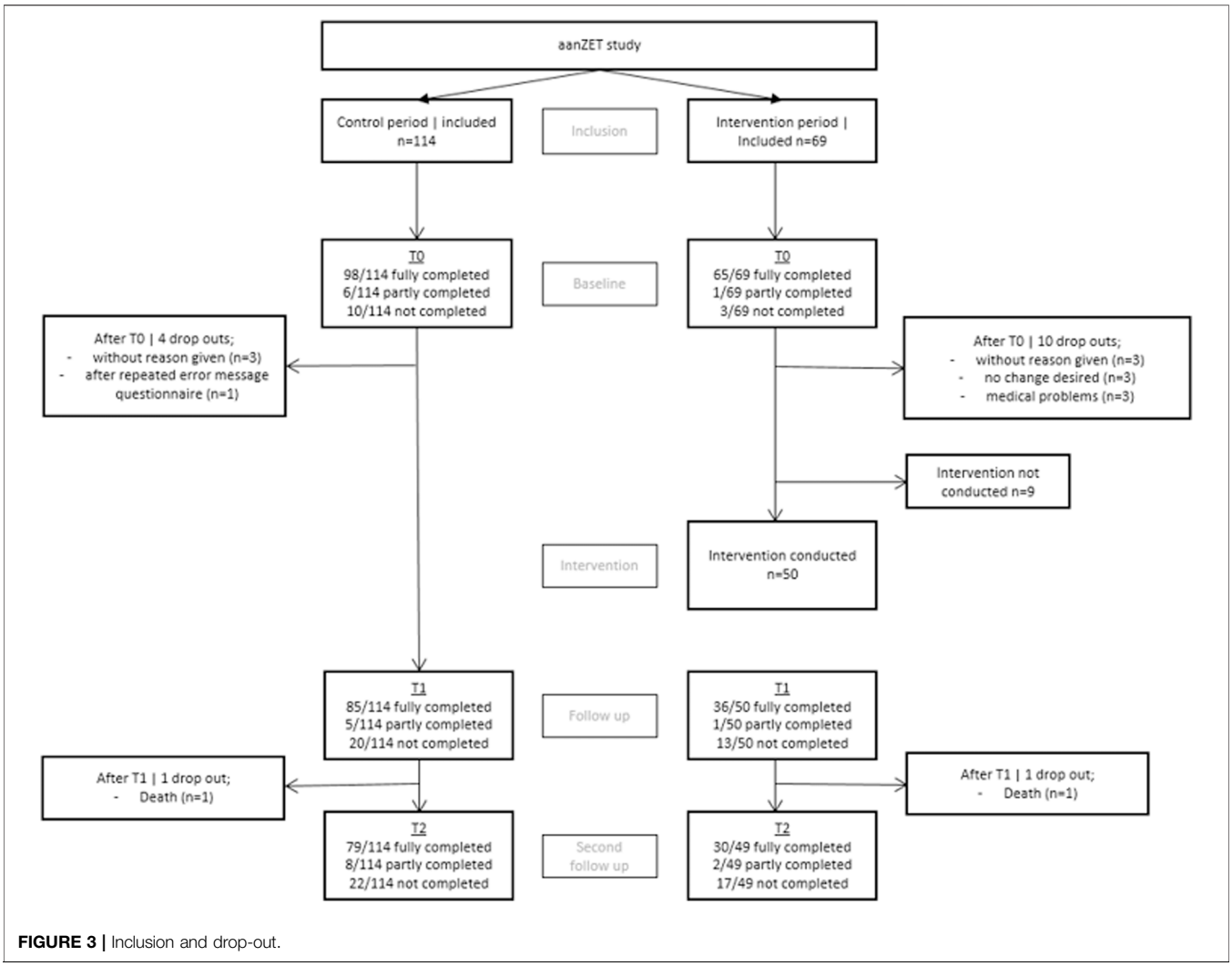


FIGURE 3 | Inclusion and drop-out.

domain as well as for the overall QoL. A higher score on the scale(s) indicates a higher level of QoL. Good validity and reliability have been established [31].

Medication adherence was measured using the Basel Assessment of Adherence to Immunosuppressive Medication Scale (BAASIS) [32]. The BAASIS is divided into two parts. The first part consists of four questions with the answer options (0) "No" and (1) "Yes." If "Yes" to any of these items, the patient is categorized as non-adherent. The second part than needs to be answered per item to indicate; how often they are non-adherent: (1) "Never" to (6) "Every day." Good validity and reliability have been established [32].

The *evaluation of experience* with the intervention was measured at T1 using the 5-item subscale "Patient-centeredness" (Cronbach's α = 0.83) of the American Consumer Assessment of Health Plan Survey (CAHPS) [33]. In addition, a visual analogue scale (1–10) was used to evaluate the overall experience of the nurse-led care. A higher score indicates a better overall experience. In addition, the participant was asked if they would recommend the ZENN-intervention to peers. Answer options were (1) "Yes, because. . ." and (2) "No, because. . ."

Socio-demographic and medical characteristics measured were gender, age, educational level, organ type and donor type. The donor type question was answered by NPs as participants are not always aware of the source of the organ.

Intervention fidelity was operationalized as adherence to the intervention protocol. Therefore, the NP completed a questionnaire about the number of consultations each participant received; how often the Self-Management Web was used; if each step of the intervention was completed and if the participant received the patient booklet. The greater the variation, the more likely intervention fidelity can be questioned [34]. A percentage of 80% per item was considered satisfactory.

Sample Size and Power

In order to obtain a power of 80% to detect a significant effect of the intervention, 82 patients per group were needed [24]. To account for the effects of correction for covariates, dropout and

TABLE 1 | Descriptive characteristics and comparison between control and experimental group.

	Total (n = 172)	Control group (n = 106)	Experimental group (n = 66)	P
Age				
Mean (SD)	53 (13.7)	53 (13.6)	53 (14.0)	0.906
Sex				
Male (%)/women (%)	107 (62.9%)/63 (37.1%)	71 (67.6%)/34 (32.4%)	36 (55.4%)/29 (44.6%)	0.111
Educational level				0.420
Low (%)	70 (41.2%)	42 (40.4%)	28 (42.4%)	
Middle (%)	53 (31.2%)	36 (34.6%)	17 (25.8%)	
High (%)	47 (27.6%)	26 (25.0%)	21 (31.8%)	
Organ – multiple response				
Kidney (%)	146 (86.4%)	91 (86.7%)	55 (83.3%)	
Heart (%)	12 (7.0%)	8 (7.6%)	4 (6.1%)	
Liver (%)	8 (4.7%)	3 (2.9%)	5 (7.6%)	
Lung (%)	9 (5.3%)	4 (3.8%)	5 (7.6%)	
Pancreas (%)	1 (0.6%)	—	1 (1.5%)	
Donor type				0.282
Living (%)	98 (57.0%)	57 (53.8%)	41 (62.1%)	
Deceased (%)	74 (43.0%)	49 (46.2%)	25 (37.9%)	
Medication (multiple response)				
Azathioprine (%)	3 (1.8%)	2 (1.9%)	1 (1.5%)	
Cyclosporine (%)	6 (3.5%)	4 (3.8%)	2 (3.0%)	
Everolimus (%)	9 (5.3%)	5 (4.8%)	4 (6.1%)	
CellCept (%)	140 (81.9%)	85 (81%)	55 (83.3%)	
Prednisolon (%)	134 (78.4%)	83 (79%)	51 (77.3%)	
Rapamycine (%)	1 (0.6%)	1 (1.0%)	—	
Tacrolimus (%)	160 (93.6%)	98 (93.3%)	62 (93.9%)	
Others (%)	2 (1.2%)	—	2 (3.0%)	

missing data, and contamination, we aimed for inclusion of 100 patients per group.

Ethical Considerations

The Medical Research Ethical Committee Erasmus MC approved this study protocol on 8th November 2019 (MEC number: MEC-2019-0671). The trial was conducted in accordance with the principles that have their origin in the Declaration of Helsinki 2013 and the principles of Good Clinical Practice.

Data Analysis

The control and experimental group at T0 were compared on patient characteristics as well as primary and secondary outcomes. The outcome was compared within each group between T0 and T1, and between T0 and T2. Descriptive statistics were presented as frequencies for categorical variables. Continuous variables were described as mean and standard deviation for normally distributed data and median and interquartile range for non-normally distributed data. The primary analysis was a univariate analysis of the effect of the intervention. Continuous outcomes at T0, T1 and T2 were compared between groups and tested using the independent samples t-test for normally distributed data or the Mann-Whitney U test for non-normally distributed data. Within-groups comparisons of continuous outcomes were performed using Wilcoxon signed-rand tests. For the BAASIS, a 2 × 2 chi-squared test was conducted and a within-groups analysis was conducted using a generalized estimating equations (GEE) model. For the multivariable analyses, a general linear model for repeated measurements (GLM) was applied to account for group (experimental or control), time-point (T0, T1 or T2), the interaction between group and time-point, the covariates "type of organ" and transplant center and other significant covariates. The within-patient correlations between repeated measurements were modeled using an unstructured covariance matrix. In addition, the results of the general linear models were summarized using the estimated marginal means, which are the predicted values of the response adjusted for covariates. These estimated marginal means were compared between participants in both groups at T1 and T2. In case of a skewed distribution of the outcome, leading to non-normally distributed residuals in the linear model, the outcome was dichotomized. This dichotomized outcome was then analyzed using a GEE model with a logit link function and a binomial distribution (i.e., logistic regression for repeated measurements). Based on the intention-to-treat principle, all models were estimated using all eligible participants from whom data was obtained. Data imputation was used when missing data occurred, as recommended in the instrument manuals. A p-value <0.05 was considered statistically significant.

RESULTS

Inclusion

For an overview of the inclusion and drop-out, see **Figure 3**. All departments included participants during the control group. Due

TABLE 2 | Univariate analyses of self-management skills, quality of life, self-regulation and evaluation of experience.

Median (IQR)	Control group T0[a]	Control group T1[b]	Control group T2[c]	Exp. group T0[d]	Exp. group T1[e]	Exp. group T2[f]	P-value between a and b	P-value between d and e	P-value between a and c	P-value between d and f	P-value between a and d	P-value between b and e	P-value between c and f
HEIQ – self-management skills	**(n = 102)[a]**	**(n = 94)[b]**	**(n = 84)[c]**	**(n = 65)[d]**	**(n = 39)[e]**	**(n = 31)[f]**							
Skill and technique acquisition	3.0 (2.8–3.5)	3.0 (3.0–3.8)	3.0 (2.8–3.5)	3.0 (2.8–3.3)	3.0 (3.0–3.8)	3.0 (3.0–3.5)	0.429	0.025**	0.507	0.564	0.025**	0.915	0.910
Health-directed activity	3.5 (3.0–4.0)	3.5 (3.0–4.0)	3.5 (3.0–4.0)	3.5 (3.0–4.0)	3.5 (3.3–4.0)	3.8 (3.3–4.0)	0.525	0.362	0.133	0.566	0.923	0.295	0.417
Positive and active engagement in life	3.2 (3.0–3.6)	3.2 (2.8–3.6)	3.2 (3.0–3.4)	3.2 (3.0–3.6)	3.2 (3.0–3.7)	3.4 (3.0–3.6)	0.705	0.427	0.448	0.103	0.531	0.678	0.085
Emotional distress	3.2 (2.8–3.7)	3.2 (2.8–3.7)	3.2 (2.8–3.7)	3.2 (2.8–3.7)	3.3 (3.0–3.7)	3.3 (3.0–3.8)	0.327	0.261	0.982	0.079	0.637	0.251	0.137
Self-monitoring and insight	3.3 (3.1–3.7)	3.3 (3.0–3.7)	3.3 (3.0–3.7)	3.3 (3.0–3.7)	3.3 (3.2–3.7)	3.3 (3.0–3.7)	0.405	0.112	0.568	0.412	0.565	0.810	0.904
Constructive attitudes and approaches	3.4 (3.0–3.8)	3.2 (3.0–3.8)	3.2 (3.0–3.8)	3.2 (3.0–3.8)	3.4 (3.0–4.0)	3.4 (3.0–4.0)	0.256	0.412	0.068	0.251	0.763	0.226	0.186
Social integration and support	3.2 (3.0–3.8)	3.2 (3.0–3.7)	3.2 (3.0–3.6)	3.2 (2.9–3.8)	3.4 (3.0–3.8)	3.0 (3.0–3.8)	0.060	0.459	0.059	0.627	0.444	0.228	0.583
Health service navigation	3.6 (3.0–3.8)	3.5 (3.0–3.9)	3.4 (3.0–4.0)	3.4 (3.0–3.8)	3.4 (3.0–4.0)	3.6 (3.0–3.8)	0.089	0.243	0.004**	0.723	0.320	0.547	0.592
WHOQoL – BREF – quality of life	**(n = 98)[a]**	**(n = 87)[b]**	**(n = 78)[c]**	**(n = 65)[d]**	**(n = 36)[e]**	**(n = 30)[f]**	**P-value between a and b**	**P-value between d and e**	**P-value between a and c**	**P-value between d and f**	**P-value between a and d**	**P-value between b and e**	**P-value between c and f**
Physical health	15.4 (13.7–17.1)	16.0 (14.3–18.3)	16.0 (13.7–17.7)	14.9 (13.1–16.6)	16.0 (13.7–17.6)	16.0 (14.7–17.9)	0.070	0.239	0.396	0.035*	0.127	0.571	0.494
Psychological	16.0 (14.7–17.3)	16.0 (14.7–17.3)	16.0 (14.0–18.0)	15.3 (14.3–16.7)	15.7 (14.7–16.7)	16.0 (14.7–17.3)	0.130	0.657	0.374	0.761	0.101	0.716	0.730
Social relationships	16.0 (14.3–17.3)	16.0 (13.3–17.3)	16.0 (13.3–17.3)	16.0 (14.7–17.3)	16.0 (14.7–17.3)	14.7 (13.3–17.3)	0.266	0.958	0.015*	0.985	0.546	0.793	0.992
Environment	16.5 (15.0–18.5)	16.5 (15.0–18.5)	16.5 (15.0–18.1)	16.8 (15.5–18.5)	17.5 (14.6–18.5)	16.5 (15.5–18.5)	0.554	0.768	0.420	0.224	0.638	1.000	0.540
Overall perception QoL	4.0 (4.0–5.0)	4.0 (4.0–5.0)	4.0 (4.0–5.0)	4.0 (4.0–4.0)	4.0 (4.0–5.0)	4.0 (4.0–5.0)	0.371	0.394	0.108	0.317	0.521	0.868	0.373
Overall perception of health	4.0 (4.0–4.0)	4.0 (4.0–5.0)	4.0 (4.0–5.0)	4.0 (4.0–4.0)	4.0 (3.0–5.0)	4.0 (4.0–4.0)	0.692	0.648	0.489	0.745	0.249	0.516	0.849
SSIt – Self-regulation	**(n = 102)[a]**	**(n = 89)[b]**	**(n = 79)[c]**	**(n = 65)[d]**	**(n = 36)[e]**	**(n = 30)[f]**	**P-value between a and b**	**P-value between d and e**	**P-value between a and c**	**P-value between d and f**	**P-value between a and d**	**P-value between b and e**	**P-value between c and f**
Setbacks	2.3 (1.7–3.0)	2.4 (2.0–3.0)	2.5 (2.0–3.0)	2.4 (2.0–3.1)	2.4 (1.9–2.8)	2.3 (1.9–2.8)	0.017*	0.888	0.042*	0.868	0.401	0.470	0.356
Successes	4.1 (3.8–4.6)	4.1 (3.8–4.6)	4.0 (3.7–4.0)	4.0 (3.9–4.4)	4.2 (4.0–4.6)	4.2 (4.0–4.5)	0.452	0.299	0.041*	0.843	0.503	0.230	0.034*
Evaluation of experience		**(n = 83)**			**(n = 35)**		**P-value between a and b**	**P-value between d and e**	**P-value between a and c**	**P-value between d and f**	**P-value between a and d**	**P-value between b and e**	**P-value between c and f**
Overall experience	—	10 (8.0–10.0)	—	—	10.0 (9.0–10.0)	—	—	—	—	—	—	0.920	—
CAHPS – total score	—	20.0 (18.0–20.0)	—	—	20.0 (18.0–20.0)	—	—	—	—	—	—	0.593	—

*p < *0.05*; **p < *0.001*. *Comparison between a and b, and c and d was conducted using a Wilcoxon signed ranked test. Comparison between a-c and b-d were conducted using a Mann-Whitney U test.*

to logistical difficulties two departments were not able to include participants in the experimental group.

Participants

For an overview of the participants characteristics, see **Table 1**.

Self-Management Skills

At T0, participants in the control group scored significantly higher on the primary outcome heiQ-STA compared to the participants in the experimental group ($p = 0.02$), see **Table 2**. There was a significant increase in heiQ-STA scores between T0 and T1 in the experimental group ($p = 0.025$) and remained stable over time (T2) ($p = 0.564$). For the control group, no significant difference between T0 and T1 was found ($p = 0.429$). Between T0 and T2 for the control group, a significant decrease was found on the secondary outcome heiQ-HSN ($p = 0.004$). The effect of the intervention could not be significantly demonstrated using the GLM based on the interaction between groups and time ($p = 0.082$), see **Table 3**. As none of the covariates were significantly related to heiQ-STA, these were not included in the GLM. There were no significant differences between the groups at T1 and T2 on the remaining subscales, see **Tables 3**, **4**.

Quality of Life

The univariate analysis showed no significant differences in QoL between the groups at the timepoints. A significant improvement after the intervention was found in outcome physical health within the experimental group between T0 and T2 ($p = 0.035$), see **Table 2**. The GLM and GEE could not demonstrate an effect of the intervention for any QoL scales, see **Tables 3**, **4**.

Self-Regulation

At T0 and T1, no significant differences between groups were found on the scales Setbacks and Successes. At T2, the experimental group scored significantly higher on the scale Successes compared to the control group ($p = 0.034$). For the control group, an increase was found between T0 and T1 on the scale Setbacks ($p = 0.017$) and between T0 and T2 ($p = 0.042$). For the subscale Successes, the control group scored significantly lower at T2 than at T0 ($p = 0.041$). For the experimental group no significant difference were found between T0, T1 and T2 on self-regulation. The GLM found no significant effect of the intervention between groups and time-points for both scales, see **Table 3**.

Medication Adherence

At T0 there was no differences in medication adherence between groups (see **Table 5**). Similarly at T1 and T2, no significant difference was found on the outcome medication adherence between groups. For the control group, a decrease of medication adherence on the scale Taking was found between T0 and T2 ($p = 0.038$). In addition for the control group, an decrease in medication adherence on the scale Timing was found between T0 and T1 was found ($p = 0.048$). The GEE found no significant effect of the intervention between groups and time-points, see **Table 4**.

Evaluation of Experience

No significant difference was found between groups on the scale Patient-centeredness, see **Table 2**. The perceived experience of the nurse-led care measured using the VAS, was considered high with a median score of 10 (IQR 8–10). Most participants (91.2%) of the experimental group indicated that they would recommend the program to peers. Reasons included the fact that it supports setting new goals, achievement of goals, as well as in everyday life after transplantation. Participants also indicated that this program gives insight and tools to help move forward. There were also participants who would recommend the program, but indicated that they did not need it because they did not experience any problems. Some of the participants would not recommend the program.

Intervention Fidelity

Table 6 shows that most participants received four sessions (84%) of the intervention, and 100% of the participants who received the intervention completed all steps of the intervention. The Self-Management Web was used during most sessions (96%). Most participants received the patient booklet (98%). For all items, intervention fidelity was found to be adequate.

DISCUSSION

In this study, we implemented and tested the ZENN-intervention in a multicenter stepped-wedge RCT among SOTx recipients.

The analyses showed that there were no significant differences in the primary and secondary outcomes at T1, suggesting that there was no effect of the intervention. However, analyses also revealed that the participants in the experimental group were less skilled in self-management when they entered the intervention and that they made significant improvements over time. After the intervention they had reached the same skill level of participants included in the control group. In addition, participants in the experimental group reported worse perceived physical health at baseline which improved over time. Moreover, the experimental group reported greater self-regulation successes at T1 compared to the control group. The differences at baseline are indicative of bias in inclusion, this could be either self-selection bias or bias by those including the recipients. As the control group did not entail participation in an intervention, this may have appealed to a broader audience to consent to participation. It is possible that those who felt the need for SMS were more likely to be approached to participate or agree to participate in the intervention. This may explain the differences at baseline as well as the difference in sample size between the groups. In the future, qualitative research on motivation to participate among recipients and inclusion choices among NPs may help shed light on the cause of this bias. Although, in this study we could not demonstrate a significant effect of the intervention, some findings point to potential of the intervention which require more investigation. It is possible that the intervention is effective in a more selected group of those in need of SMS, whereby a matched control group on self-management skills would offer a better comparison.

TABLE 3 | General linear model for self-management skills, quality of life and self-regulation.

	Follow up T1 mean difference (experimental – Control, 95% CI)	P-value*	Follow up T2 mean difference (experimental – Control, 95% CI)	P-value*	P-value for interaction**
HeiQ					
Skills and technique acquisition	–0.013 (–0.189–0.163)	0.886	–0.009 (–0.196–0.178)	0.922	0.082
Positive and active engagement in life	0.036 (–0.158–0.230)	0.714	0.168 (–0.018–0.354)	0.077	0.180
Emotional distress	0.110 (–0.087–0.308)	0.272	–0.161 (–0.061–0.383)	0.153	0.094
Self-monitoring and insight	–0.063 (–0.205–0.079)	0.381	–0.004 (–0.153–0.144)	0.954	0.631
Constructive attitudes and approaches	0.152 (–0.039–0.342)	0.118	0.215 (0.026–0.405)	0.026	0.036*
Social integration and support	0.123 (–0.070–0.316)	0.210	0.094 (–0.102–0.290)	0.346	0.162
WHOQoL-BREF					
Physical health	–0.799 (–1.867–0.269)	0.142	–0.148 (–1.269–0.973)	0.795	0.135
Psychological health	–0.128 (–0.995–0.739)	0.771	–0.073 (–0.969–0.823)	0.872	0.392
Social relationships	0.184 (–0.868–1.236)	0.731	0.319 (-0.751–1.390)	0.556	0.448
Environment	0.109 (–0.776–0.994)	0.808	0.249 (–0.601–1.099)	0.563	0.934
SSIt					
Setbacks	–0.082 (–0.344–0.179)	0.536	–0.121 (–0.151–0.393)	0.379	0.190
Successes	0.106 (–0.093–0.306)	0.293	0.108 (–0.105–0.321)	0.317	0.093

*P-*value for the difference in estimated marginal means between the experimental group and the control group.*

**P-*value for the interaction between time-point and group.*

TABLE 4 | Results of generalized estimating equation models for dichotomized variables of self-management, quality of life and treatment adherence.

	Follow up T1 Odds ratio (95% CI)	P-value*	Follow up T2 Odds ratio (95% CI)	P-value*
HeiQ				
Health-directed activity	0.905 (0.791–1.036)	0.149	1.048 (0.895–1.229)	0.560
Health service navigation	0.969 (0.880–1.068)	0.529	0.940 (0.866–1.020)	0.139
WHOQoL-BREF				
Quality of life assessment	0.908 (0.700–1.178)	0.468	0.755 (0.565–1.010)	0.059
Satisfaction with health	1.014 (0.702–1.463)	0.943	0.848 (0.592–1.214)	0.368
BAASIS				
Adherence vs. non-adherent	1.905 (0.621–5.843)	0.260	1.848 (0.606–0.5.638)	0.280

In addition, we were unable to include and retain sufficient participants in the experimental group for a sufficiently powered analysis. Three main factors contributed to the low number of inclusions. Firstly, while we implemented inclusion and exclusion criteria, a needs assessment was not part of the recruitment strategy. For example, there were participants who indicated that they thought it was a good program but did not consider it necessary for themselves as they were not experiencing self-management issues. So, some recipients may have been less in need of, and thus less engaged in the intervention. This may also have led to a ceiling effect on the questionnaires. Therefore, when using the intervention, it may be better to include a screening step, for example, using the Self-Management Web. If self-management problems are identified, the intervention could be continued.

Secondly, the COVID-19 pandemic had an impact on the inclusion rate. The study started later due to the pandemic and NPs were given additional duties, for example, temporarily working in the intensive care unit. Consequently, there were staffing shortages and a backlog of work to be caught up on. During the control period, the role of the NPs was to recruit the participants and register them with the investigator. The combination of these administrative tasks with implementing the intervention during the experimental period required a greater time investment which proved challenging in the post-COVID period.

Thirdly, the pandemic also affected the training of the NPs. Initially, the plan was to provide the training in two steps consisting of theory through an e-learning module, and a practical interpersonal skills training in a live group session. Due to the restrictions on visiting other hospitals, this proved impossible. The live training was therefore completed online. It is not clear whether this had adverse effects on the self-efficacy and development of the skills needed to implement the intervention. How NPs experienced this is also unclear. It would therefore be useful to gain insight into this through interviews with those who delivered the intervention.

Research on successful self-management interventions shows that effective support is found in tools such as reminders,

TABLE 5 | Univariate analyses of medication adherence.

N (%)	Control group T0[a] (n = 98)	Control group T1[b] (n = 85)	Control group T2[c] (n = 77)	Exp. group T0[d] (n = 65)	Exp. group T1[e] (n = 36)	Exp. group T2[f] (n = 28)	P-value between a and b	P-value between d and e	P-value between a and c	P-value between d and f	P-value between a and d	P-value between b and e	P-value between c and f
Medication adherence –overall	80 (81.6%)	60 (70.6%)	56 (72.7%)	51 (78.5%)	28 (77.8%)	22 (78.6%)	0.134	1.00	0.405	1.00	0.618	0.417	0.545
Adherent (%)	18 (18.4%)	25 (29.4%)	21 (27.3%)	14 (21.5%)	8 (22.2%)	6 (21.4%)							
Non-adherent (%)													
Medication adherence –taking	93 (94.9%)	76 (83.5%)	66 (85.7%)	62 (95.4%)	34 (94.4%)	27 (96.4%)	0.118	0.842	0.038*	0.726	0.888	0.379	0.127
Adherent (%)	5 (5.1%)	9 (10.6%)	11 (14.3%)	3 (4.6%)	2 (5.6%)	1 (3.6%)							
Non-adherent (%)	1 (1%)	9 (10.6%)	8 (10.4%)	3 (4.6%)	1 (2.8%)	1 (3.6%)							
One time (%)	—	—	2 (2.6%)	—	1 (2.8%)								
Two times (%)	—	—	—	—	—								
Three times (%)	4 (4.1%)	—	1 (1.3%)	—	—								
Four or more times (%)	—	—	—	—	—								
Missing (%)													
Follow up question – drug holiday	4 (80%)	9 (100%)	10 (90.9%)	3 (100%)	2 (100%)		—	—	—		—	—	—
No (%)	—	—	—	—	—								
One time (%)	—	—	—	—	—								
Two times (%)	1 (20%)	—	1 (9.1%)	—	—								
Three times (%)	—	—	—	—	—								
Four or more times (%)													
Missing (%)													
Medication adherence – timing	80 (85.1%)	64 (75.3%)	60 (77.9%)	52 (81.3%)	30 (83.3%)	23 (82.1%)	0.048*	0.779	0.175	0.910	0.521	0.332	0.638
Adherent (%)	14 (14.9%)	21 (24.7%)	17 (22.1%)	12 (18.8%)	6 (16.7%)	5 (17.9%)							
Non-adherent (%)	8 (8.5%)	12 (14.1%)	10 (13.0%)	9 (14.1%)	3 (8.4%)	3 (10.7%)							
One ime (%)	5 (5.3%)	6 (7.1%)	4 (5.2%)	2 (3.1%)	3 (8.4%)	2 (7.2%)							
Two – three times (%)	1 (1.1%)	2 (2.4%)	2 (2.6%)	1 (1.6%)	—	—							
About once a week (%)	—	1 (1.2%)	-	—	—	—							
Few times a week (%)	—	—	1 (1.3%)	—	—	—							
Almost every day (%)	—	—	—	—	—	—							
Missing (%)													
Reduction of dose													
Adherent (%)	97 (100%)	85 (100%)	77 (100%)	64 (100%)	36 (100%)	28 (100%)	1.000	1.000	1.000	1.000	1.000	1.000	1.000
Non-adherent (%)	—	—	—	—	—	—							
Persistence													
Adherent (%)	97 (100%)	85 (100%)	77 (100%)	64 (100%)	36 (100%)	28 (100%)	1.000	1.000	1.000	1.000	1.000	1.000	1.000
Non-adherent (%)	—	—	—	—	—								

*p < *0.05*; **p < *0.001*. *Comparison between a-b, a-c, d-e and d-f were conducted using a GEE. Comparison between a-d and b-e was conducted using a Chi-square test.*

TABLE 6 | Descriptive statistics of the intervention fidelity.

N (%)	Experimental group T1 (n = 50)
How many intervention sessions did the participant received?	—
One session (%)	3 (6%)
Two sessions (%)	5 (10%)
Three sessions (%)	42 (84%)
Four sessions (%)	—
More than four sessions (%)	
Have all the steps been completed?	
Yes(%)/No(%)/	49 (100%)/0 (0%)
How often was the Self-Management Web used?	
Never	1 (2%)
Sometime, but not every session	48 (96%)
Throughout all sessions	1 (2%)
Did the recipient receive the participant booklet during the first session? Yes(%)/No(%)/Don't know (%)	49(98%)/0(0%)/1 (2%)

medication logs, registration of symptoms, rehabilitation guidance modules, decision support tools and tools for healthcare providers for care assessment [35]. These are practical tools to SMS, while the ZENN-intervention primarily focuses on patient empowerment and skills to set and achieve their own personal goals and take matters in their own hands, with guidance from the NP. This intervention is primarily based on behavior change theories'; it is well established that interventions based on behavior change theories make an important contribution to improving self-management skills in the long term [36–38]. Recipients are stimulated to set goals in the different areas of life. These will not always be health-related such as medication use or monitoring symptoms. Goals can also be, for example, about roles and relationships or solving financial problems. The intervention aims to provide generic skills that can be used for all kinds of goals. The analysis of self-regulation skills shows that at T2 there is a difference between the groups on the success subscale, whereby the intervention group was achieving higher scores on success compared to the control group. This could be an indication that there has been an increase over time in the skills needed to self-manage life. Further research is needed to replicate and confirm the effect.

PRACTICAL IMPLICATIONS AND FURTHER RESEARCH

In this study, there were differences between groups at baseline which were not expected. Conducting qualitative research among those who implemented the study could help to understand the processes that resulted in these differences and how to avoid this source of bias in future studies. Similarly, qualitative research among participants on their experiences with the intervention and whether this type of intervention matches support needs could be insightful. Suggestions for improvement could be generated as a result.

For the future, it is useful to examine the way in which the intervention or parts of the intervention can be integrated into daily care practice. A possible idea would be to integrate the Self-Management Web within patient dashboards or the Patient Reported Outcome Measures (PROMs) and Patient Reported Experience Measures (PREMs). The Web could act as a starting point for a conversation on self-management and personalized counseling which fits seamlessly with the goals of Value Based Healthcare [39].

Further research could focus on cost-benefit analysis, implementation and evaluation of the intervention and the Self-Management Web among other populations of individuals with a chronic condition. With this intervention, people receive guidance in optimizing skills that are not only useful for recipients after a SOTx and can be of added value in managing life with a chronic disease.

CONCLUSION

The analysis demonstrated no effect of the intervention at T1. Secondary analyses demonstrated baseline differences and an increase in self-management skills over time in the experimental group. This suggests that the intervention may be beneficial for a subgroup of transplant recipients with lower self-management skills. Further research will be required to assess which groups of recipients can benefit most from this SMS approach. Participants were generally positive about the program and reported added value.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving humans were approved by Medical Research Ethical Committee Erasmus MC. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

RV and EM conducted the research and did the project management. RV, MV, JV, and EM analyzed the data and described results in manuscript. RZ wrote the original draft manuscript. All authors contributed to the article and approved the submitted version.

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CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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ORIGINAL RESEARCH
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The SElf-Care After REnal Transplantation Study: A Retrospective Evaluation of a Home-Monitoring Program Implemented as Standard Care

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After transplantation self-management is essential for graft survival and optimal quality of life. To address the need for home-based support in self-management, we implemented the "SelfCare after Renal Transplantation" (SeCReT) box, containing home-monitoring equipment combined with a smartphone application that was linked to the electronic patient records. This study investigated the uptake and continuation, protocol adherence, and subjective evaluation of this home-monitoring program. All "*de novo*" kidney recipients who received the SeCReT-box in the study period (Aug 2021–Dec 2022) were eligible for inclusion. Protocol adherence was defined as ≥75%. Subjective evaluation was assessed with a 5-item questionnaire. Of the 297 recipients transplanted, 178 participants (60%) were included in the analysis. Protocol adherence was 83%, 73%, 66%, and 57% respectively at 5, 10, 20, and 40 weeks of the protocol. With regard to continuation, 135 participants were still in the program at the end of the study period (75% retention rate). Regarding subjective evaluations, 82% evaluated the program positively, and 52% reported lower care needs due to home-monitoring. Results are positive among those who entered and continued the program. Qualitative research is needed on barriers to entering the program and facilitators of use in order to promote optimal implementation.

Keywords: kidney transplantation, self-management, telemedicine, eHealth, adherence, self-monitoring

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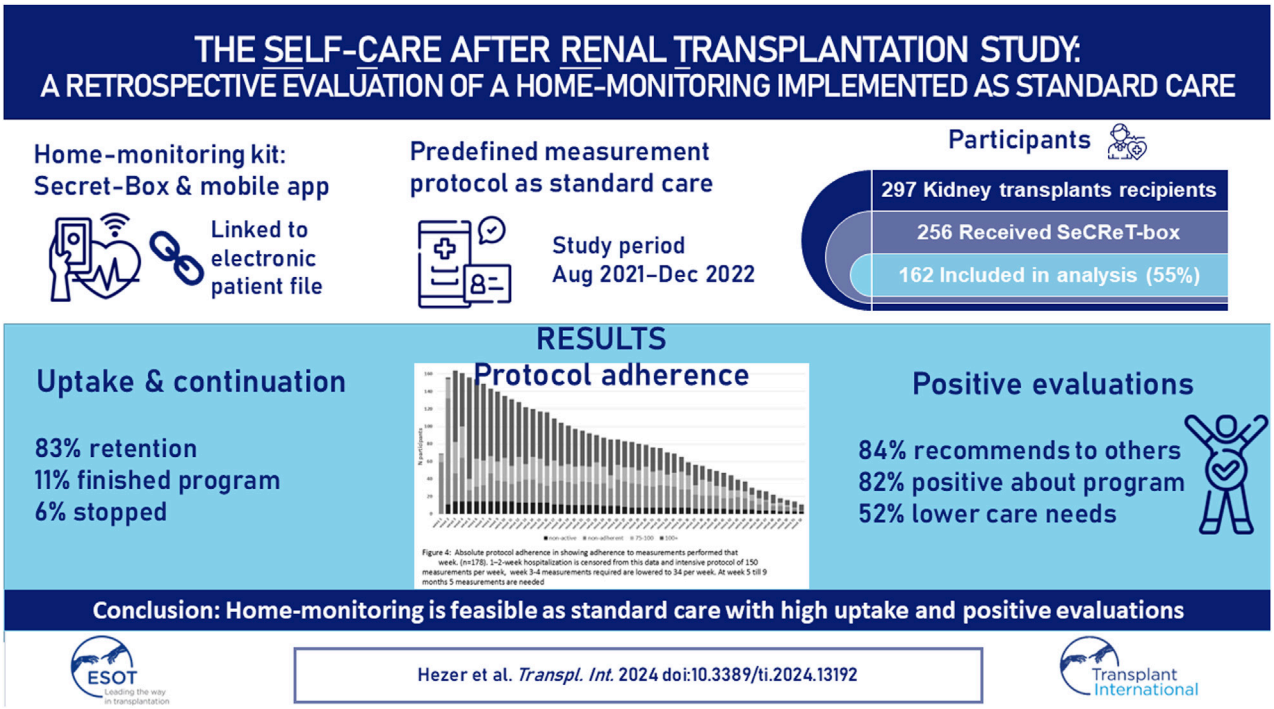
INTRODUCTION

Monitoring physical and lifestyle parameters are essential components of self-management after transplantation. Monitoring has traditionally taken place in the hospital, with measurements carried out by the physician. With increasing technical developments, it has also become feasible for patients to perform reliable medical measurements themselves, outside the healthcare institution. By combining these self-measurements with the use of information and communication technologies, telemedicine becomes possible and is increasingly implemented to support (post-transplant) self-management and care from a distance. Telemedicine is the use of electronic devices to provide medical care from a distance, including teleconsultations and home-monitoring of clinical parameters. Innovations in telemedicine are developing rapidly in the field of kidney transplantation, accelerated by the COVID-19 pandemic. Publications prior to COVID-19 already highlighted the potential benefits of telemedicine in



GRAPHICAL ABSTRACT

transplantation. There was some evidence that telemedicine was feasible and acceptable among kidney transplant recipients (KTRs) [1, 2], however, the number of studies among adult KTRs was limited and sample sizes were often small [3, 4]. Implementation of home-monitoring after transplantation has been hindered by barriers such as low eHealth literacy [5], availability of equipment, reimbursement of costs and accessibility to internet [6, 7]. Another factor that may negatively influence patient satisfaction and ultimately engagement with the system is the burden associated with carrying out the home-monitoring. However, adherence to home-monitoring protocols and associated satisfaction has yet to be investigated. Potential benefits of being able to monitor vital post-transplant parameters at home include increased accuracy of measurements conducted [8] and improved self-management and disease understanding [9]. From an economic perspective telemedicine also has the potential to reduce costs for patients [2] and for (medium and high volume) transplant centers [10].

Plans to implement home-monitoring in our center were triggered by the COVID-19 pandemic during which KTRs were at increased risk of morbidity and mortality [11] due to their suppressed immune system and poorer response to vaccination compared to controls [12]. Given this heightened risk and social distancing recommendations, hospital-based post-transplant monitoring and care became a challenge [13–15]. To address the need for home-based monitoring and treatment, we developed and implemented the "SelfCare after Renal Transplantation" (SeCReT) box containing home-monitoring equipment combined with a smartphone application that was linked to the electronic patient records. This home-monitoring system has since been adopted as standard care for all KTRs at our transplant center. This study is the first evaluation of this home-monitoring system and aims to evaluate uptake and continuation, adherence to the measurement protocol, subjective evaluation and the relationship between the latter two. Findings can provide targets for future improvement of the system.

MATERIALS AND METHODS

Participants

Patients above 18 years who receive a kidney transplant at our center all receive a SeCReT-box as standard. Recipients who followed the "do novo kidney transplant" home-monitoring protocol during the study period (Aug 2021–Dec 2022) were included in this analysis. Exclusion criteria were insufficient understanding of Dutch or English, following an alternative home-monitoring protocol, more than 4 weeks between transplantation and registration and imminent transfer to another hospital.

Home-Monitoring System

Secret-Box

The SeCReT-box contains the following medically certified devices: a thermometer (either Braun, Kronenbreg, Germany;

IRT6520 (Thermoscan 7) or Braun IRT3030), pulse-oximeter (iHealth Air Pulse Oximeter PO3M, San Jose, California, United States), optional weighing scale (iHealth Lina Smart Scale) and blood pressure monitor (iHealth Track Blood Pressure Monitor KNT550BT) with Bluetooth capabilities.

Luscii® Application

Devices in the SeCReT-box are used to measure vital parameters and data is entered by patients manually into the Luscii® smartphone and tablet application (Utrecht, Netherlands). Data from the Luscii® application is integrated into the electronic patient records so that professionals can view and discuss the data during consultations in the outpatient clinic. A kidney transplant-specific home-monitoring protocol was developed in Luscii® that allows data entry from the SeCReT-box, provides information about kidney transplantation, collects data via questionnaires and provides a dashboard for recipients to enter measurements from the various devices. Participants were required to enter measurements such as heart rate, blood pressure and temperature as well as answer survey questions. Frequency of measurements per parameter was predefined for the first 12 months post-transplant and an overview was available for patients in the app homescreen, see **Figure 1**. Vital signs such as heart rate, blood pressure and temperature were asked frequently (daily/twice weekly/monthly) while other symptoms such as smoking were asked at specific intervals. Intensity of the protocol decreased over time (see **Figure 2** and Annex of the **Supplementary Material**). The app produces a notification signal when a measurement should be taken. If values entered were outside the target value, patients received an alert with instructions on the required action (e.g., contact the outpatient clinic or other). In the app, information was included on how to use the app, how to perform measurements correctly at home, useful websites, advice on living with kidney transplant, medication use and side effects, nutritional advice, sex after transplantation, mental health support sites and how and when to contact the hospital. For technical support we had different lines to communicate: A physical location for SeCReT-box related problems; via Luscii® communication for app-related and our staff to guide patients. The holiday mode in the app allowed for a pause in home-monitoring protocol in the case of holiday or short hospital admissions. For longer admissions, patients were transferred to an alternative protocol and were not included in this analysis.

Procedure

Recipients were offered the SeCReT-box and the access to the smartphone application as soon as possible in the first week after transplantation during the hospital admission, free of charge and as part of standard care. The patient was required to have their own smart telephone or tablet. During hospital admission professionals gave tutorials individually to the patient on how to use the devices and Luscii application in order to familiarize them with the process and give them the opportunity to ask questions if needed. Data was collected after following the tutorial during hospitalization. For this study we include data from the day of discharge, once the patient's is back home. Data from the Luscii® application used in this analysis were extracted on 31-12-2022 and combined with data from the medical records. The study protocol was approved by Institutional Review Board (IRB) of our transplant center (MEC-2023-0143).

Measures

Participant Characteristics

The following socio-demographic characteristics and medical variables were collected from the medical records: age (years), gender (M/F), number of kidney transplants, and date of transplant.

Uptake and Continuation

Luscii® records the date of registration, date of activation and date of deactivation. These time-points were used to assess frequency of uptake and continuation. To measure uptake, we define "active users" as those who registered for the home-monitoring system, who activated the app and entered at least one measurement. "Non-active users" were those who registered but did not activate the app or make a minimum of one measurement. Continuation was defined as active participation (entry of measurements) up to the moment of data extraction from the app. The protocol is predefined for 12 months until the KTR is referred to a regional hospital who will take over the care of the transplant (end of program). Currently, use of the SeCReT-box and Luscii app is not transferred with the participant to the regional hospital.

Protocol Adherence

Protocol non-adherence was defined as <75% of protocolled measurements required that week or overall. To determine total weekly protocol adherence, we summed the number of measurements over all parameters and compared this to the number of measurements stipulated by the protocol for each week that the participant was in the program. All protocol measurements were clustered within each week (7 days) from date of discharge (end of run-in period). We presented the total weekly protocol adherence as a percentage: participants who on average scored <75%, 75%–100%, and ≥100%. For protocol adherence per parameter the number of measurements carried out over the study-period were compared to the number of measurements stipulated by the protocol.

Subjective Evaluation

Experience with the home-monitoring system was explored using 5 items provided by Luscii® that were rated on a Likert scale. The specific questions were: What do you think of the remote care service in general (1 – I completely dislike this type of care service; 5 – I think this type of care service is fantastic); Remote monitoring with this app makes me feel safe (1 – strongly disagree; 5 - strongly agree); Thanks to this way of remote monitoring I don't have to go the hospital or GP as often (1 – strongly disagree; 5 - strongly agree); Remote monitoring with this app improves my insight in my medical condition (1 – strongly disagree; 5 - strongly agree); and How likely is it that you would recommend remote care using this app to other patients? (0- completely unlikely, 10 – very likely). The Likert 5-scale was converted into three categories: negative (score = 1-2), neutral (score = 3), and positive (score = 4-5). The Likert 10-scale

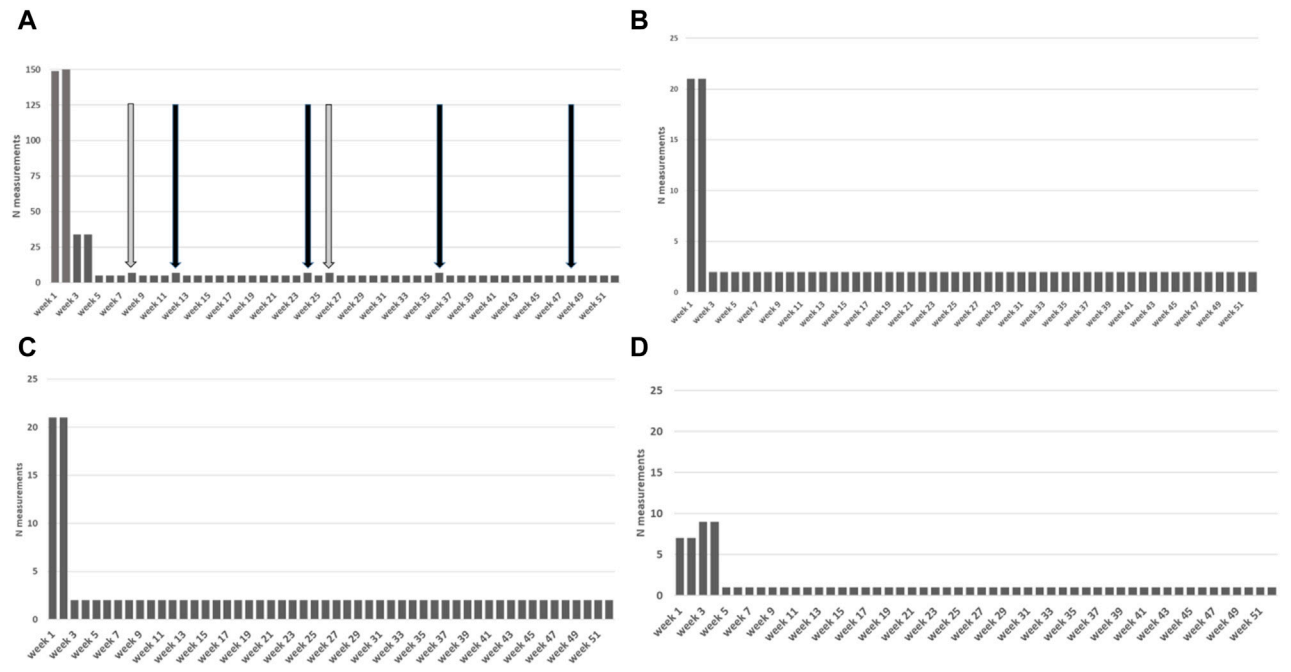


FIGURE 1 | Total number of measurements stipulated by the protocol per week for the first year. **(A)** Total measurements. Black arrows: subjective evaluations/ medication; Grey arrows: smoking/sex surveys. **(B)** Heart rate measurements **(C)** Blood pressure measurements **(D)** Weight measurements.

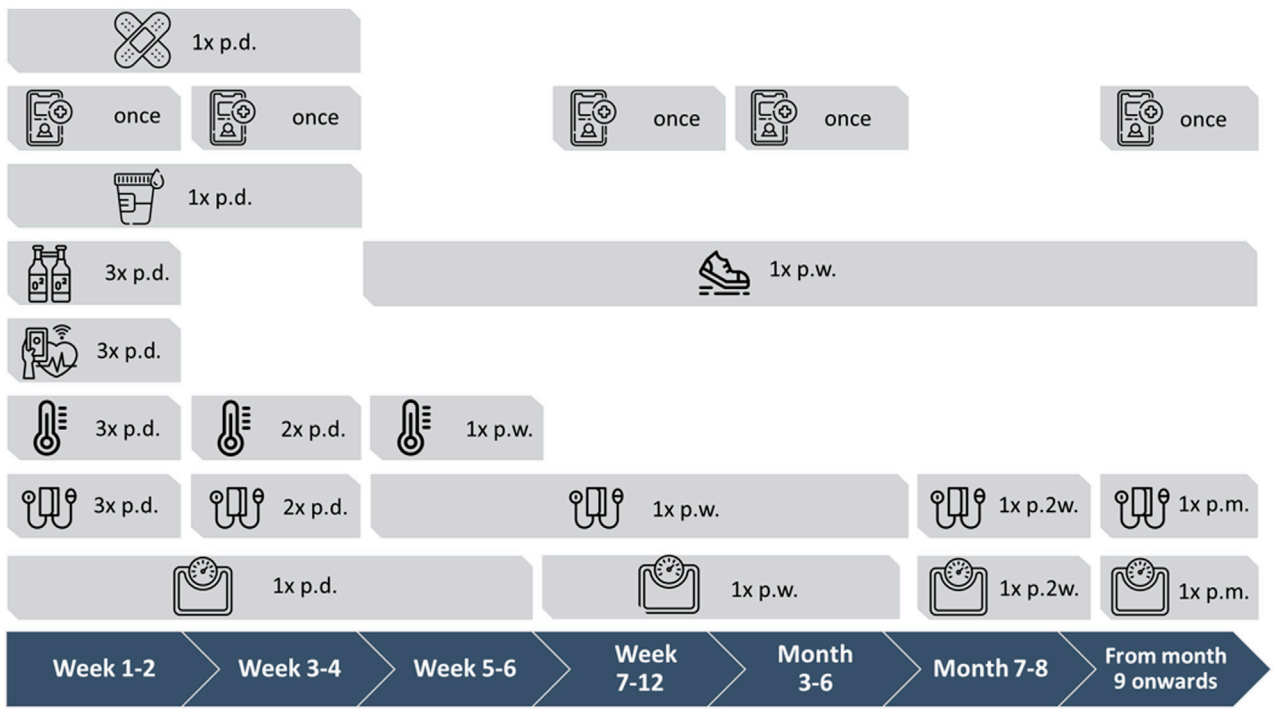


FIGURE 2 | Measurement protocol visualized over 1 year period with measurement frequencies. Frequencies: p.d. = per day, 1x = single time, p.w. = per week, p.2w. = per 2 weeks, p.m. = per month Icons: Band aid = wound checkup; telephone with plus icon = surveys (sex, smoking, subjective evaluation); urine cup = urine and intake liquid volumes; O_2 bottles = oxygen saturation; shoes = number of steps; heart = heart rate; thermometer = temperature; blood pressure monitor = blood pressure; weighing scale = weight.

was converted into the same three categories: negative (score = 1–4, neutral (score = 5-6), positive (score = 7–10). Each item was analyzed individually. Multiple responses were averaged per participant and first and last scores were compared to assess change over time.

Statistical Analysis

SPSS version 22 (IBM) was used to analyze the data. Student t-tests were used to compare means between active and non-active users. Frequencies were explored to assess uptake and continuation. In line with the intention to treat principle both groups active and non-active were included in analyses of protocol adherence. Protocol adherence was calculated per week according to the proportion of participants adherent and non-adherent. Mean subjective evaluations were calculated per item. First and last evaluations were compared using a paired t-test for the 50 users with multiple evaluations. Subjective evaluation items were analyzed using a within group linear model to assess if subjective evaluation changed over time. The level of protocol adherence was compared between participants who evaluated the app as positive, neutral, negative or did not give an evaluation. These groups were compared using one-way ANOVA.

RESULTS

During the study period 297 recipients received a kidney transplantation (see **Figure 3**). Of these, 256 were registered for home-monitoring; 41 recipients were not registered (no registration of reasons). Of the 256 registered, 59 recipients used the home-monitoring system according to an alternative protocol (blank protocol without predetermined measurement schedule and/or a COVID protocol), resulting from COVID-19 infection or hospitalization. These KTRs were not included in this analysis. Of the 197 participants who registered for the "*de novo* kidney transplant" protocol, 7 recipients requested their data to be anonymous in Luscii®, 12 participants were transplanted and registered during the inclusion period but entered the program more than 4 weeks after transplantation, 13 participants did not activate the app and 3 participants did not record any measurements after activation. 162 participants did record measurements out of this group 6 recipients were still in the run-in period after transplantation.

Uptake and Continuation

Table 1 presents demographic and medical characteristics of the registered participants who were divided into two groups: active users (minimum 1 measurement registered; n = 162) and non-active users (non-activated participants and no-measurements performed participants; n = 16) (**Figure 3**). Active users were significantly younger than non-active users ($p = 0.002$). Among active users the age ranged from 20 to 82 years with median of 55; and among non-active users the age ranged from 46 to 79 years with median of 67. In the active user group, there was a higher proportion in patients who had received a kidney from a living donor than in the non-active group ($p < 0.001$). There were no significant differences between active and non-active participants on gender ($p = 0.706$) and number of kidney transplants, with the majority being first time KTRs (range 1–5) ($p = 0.782$).

As the non-active users had initially registered, we included this group in the subsequent analyses according to the intention to treat principle. With regard to continuation, among the active and non-active users (n = 178), 135 participants were still in the program at the end of the study period, average of time in program of 198 days (range 1–508 days). This is an 76% retention rate. Of the 27 who stopped home-monitoring, the majority (n = 18) were transferred back to their referring regional hospital (on average 290 ± 71 days after start of home-monitoring program). Of the remaining 9: 5 stopped due to technical difficulties, 2 stopped without giving reason and 2 participants died. The overall dropout rate in our study was 13% (24/178) (no measurements & program stopped other than completion of program).

Protocol Adherence

Protocol adherence per parameter (after the run-in period during admission) is presented in **Table 2**. At the date of data extraction, 6/162 participants were still in the run-in period and were not included in the analysis of protocol adherence. Participants were most adherent to measuring temperature (76.3% n = 119/156), followed by blood pressure measurements (75.6% n = 118/156). Participants were least adherent to protocol for the survey on smoking (156/419, 7.1%, n = 87/154), followed by medication taking (249/390, 34.2%, n = 52/152), subjective evaluations (171/263, 41.7% n = 48/115), the median adherence was 67% which corresponds to 1 evaluation and sex (138/205, 49.6%, n = 83/129).

Figure 4 shows the number of participants achieving protocol adherence divided into non-adherent (<75%), adherent (≥75–100%), and over adherent (≥100%), which also starts after the run-in period of the hospitalization period. Throughout the study there was a group of participants who were >100% adherent entering more measurements than stipulated according to protocol. In the 5th week, the intensity of the protocol decreases. At week 5, 156 participants were still in the sample. Of these, 13 were non-adherent, 13 were adherent, and 116 were over adherent (14 were non-active). This resulted in an overall adherence rate of 83% at week 5. At week 10 there were 135 participants, of which 23 were non-adherent, 27 participants were adherent, and 71 were over adherent and, (14 were non-active). This results in an overall protocol adherence rate of 73% at week 10. At week 20 there were 97 participants, of which 24 were non-adherent, 20 were adherent, 43 were over adherent (10 were non-active). This resulted in an overall protocol adherence rate of 66% at week 20. At week 40 there were 49 participants, 15 were non-adherent, 11 were adherent, 17 were over adherent (6 were non-active). This resulted in an overall protocol adherence rate of 57% at week 20. At the end of the retrospective study period 22.4% of all participants had an overall adherence to the protocol with all measurement types (**Table 2**).

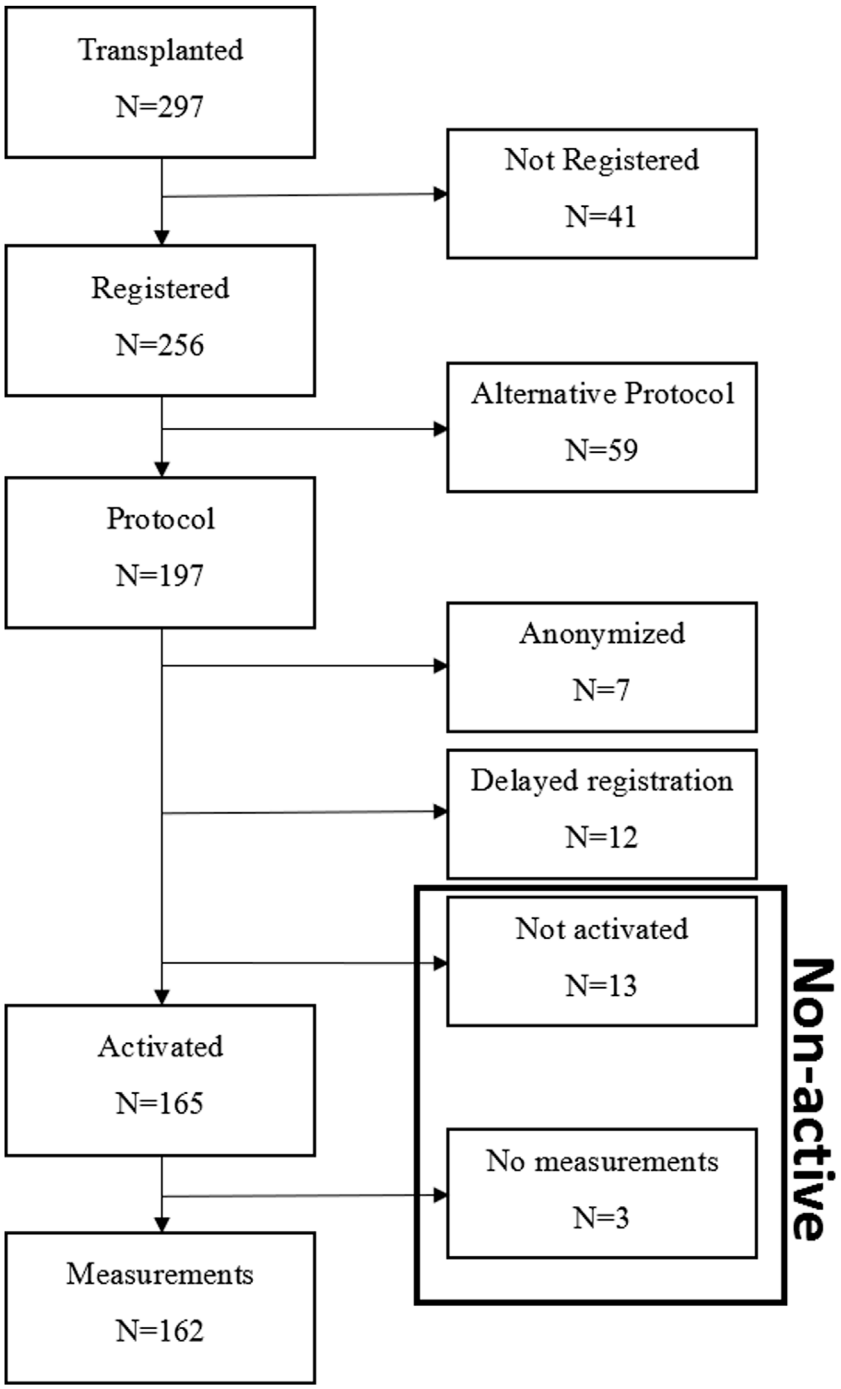


FIGURE 3 | Flow-chart of inclusion. Black box indicates the non-active user group who are included according to the intention to treat principle.

Subjective Evaluations

Questions on subjective evaluation of the home-monitoring system were completed by 79 individuals (69% of individuals prompted n = 79/115, 44% of total group n = 79/178), of whom 45 answered this questionnaire multiple times (n = 171 evaluations). On the first item measuring overall experience of the home-monitoring system responses were positive, with on average a score >4 on a 5-point scale (4.19 ± 0.86) (see **Table 3**). Also participants generally agreed

TABLE 1 | Participant characteristics (active vs. non-active users).

	Non-active users (n = 16)	Active users (n = 162)	*p*-value
Age: median (range)	67 (46–79)	55 (20–82)	<0.001
Gender: n female (%)	7 (43.8)	63 (38.9)	0.706
Graft functioning	8	133	
Delayed	4	26	
Primary non-function	3	1	
Unknown[a]	1	2	
Number of transplants: (range)	1 (1–5)	1 (1–3)	0.782
Donor Type: Living	2/16	85/162	<0.001

[a]*Unknown due to patient being from another center.*

TABLE 2 | Overall protocol adherence per parameter (n = 156)[a]

Parameter	Total number of measurements recorded	Protocolled number of measurements[b]	Percentage of participants meeting criteria for protocol adherence[c]
Blood pressure	15,315	10,293	75.6% (118/156)
Heart rate	12,051	10,293	61.5% (96/156)
Weight	8,044	7,016	61.5% (96/156)
Temperature	9,681	4,904	76.3% (119/156)
Fluid intake	3,482	3,004	53.5% (81/156)
Urine production	3,305	3,004	51.9% (87/156)
Oxygen saturation	4,654	2,850	58.2% (85/146)
Pain score	1,842	2,850	37.7% (55/146)
Steps	1,788	950	33.6% (49/115)
Wound	1,585	950	53.4% (78/146)
Smoking	156	419	7.1% (11/154)
Medication problems	249	390	34.2% (52/152)
Subjective evaluation	171	263	41.7% (48/115)
Sex	138	205	49.6% (64/129)
Problems with defecation	90	98	61.5% (56/91)
Other (glucose)	4,261 (3,399)	0	-
Total	**66,812**	**47,489**	**22.4%**

Legend.
[a]*Patients (n = 6) still in the run-in period not included in this analysis.*
[b]*Total number of protocolled measurements required taking into account the number of weeks in the program per participant.*
[c]*Adherence protocol calculated based on >75% of measurements as stipulated by the protocol, summed over the total group of participants on the date of data extraction (31-12–2022).*
Bold values are to highlight total measurements performed, required and protocol measurment adherence.

that they felt safer with home-monitoring (3.81 ± 0.95), that it reduced visits to the hospital (3.56 ± 1.4) and it gave better insight into health (3.77 ± 0.87). Participants were highly likely to give recommendations' of the system to others (8.15 ± 2.19), see **Figure 5**.

A subgroup analysis was conducted among those with multiple subjective evaluation measurements (see **Table 3**). Paired T-test between start and last measurement showed significant increase score in time with "recommendations" ($p = 0.010$). There was no significant change over time in subjective evaluation items "experience" ($p = 0.321$), "safety" ($p = 0.127$), "outpatient visits" ($p = 0.221$) and "insight" ($p = 0.241$).

Finally, total protocol adherence was compared between participants who differed in their subjective evaluation of the home-monitoring (see **Figure 6**). Four groups were defined based on average subjective evaluation scores: no evaluations (n = 82), negative evaluation (n = 4), neutral evaluation (n = 16), positive evaluation (n = 60). One-way ANOVA did not show any differences between groups in protocol adherence ($p = 0.25$).

DISCUSSION

After implementing home-monitoring as standard care in our center, these findings show that KTRs are more than ready to adopt the new technology. Out of the 297 KTRs, 256 had registered for one of the home-monitoring packages. The 178 KTRs who started the "*de novo*" home monitoring program showed high retention to the protocol with 76% still in use at our cutoff date. After the run-in period and discharge from hospital, protocol adherence was high for the majority of participants although this tapered off over time. There was a subgroup of participants that were more than 100% protocol adherent throughout in total measurements. Lastly, subjective evaluations were carried out by 69% of participants who made it in the protocol, and were generally positive. A positive evaluation does not appear to be related to protocol adherence, however, those who do not complete a subjective evaluation were on average less adherent to the protocol.

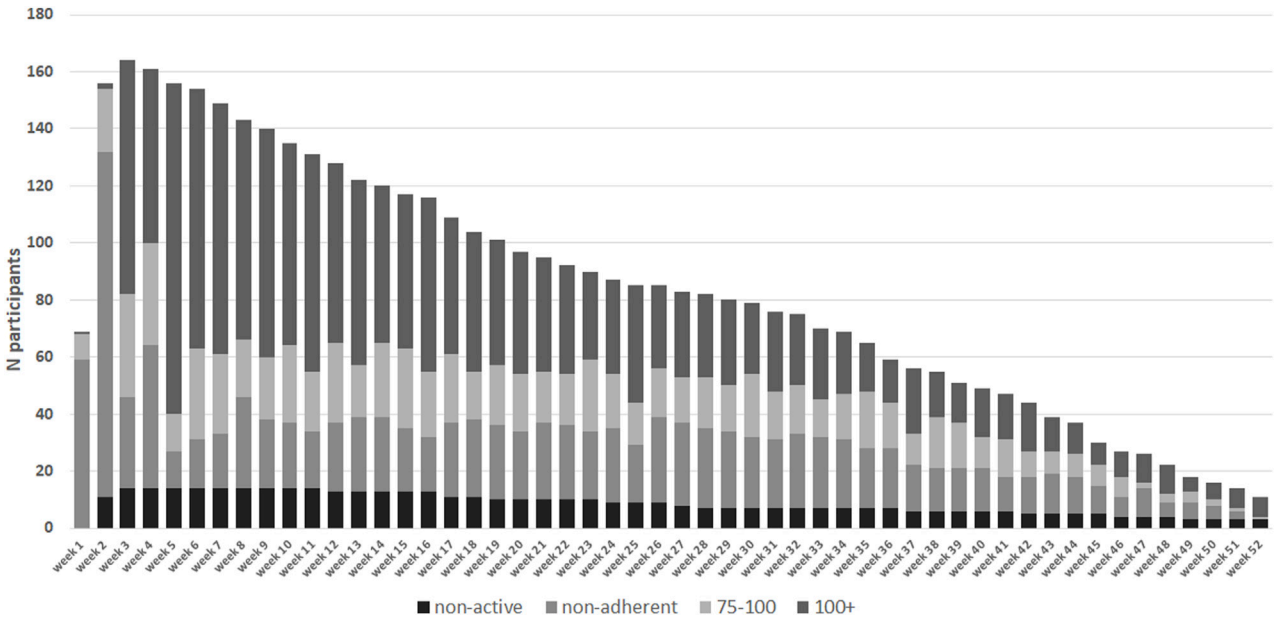


FIGURE 4 | Absolute number of participants in each protocol adherence group (n = 178). Adherence per week from day of discharge from hospital. In week 1 and 2 data collection commences on day of discharge. Measurements collected during hospital admission in week 1 and 2 have been excluded. Black dashed bars represent the non-active group who have had not activated their home-monitoring app or entered any measurements.

TABLE 3 | Subjective evaluation average scores and change over time.

Items	Average overall (n = 79)	First entry average (n = 45)	Last entry average (n = 45)	Delta (n = 45)	*p*-value
Experience using home-monitoring	4.19 ± 0.86	4.16 ± 0.90	4.2 ± 0.94	0.04	0.321
"I feel safer with home-monitoring"	3.81 ± 0.95	3.82 ± 0.96	3.98 ± 0.92	0.16	0.127
HM reduces outpatient visits	3.56 ± 1.04	3.44 ± 0.99	3.56 ± 1.20	0.12	0.221
Better health insight	3.77 ± 0.87	3.84 ± 0.80	3.73 ± 0.92	–0.09	0.241
Recommendation home-monitoring to others	8.15 ± 2.19	7.38 ± 2.60	8.27 ± 2.35	0.66	0.010*

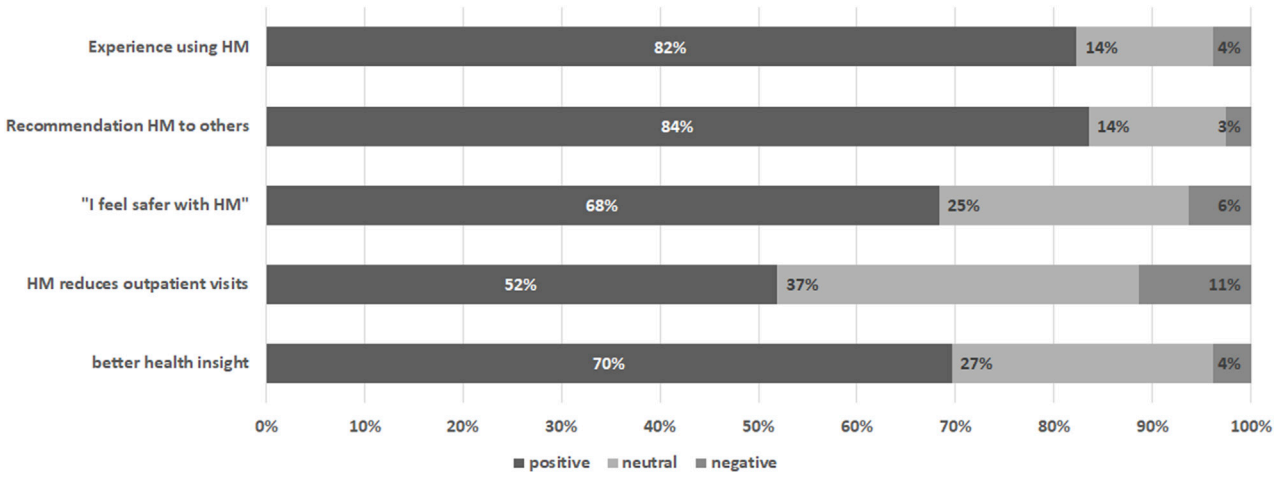


FIGURE 5 | Subjective evaluation of the home-monitoring system per item. Percentages are based on the average score of the participant rounded to nearest likert 5-scale value.

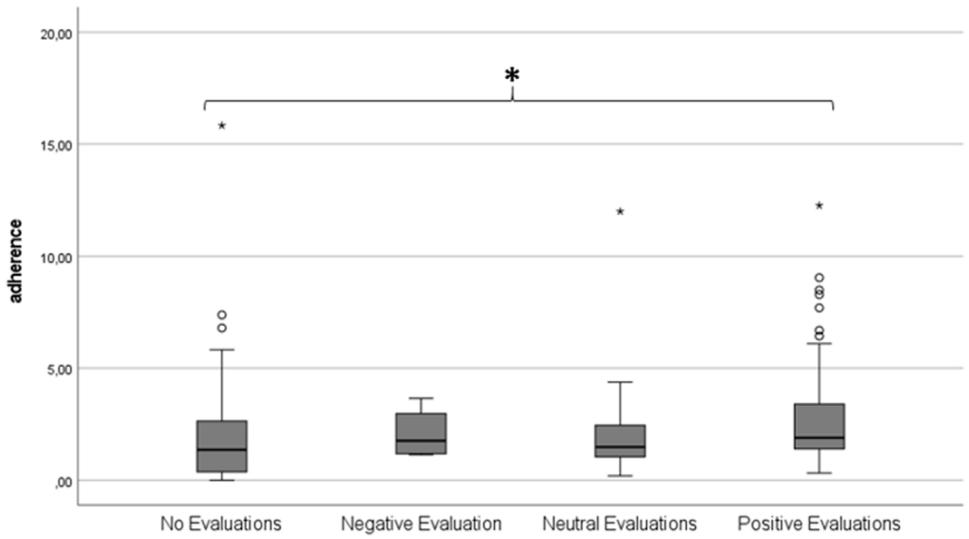


FIGURE 6 | Boxplot showing total average protocol adherence according to subjective evaluation group. A score of 1.00 represents 100% protocol adherence.

High uptake of home-monitoring has been reported previously [3]. Interestingly in our study, we also found high uptake among older transplant recipients. In the Netherlands, elderly are more reluctant in using eHealth based smartphone apps compared to younger adults [16]. However, in this specific group of KTRs we were able to include the entire spectrum of ages. In general, reluctance to using the home-monitoring was low, given that only 8% (16/178) were non-active users. This is low compared to a study in Berlin by Duettmann that reported 19% refusal from participation. We note however, that non-active users, that is those who initially agreed to use the home-monitoring system but at a later date did not proceed, were more likely to be older. Although reasons of not using the app were not recorded, it is possible that this sub-group require more assistance or support to use the system. Greater insight into reasons for refusal as well as barriers to activation would offer targets for improving the system, and specifically whether support needs to differ according to age.

For those who were offered the program and actively home-monitored, continuation was high. The overall dropout rate in our study was 13%, resulting in a continuation rate that was comparable or higher than other studies. For example, a study in Berlin showed a similar dropout rate of 6% (8/139) [17]. Whereas a study in Seoul reported high dropout rates of 53% after 1 month [18], however, their sample was enrolled after transplantation in a randomized control trial and not part of standard care which may explain the higher drop-out rate. We also note that participation in our home-monitoring system is typically up to 12 months when KTRs are transferred back to their original regional hospital for further follow-up, where we were not able to measure continued use on the long-term.

Protocol adherence is an important indicator of whether the protocol developed by professionals is acceptable and achievable for recipients. In this study, after the run-in period and discharge from the hospital, protocol adherence was high when protocol measurements were lower. Vitals such as blood pressure, heart rate, weight and temperature were measured more than the protocol suggested, which shows interest and/or dedication by KTRs participants. Also, certain topics measured by questionnaires, such as smoking and sex, were completed on different times than the protocol stipulated compared to other topics such as urine production, liquid intake or medication. Some topics may be more important to patients than others. From a clinical perspective, the information generated from the questionnaires on accurate medication taking are important but protocol adherence for these were relatively low. There may be a lack of awareness as to the reason for repeated administration. For some questionnaires it is possible that questionnaire burden reduced the rate of completion. Some topics (such as sex or taking medication) may be more sensitive and KTRs may be reluctant to submit answers on them through an app. Further research is needed to understand how these psychological factors may influence engagement with the home-monitoring system.

Our retrospective study highlights an important consideration for professionals developing home-monitoring protocols not over-burden users while still obtaining enough information to allow effective monitoring. In the first 2 weeks, recently discharged participants had low adherence and overall within the protocol only 22.4% were adherent to the entire protocol during the entire study period. Participants were less protocol adherent to certain parameters than others. To make improvements it will be important to understand why protocol adherence differs across parameters. Furthermore, previous studies suggest that active involvement of health professionals (e.g., discussing results) and reminders positively influence adherence to measurements and medication [4, 19, 20]. In the home-monitoring system in this study, it is likely that reminders sent through the app promoted protocol adherence. Whilst these notifications can be turned off, what the setting was with our participants was not clear. Notification settings could be

linked with non-adherence/adherence as one factor for dropout rate and adherence. The long-term engagement and retaining of transplant recipients in home-monitoring programs is paramount for sustained benefits. This study identifies the great potential of home-monitoring as standard care for KTRs and other organ recipients. Implementing home-monitoring as standard care is likely to have contributed to the high level of uptake.

Introduction of the technology and instruction on use during hospital admission for transplantation may help remove barriers to use as recipients can ask questions and ask for guidance when needed before discharge. Starting during hospitalization with entering measurements could provide routines for patients which could be linked to the high number of records on heartrate, temperature and blood pressure. When considering development of a home-monitoring protocol, professionals should involve recipients to help assess feasibility and limit undue burden as an unduly intensive schedule may subsequently have a negative influence on protocol adherence as seen in our center early on with high intensity measurement protocol in the first month. We note that there were active users that had a protocol adherence level above 100%. The potential reasons for and consequences of this are not yet clear, a possibility could be due influence from the health professional, suggesting alternative protocols or caution. Another is the routine learned/acquired in the hospital/early discharge.

Patient attitude towards home-monitoring were positive, evidenced by active participation in large number of recorded measurements and overall positive subjective evaluations. The positive evaluations are in line with other studies implementing home-monitoring modalities [2, 17, 21]. A shortcoming in our study was that we were not able to capture the perspectives of those who did not engage with the home-monitoring system.

Despite the positive results, further improvements are still possible to enhance implementation of home-monitoring the facilitators and barriers experienced of KTRs and home-monitoring. For future research on how to improve the system a number of target groups can be identified, for example, those who do not engage with home-monitoring, those who monitor on paper, and those who are more than 100% adherent. It is not known if some users become overly involved or compulsive about monitoring and what kind of effect this may have on quality of life. In addition to KTRs, investigation of the perspectives of transplant professionals would be help further development of the system and improve on the barriers that they might see themselves in the integration of home-monitoring for KTRs care. In the future it will be also important to investigate the level of engagement by professionals with the home-monitoring system and their influence on recipient behavior. Qualitative research that explores attitudes and acceptance, perceived benefits for both patients and the healthcare system, and willingness to discuss data and perceived barriers to implementation would be informative.

In our center this home-monitoring has now been implemented as standard care, but we will continue to make improvements, which may also lead to (further) changes in the roles and responsibilities of patient and transplant professionals [22]. Developing the home-monitoring system into a more autonomous self-managed care approach is a promising avenue in which monitoring protocols are (better) tailored to individual patient needs, medical histories, and (known) risk profiles. In the future, home-monitoring may go one step further by reducing the role of professionals by "closing the loop." In a closed loop home-monitoring system patients carry out blood assays at home for medication dosing which is adjusted based on algorithms that can take many clinical factors into account. Moreover, it may be possible to combine data from home-monitoring with other data sources such as patient-reported outcomes, quality of life assessments, and long-term clinical outcomes through integrated dashboards and interactive feedback. This approach will contribute to a more comprehensive understanding of recipient health and wellbeing.

In conclusion, this study demonstrated the feasibility of implementing home-monitoring as standard care after kidney transplantation. We found high uptake, high protocol adherence and the continued use of home-monitoring among KTRs, with positive subjective evaluations and recommendation of the system to others. Areas for further investigation and improvement of the system were identified.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving humans were approved by the Medisch Ethische Toetsings Commissie Erasmus MC. The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because All kidney transplant recipients provide written informed consent for the use of their clinical data as part of an ongoing quality improvement program and for datasharing with the national registry (NOTR).

AUTHOR CONTRIBUTIONS

BH and EM wrote the paper with input from all authors. DH, MR, MH, and JW conceived the idea and planned the first implementations. MT together with DH, MR, MH, and JW implemented the process into standard care. BH analyzed the data. All authors contributed to the article and approved the submitted version.

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CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontierspartnerships.org/articles/10.3389/ti.2024.13192/full#supplementary-material

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ORIGINAL RESEARCH
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Trust in the Transplant Team Associated With the Level of Chronic Illness Management—A Secondary Data Analysis of the International BRIGHT Study

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A trustful relationship between transplant patients and their transplant team (interpersonal trust) is essential in order to achieve positive health outcomes and behaviors. We aimed to 1) explore variability of trust in transplant teams; 2) explore the association between the level of chronic illness management and trust; 3) investigate the relationship of trust on behavioral outcomes. A secondary data analysis of the BRIGHT study (ID: NCT01608477; https://clinicaltrials.gov/ct2/show/NCT01608477?id=NCT01608477&rank=1) was conducted, including multicenter data from 36 heart transplant centers from 11 countries across four different continents. A total of 1,397 heart transplant recipients and 100 clinicians were enrolled. Trust significantly varied among the transplant centers. Higher levels of chronic illness management were significantly associated with greater trust in the transplant team (patients: AOR= 1.85, 95% CI = 1.47–2.33, $p < 0.001$; clinicians: AOR = 1.35, 95% CI = 1.07–1.71, $p = 0.012$). Consultation time significantly moderated the relationship between chronic illness management levels and trust only when clinicians spent ≥30 min with patients. Trust was significantly associated with better diet adherence (OR = 1.34, 95%CI = 1.01–1.77, $p = 0.040$). Findings indicate the relevance of trust and chronic illness management in the transplant ecosystem to achieve improved transplant outcomes. Thus, further investment in re-engineering of transplant follow-up toward chronic illness management, and sufficient time for consultations is required.

Keywords: trust, chronic illness management, heart transplant, transplant team, behavioral outcomes

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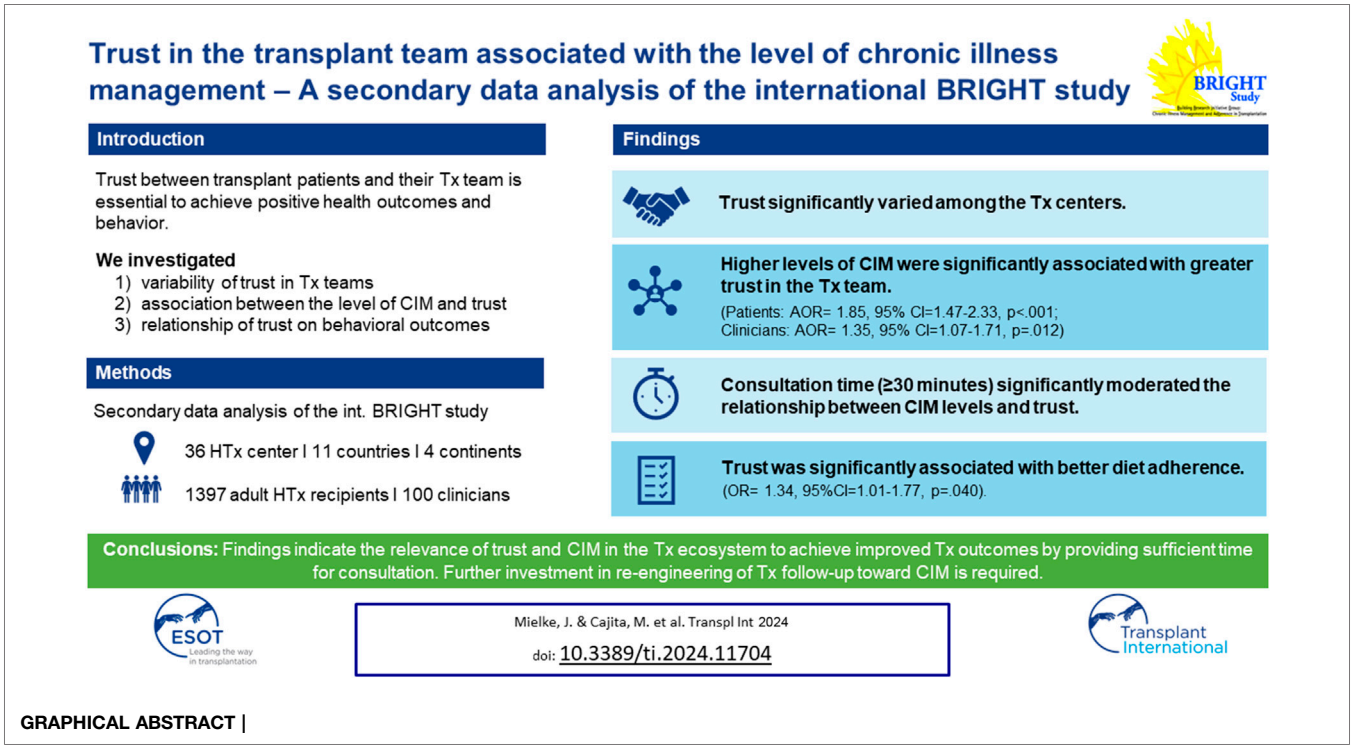
Abbreviations: AOR, adjusted odds ratio; BRIGHT, Building Research Initiative Group: Chronic Illness Management and Adherence in Transplantation (BRIGHT) study; CCM, Chronic Care Model; CIM, chronic illness management; CIMI-BRIGHT, The Chronic Illness Management Implementation—Building Research Initiative Group: Chronic Illness Management and Adherence in Transplantation (CIMI-BRIGHT) instrument; HTx, heart transplantation; PACIC, Patient Assessment of Chronic Illness Care (PACIC) instrument.



GRAPHICAL ABSTRACT |

INTRODUCTION

The importance of interpersonal trust (i.e., trust between patients and healthcare providers) in the healthcare context has been widely reported [1]. Trust occurs in vulnerable situations where an individual believes that another individual will act in their best interest [2]. This is especially true for chronically ill populations such as heart transplanted (HTx) patients. HTx patients face a high level of vulnerability due to potentially life-threatening complications and lifelong dependency on the HTx team providing follow-up care [3]. Trust has to be understood as a continuum, meaning that it is a complex and evolving phenomenon that can increase or decrease over time. Interpersonal trust relationships are supposed to positively affect patients' attitudes, experiences (e.g., satisfaction with care [4–6]) and behavior (e.g., increased adherence to medication and treatment [6–8]). Further, trust is linked to patients' health outcomes [2, 4, 6], health-related quality of life [4], and symptom-related outcomes [4].

Several factors are associated with higher interpersonal trust, and either relate to the patient (e.g., patients who are white, women, or older, or those with a better health status or a higher number of healthcare visits) or the physician (e.g., better communication skills, higher competence, or higher consultation time). In addition, service factors, e.g., the type of delivery system, continuity in care, and absence of economic or other pressures, affect patients' trust in healthcare professionals [2, 7, 8].

While patient and clinician factors have been extensively examined, the relationship between trust and service outcomes—level of chronic illness management (CIM)—remain understudied [9]. Chronic illness management refers to a comprehensive and coordinated approach that focusses on optimizing the care provided to individuals living with long-term medical conditions. CIM programs based on the Chronic Care Model (CCM) [10] are designed to transform acute care driven health programs into patient centered integrated care and to address needs of the chronically ill, i.e., continuity of care, behavioral, self-management, and psychosocial support and patient participation [11]. The CCM is a framework that guides the development of care delivery models for the chronically ill to effectively improve patients' clinical and behavioral outcomes and to enhance proactive patient and healthcare provider interactions [12]. Such interactions (e.g., during consultations) require interpersonal trust [13]. To assess, how well elements of the CCM have been implemented in a specific care program, the level of chronic illness management can be determined. CIM is a construct that can be assessed using validated instruments that allow patients and healthcare professionals to report how they perceive characteristics of clinical care processes [14, 15]. The higher the level of CIM, the more CCM elements were implemented. To our knowledge, there is no evidence on the association between CCM-based CIM programs and interpersonal trust, yet it is an important association with regards to teasing out a favorable ecosystem for HTx patients' follow-up care, i.e., multilevel characteristics of care systems or processes that allow a CIM model of care to be implemented and sustained. Typically, HTx patients are cared for by an interdisciplinary HTx

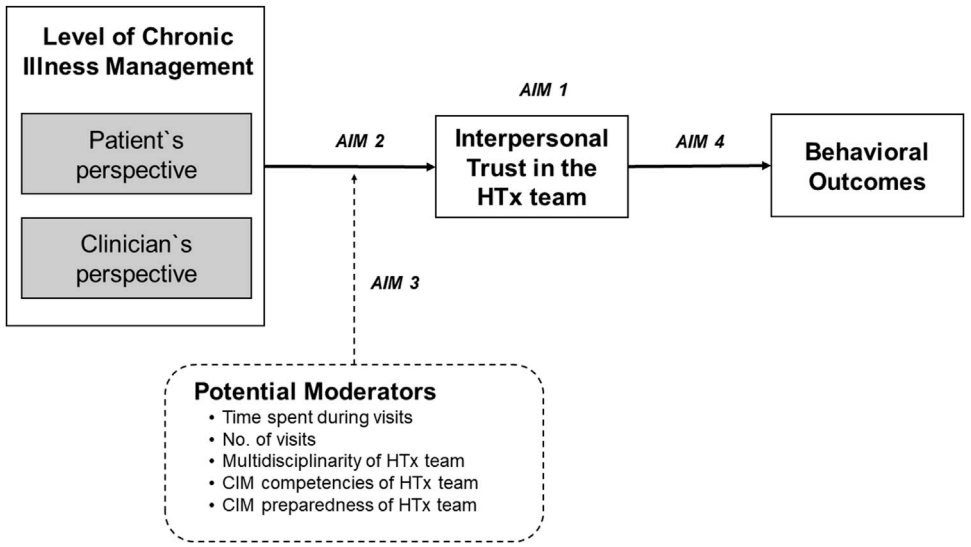


FIGURE 1 | Conceptual model of studied variables and outcomes. Conceptualization of the Relationship between the Level of Chronic Illness Management (CIM) and Patients' Interpersonal Trust in the Heart Transplant Team (HTx) on Health and Behavioral Outcomes.

team across the transplant continuum in an HTx center with specific structural and care process characteristics. Studies that focus on interpersonal trust, however, do not consider the context in which these relationships occur. Therefore, this study aimed to 1) explore the variability of interpersonal trust in HTx teams among 36 HTx centers internationally; 2) explore whether the level of CIM of an HTx center is associated with trust in the HTx team; 3) investigate whether meso-level factors (e.g., time spent with the HTx team during follow-up) moderate the relationship between level of CIM and trust in the HTx team, and 4) investigate the relationship of trust in the HTx team on behavioral outcomes (**Figure 1**).

MATERIALS AND METHODS

Design, Setting, and Sample

This study presents a secondary data analysis of the international, multicenter, cross-sectional Building Research Initiative Group: Chronic Illness Management and Adherence in Transplantation (BRIGHT) study (ID: NCT01608477; https://clinicaltrials.gov/ct2/show/NCT01608477?id=NCT01608477&rank=1). Detailed study procedures are described elsewhere [16, 17]. Briefly, using a multistage sampling approach of HTx centers, clinicians, and patients, CIM practice patterns and multilevel factors related to medication non-adherence were examined in 36 HTx centers from 11 countries across four continents (Europe, North America, South America, and Australia). A minimum of two HTx centers per country were included, if they had performed more than 50 HTx during the past 12–60 months. A convenience sample of 100 clinicians (1–5 per center) was chosen, using a random sample if more than five were eligible who had worked in the center for more than 6 months. Clinicians had to have spent more than 50% of their employment in direct clinical practice and have been familiar with the posttransplant outpatient care at the center. HTx patients (≥18 years of age) followed up in a participating center were included randomly if they were between 1–5 years post-transplant, first and single-organ transplant, able to read, understand and provide written informed consent. Data were collected between March 2012 and October 2015. The study was approved by the ethics committee of the University Hospital Leuven, Belgium and the ethics committees of each participating center. Written informed consent was obtained from all participating patients.

Variables and Measurement

Data were collected from transplant directors, clinicians, and patients who completed a specific self-report BRIGHT questionnaire for each of these samples. In addition, patients' sociodemographic data were collected during the enrollment interview and their clinical information was extracted from medical records (**Table 1**).

Main Outcomes

Trust in the healthcare team was part of the patient questionnaire and adapted from the 10-item Wake Forest University Trust scale measuring the level of interpersonal trust, i.e., fidelity (caring and advocating for the patient's welfare), competence, honesty, confidentiality, and global trust in the healthcare team [18]. The three negatively worded items were recoded and an average score was calculated for each patient-participant with a higher overall score (range 1–5) indicating higher trust. Given that the trust variable was not normally distributed, it was dichotomized using the median score for the patient-sample for easier interpretation of interaction terms. Sensitivity analysis was performed using tertiles instead of the median with similar results.

The *level of CIM implemented* in the HTx program was measured from two perspectives. First, patient-participants

TABLE 1 | Overview of variables and measurement tools.

Variable	Description (number of items, response options, scoring)	Instrument and psychometrics
Trust in the healthcare team	• 10 items measuring the level of interpersonal trust in the HTx-team covering the dimensions fidelity (caring and advocating for the patient's welfare), competence, honesty, confidentiality, and global trust in the healthcare team • 5-point Likert scale (1 = strongly disagree (low trust) to 5 = strongly agree (high trust)) • Higher average scores indicate more trust in the transplant team	Adapted from the Wake Forest University Trust scale [18, 19]
Level of chronic illness management (CIM)	Patient's perspective • 11 items assessing practice patterns related to chronic illness management implemented in the HTx left • 5-point Likert scale (1 = almost never to 5 = almost always) • Total score ranging from 11 to 55 with higher scores indicating a higher degree of CIM	Short version of the Patient Assessment of Chronic Illness Care (PACIC) instrument [20, 21]; Cronbach`s α = .88 [17]
	Clinician`s perspective • 52 items covering the five building blocks of the Innovative Care for Chronic Conditions framework: 1) promote continuity and coordination (12 items); 2) encourage quality through leadership (7 items); 3) organize and equip healthcare teams (8 items); 4) support self-management (19 items); 5) use of information system (9 items) • 4-point Likert scale (1 = strongly disagree to 4 = strongly agree) • Average score with higher scores indicating higher level of CIM implemented	CIMI-BRIGHT [22] Scale content validity = 0.86 Interrater reliability (pilot tested): 75%–85% [22]; Cronbach`s α = .94 [17]
Socio-demographic factors	6 items assessing the patient`s demographic profile (i.e., age, gender, race, country, educational level, employment status)	BRIGHT patient interview questionnaire [17]
Clinical information	2 items assessing patient`s clinical profile, i.e., the number of years post HTx, comorbidities and the number of rejections experienced (expressed as the number of treated rejections until time of study enrolment, divided by the years in post-transplant follow-up in years)	Medical record
Potential meso-level moderators		
Time spent with patients during follow-up visits	Patient`s perspective on time spent with all members of the HTx team during one follow-up visit • 1 item • five choices (<5 min, 5–10 min, 11–20 min, 21–30 min, >30 min)	BRIGHT patient self-report (written) questionnaire [17]
	Clinician`s perspective on time spent with each patient during one follow-up visit • 1 item • Average total time per patient (in minutes)	BRIGHT clinician questionnaire [17]
Number of visits	3 items assessing the total number of visits scheduled for patients within the first month, first 6 months, 1 year and 3 years	BRIGHT transplant director questionnaire [17]
Multidisciplinarity of the HTx team	• 1 item assessing multidisciplinarity of the HTx team, i.e., HTx team is composed of physician (s), nurse (s), and at least one other type of healthcare professional (either a social worker, psychiatrist, psychologist, pharmacist, dietitian, physical therapist, or occupational therapist) • Dichotomous answer format (yes/no)	BRIGHT transplant director questionnaire [17]
Chronic illness management competencies	• 24 items assessing CIM competencies of the HTx team including 1) patient-lefted care (7 items); 2) partnering (2 items); 3) quality improvement (8 items); 4) information and communication technology (4 items); 5) public health perspective (3 items) • 4-point Likert scale (1 = strongly disagree to 4 = strongly agree; 5 = don`t know; set to missing) • Average score with higher cores reflecting higher degree of core competencies	BRIGHT clinician questionnaire Cronbach`s α = .96 [17]
Chronic illness management level of preparedness	• 5 items assessing level of preparedness in view of the skills and availability of equipment or tools to facilitate chronic care • 4-point Likert scale (1 = strongly disagree to 4 = strongly agree; 5 = don`t know; set to missing) • Average score with higher cores reflecting higher degree of preparedness	BRIGHT clinician questionnaire Cronbach`s α = .82 [17]

(Continued on following page)

TABLE 1 | (*Continued*) Overview of variables and measurement tools.

Variable	Description (number of items, response options, scoring)	Instrument and psychometrics
Behavioral Outcomes		
Physical activity	• 2 items asking if a patient was sufficiently active (yes/no) • Sufficiently active was defined as ≥ 3x/week 20 min of vigorous and/or ≥ 5x/week 30 min of moderate physical activity	2-item Brief Physical Activity Assessment tool [23] Criterion validity of self-report against electronic monitoring gold standard measurement: κ statistic 0.14–0.40 [23]
Dietary adherence	• 5 items measuring patient`s adherence to low salt, low calorie, low saturated fat, low sugar or other kind of dietary guidelines • 5-point Likert scale (1 = never to 5 = always) • Adherent were those who were prescribed a diet, scoring often/always to any of the 5 diets	BRIGHT patient self-report (written) questionnaire [17]
Sun protection	• 4 items assessing consistency of sun protection • 5-point Likert scale (1 = never to 5 = always) • Average score	Swiss study on health of people with cancer, leukemia, tumor in childhood (Swiss Childhood Cancer Registry) [24] and Cambridge University Hospitals' perception of skin cancer in transplant recipients scale [25]; Cronbach`s α = .59 [17]
Smoking status	1 item assessing smoking status, i.e., currently smoking, stopped less than 1 year ago, stopped more than 1 year ago, or never smoked	Item from Swiss Health survey (Swiss Federal Statistical Office 2008) [26]
Alcohol intake	• 2 items measuring the level of alcohol intake, i.e., whether the patients used alcohol (yes/no), and in case they did, how many alcoholic drinks were consumed per week • Categorization into non-drinkers; moderate drinkers (1 drink/day for women, 2 drinks/day for men), or heavy drinkers (>1 drink/day for women, >2 drinks/day for men) [27]	BRIGHT patient self-report (written) questionnaire [17]
Language congruency	• 1 item measuring if the HTx team communicated in the patient`s mother tongue or in a language they mastered fluently (either via an interpreter or directly) • Dichotomous answer format (yes/no)	BRIGHT patient interview questionnaire [17]
Health literacy	• 1 item rating patient`s confidence in filling out medical forms • 5-point Likert scale (1 = none of the time to 5 = all of the time) • Dichotomized into adequate (≥4) and inadequate (≤3) health literacy [28]	Subjective Health Literacy Screener [28] Concurrent validity: with the Short Test of Functional Health Literacy in (AUC = .72-.74; with the Rapid Estimate of Adult Literacy in Medicine (AUC = .81-.84) [29]
Number of comorbidities	• 19 items assessing post-HTx comorbidity • Dichotomous answer format (yes/no)	Adapted Charlson Comorbidity Index [30]

Note. Abbreviations: CIM, chronic illness management; HTx, heart transplantation.

completed the 11-item short version of the Patient Assessment of Chronic Illness Care (PACIC) instrument [20]. This instrument measures specific actions or qualities of care in the delivery system, which are congruent with the CCM and were observed over a recall period of 6 months. The items were aggregated for each patient-participant, with the total score ranging from 11 to 55. Higher scores indicate a higher degree of CIM. The median score of the patient-sample was used to dichotomize the PACIC variable. Second, implementation of CIM was measured from the clinician's perspective by applying the investigator-developed CIMI-BRIGHT clinician questionnaire (The Chronic Illness Management Implementation—Building Research Initiative Group: Chronic Illness Management and Adherence in Transplantation (CIMI-BRIGHT) instrument), which consists of 52 items covering the five building blocks of the Innovative Care for Chronic Conditions framework [22]. An average score was calculated for each clinician-participant and then the median score for the clinician-sample was used to dichotomize the CIMI-BRIGHT variable.

Potential Meso-Level Moderators

Time spent with patients during follow-up visits was assessed from two perspectives. Patient-participants were asked how much time all members of their HTx team spend with them on regular follow-up visits. Each participating clinician was asked for the average total time (in minutes) they spend with each patient at the outpatient HTx clinic. Both *time* variables were then dichotomized using 20 min and 30 min as the cut-off points—these time points were chosen given the distribution of the continuous clinician-time variable and how it aligned with the ordinal patient time-variable.

The typical *number of visits* within the first month, first 6 months, 1 year, and 3 years were extracted from the transplant director's BRIGHT questionnaire. Similarly, information regarding the *multidisciplinarity* of the HTx team was collected from the director's questionnaire. The *CIM competencies* of HTx team and *CIM level of preparedness* of healthcare workers were assessed using the investigator-developed clinician questionnaire including 24 and five items, respectively. Scores were averaged, with higher scores reflecting a higher degree of core competencies and preparedness.

Behavioral Outcomes

The patient questionnaire also included five health behaviors: *Physical activity* was measured by the 2-item Brief Physical Activity Assessment tool [23], asking if a patient was sufficiently active. *Dietary adherence* recorded patient's self-reported adherence,

TABLE 2 | Patients' demographic and clinical characteristics.

Variable	
Patients	
Age[a] (*n* = 1,379)	53.5 ± 13.3 years
Gender[b] (*n* = 1,390)	
Male	1,011 (72.7)
Female	379 (27.3)
Race/Ethnicity[b] (*n* = 1,381)	
White	1,186 (85.9)
Black	80 (5.8)
Asian	27 (1.9)
Hispanic	29 (2.1)
Other	59 (4.3)
Country[b,c] (*n* = 1,379)	
Belgium	74 (5.3)
Spain	227 (16.2)
France	160 (11.5)
Canada	121 (8.7)
USA	340 (24.3)
Australia	51 (3.7)
Italy	111 (7.9)
United Kingdom	99 (7.1)
Germany	67 (4.8)
Switzerland	47 (3.4)
Brazil	100 (7.2)
Educational Attainment[b] (*n* = 1,377)	
Primary School	187 (13.6)
Secondary School	426 (30.9)
University	764 (55.5)
Employment Status[b] (*n* = 1,391)	
Employed	413 (29.7)
Unemployed	978 (70.3)
Years post HTx[a] (*n* = 1,378)	3.37 ± 1.4 years
Health Literacy[b] (*n* = 1,364)	
Adequate	912 (66.9)
Inadequate	452 (33.1)
Language Congruency[b] (*n* = 1,390)	
Spoke different languages	15 (1.1)
Spoke the same language	1,375 (98.9)
Number of Comorbidities[a] (*n* = 1,394)	1.44 ± 1.6
Trust in the healthcare team[a] (*n* = 1,378)	4.59 ± 0.49
Level of CIM[a] (PACIC)	38.32 ± 10.9[d]
Time spent with clinicians[b] (*n* = 1,374)	
<5 min	8 (0.57%)
5–10 min	68 (4.87%)
11–20 min	382 (27.34%)
21–30 min	388 (27.77%)
>30 min	528 (37.8%)
Clinicians	
Age[a] (*n* = 98)	45.83 ± 10.2
Gender[b] (*n* = 99)	
Male	12 (12.1%)
Female	87 (87.9%)
Profession[b] (*n* = 100)	
Nurse	90 (90%)
Physician	3 (3%)
Other	7 (7%)
Years practicing in Tx[a] (*n* = 99)	11.9 ± 7.7
Level of CIM[a] (CIMI-BRIGHT)	2.9 ± 0.27[e]
Time spent with patients in minutes[a] (*n* = 94)	36.8 ± 34.0

Note: Abbreviations: HTx, heart transplantation.
[a]*Values given are mean ± SD.*
[b]*Values given are n (%).*
[c]*Country where the center is located.*
[d]*Total scores ranging from 11 to 55 with higher scores indicating a higher degree of CIM.*
[e]*Average scores ranging from 1 to 4 with higher scores indicating higher level of CIM, implemented.*

as applicable, to low salt, low calorie, low saturated fat, low sugar, or other kind of dietary guidelines. *Sun protection* was measured using 4 items assessing consistency of protection against the sun [24, 25]. *Smoking status* was based on whether patients were currently smoking, stopped less than 1 year ago, stopped more than 1 year ago, or never smoked [26]. *Alcohol intake* assessed the level of alcohol consumption by two items i.e., whether the patient used alcohol, and in case they did, how many alcoholic drinks were consumed per week. They were then categorized into non-drinkers; moderate drinkers, or heavy drinkers [27].

Language congruency was measured by asking patients during the interview if the HTx team communicated in their mother tongue or in a language they mastered fluently (either via an interpreter or directly). *Health literacy* was assessed as part of the written questionnaire by rating confidence in filling out medical forms, using a 5-point scale (1 = none of the time to 5 = all of the time) and then dichotomized into adequate (≥4) and inadequate (≤3) health literacy [28]. Lastly, *number of comorbidities* post-HTx was assessed using an adapted Charlson Comorbidity Index [30].

Statistical Analysis

Descriptive statistics were calculated for all study variables. The Kruskal-Wallis test was used to examine whether there were differences in trust in the HTx team across the 36 HTx centers. Whether level of CIM was associated with trust in the HTx team was examined using simple and multiple logistic regression. Meanwhile, moderation analysis was performed to determine whether meso-level factors affected the direction and/or strength of the relationship between level of CIM and trust. To examine whether trust could predict behavioral outcomes, simple and multiple logistic regressions were performed, whereby the multiple models were equally controlled for potential confounders that were statistically significant. Finally, marginal effects were calculated to better communicate the practical significance of the findings [31]. Analyses were conducted in Stata v16.1.

RESULTS

Characteristics of the participants are shown in **Table 2**. The proportion of physicians and nurses included reflected the composition of HTx teams in clinical practice. Less than 2% of the data were missing; hence, no imputation was performed.

There was significant variability in the level of CIM [PACIC: chi-square (35 df, N = 36) = 209.3, $p < 0.001$; CIMI: chi-square (35 df, N = 36) = 1,396, $p < 0.001$] and trust in the healthcare team [chi-square (35 df, N = 36) = 221.5, $p < 0.001$] among the 36 HTx centers (**Supplementary Material**). HTx recipients who indicated that they had received higher levels of CIM were more likely to have greater trust in the HTx team. This finding was consistent whether level of CIM was measured from the patient's perspective (adjusted odds ratio [AOR] = 1.85, 95% CI = 1.47 to 2.33, $p < 0.001$) or from the clinician's perspective (AOR = 1.35, 95% CI = 1.07 to 1.71, $p = 0.012$), and even after controlling for potential confounders (age, gender, race, education level, employment

TABLE 3 | Associations between chronic illness management level and trust.

Independent variables	Unadjusted bivariate analysis		Adjusted multivariate regression analysis		
	OR	95% CI	OR	95% CI	*p*-value
PACIC[a]	1.91	1.54–2.36	2.08	1.62–2.65	<0.001
CIMI-BRIGHT[b]	1.33	1.08–1.65	0.94	0.67–1.30	0.703
Age			*1.02*	*1.00–1.03*	*<0.001*
Gender			*1.20*	*0.92–1.56*	*0.184*
Race					
Black			0.93	0.55–1.57	0.786
Asian			0.78	0.32–1.90	0.587
Hispanic			0.50	0.21–1.17	0.109
Other			0.79	0.43–1.47	0.462
Education					
High school			1.67	1.10–2.54	0.017
College			1.96	1.27–3.02	0.002
Employment			1.09	0.84–1.42	0.497
Country					
Belgium			1.00	0.58–1.75	0.988
Spain			0.96	0.60–1.54	0.861
France			0.46	0.28–0.77	0.003
Canada			1.86	1.13–3.07	0.015
Australia			0.82	0.39–1.73	0.598
Italy			1.62	0.95–2.75	0.074
United Kingdom			1.86	1.12–3.08	0.017
Germany			0.16	0.08–0.33	<0.001
Switzerland			0.23	0.10–0.51	<0.001
Brazil			1.46	0.85–2.49	0.166
Years post-HTx			0.94	0.86–1.02	0.141
Health literacy			1.58	1.23–2.03	<0.001
Language congruence			1.77	0.49–6.35	0.381
Comorbidities			1.03	0.96–1.11	0.372

Note. Abbreviations: CI, confidence interval; OR, odds ratio.

[a]*Short version of the Patient Assessment of Chronic Illness Care (PACIC) instrument [20, 21].*

[b]*The Chronic Illness Management Implementation—Building Research Initiative Group: Chronic Illness Management and Adherence in Transplantation (CIMI-BRIGHT) instrument [22].*

Reference groups: race (White), education (primary school), country (United States).

TABLE 4 | Associations between trust and health outcomes.

	Outcome variables	Unadjusted bivariate analysis		Adjusted multilevel regression analysis	
		OR	95% CI	OR	95% CI
IV: Trust	Physical activity	0.95	0.71 to 1.28		
	Diet adherence	1.40[a]	1.08 to 1.82	1.34[a]	1.01 to 1.77
	Sun protection	1.27	.96 to 1.69		
	Smoking	0.46	0.25 to 0.84	0.59	0.31 to 1.11
	Alcohol intake	0.75	0.53 to 1.06		

Note. Abbreviations: CI, confidence interval; OR, odds ratio.

[a]*P < 0.05; For aim 4, trust was treated as the predictor variable and the health outcomes were the response variables. The final model was adjusted for age, gender, race, education, employment status, years post HTx, health literacy, and comorbidities.*

status, number of years post HTx, health literacy, language congruency, and comorbidities) (**Table 3**). However, when controlling for the country where the HTx center was located, the level of CIM from clinicians was no longer significant (AOR = 0.94, 95% CI = 0.67 to 1.30, $p = 0.703$). Using USA as reference group, HTx patients from France, Germany, and Switzerland had lower odds of having high trust (AOR = 0.16–0.46), while HTx patients from Canada and the UK had higher odds of having higher trust (AOR = 1.86). Meanwhile, education became significant ($p = 0.002$- and $p = 0.017$), indicating that patients with higher education had greater odds of having higher trust (AOR = 1.67–1.96). The calculated marginal effects showed that an average HTx recipient who received lower levels of CIM had a 42.4% probability of trusting their HTx team. Meanwhile, a comparable HTx recipient who received higher levels of CIM had a 57.7% probability of trusting their HTx team.

Among the potential moderators, only time spent with the patients during follow-up visits was significant, i.e., the association between CIM and trust was stronger when consultation time was ≥30 min. This moderation effect was only present when consultation time was >20 min, measured from both the patient's (OR = 1.61, 95% CI 1.03 to 2.53, $p = 0.037$) and from the clinician's perspective (OR = 1.56, 95% CI 1.00 to 2.42, $p = 0.048$).

Results of the bivariate and multiple logistic regressions are presented in **Table 4**. Bivariate analyses showed that trust in the HTx team was significantly associated with smoking and diet adherence. Wherein patients, who had greater trust in their HTx team, were less likely to smoke (OR = .46, 95% CI .25 to .84, $p = 0.012$) and more likely to adhere to their recommended diets (OR = 1.40, 95% CI 1.08 to 1.82, $p = 0.012$). However, after controlling for age, gender, race, education, employment status, years post HTx, health literacy, and comorbidities, only the relationship between trust and diet adherence remained significant (OR = 1.34, 95%CI 1.01 to 1.77, $p = 0.040$). The calculated marginal effects showed that an average HTx recipient who highly trusts their HTx team (i.e., Trust score = 5) is 2.5 times more likely to adhere to their recommended diet compared to an average HTx recipient who has low trust towards their HTx team (i.e., trust score = 1).

DISCUSSION

In this study, we observed significant variability in trust in HTx team across the 36 HTx centers. Additionally, associations of CIM, trust in the HTx team and one patient behavioral outcome in HTx follow-up were identified.

First, higher levels of CIM were associated with greater trust in the HTx team, even after adjusting for potential confounders. However, when we controlled for country, the level of CIM from the clinician's perspective was no longer significant, indicating that the association between clinician-reported CIM levels and trust may be contingent upon the country context. Although country may not serve as an ideal indicator of social and cultural disparities, it is posited to be a more suitable indicator compared to race. Previous studies only focused on patient-level aspects of CIM, e.g., continuity of care [2, 7, 8] or physicians` communication skills [2, 7], were positively associated with greater trust in individual healthcare professionals. Yet, the strength of our study is having examined CIM meso-level factors with validated measurement tools from both the patient and clinician perspectives, resulting in consistent findings in each case.

Also, visit duration has been described as important for establishing interpersonal trust [8, 32]. In Fiscella et al.'s [32] study, visit duration independently predicted trust (0.05 SD, 95%CI 0.03–0.06). Patients' trust in their primary care physician increased by every minute increase in visit duration (0.01 SD, 95% CI 0.001–0.02) [32]. However, in our study, a stronger association between the level of CIM and trust was found when visit duration was ≥30 min. Indeed, given the complexity of HTx follow-up care and its importance on patients' health outcomes, it seems reasonable that HTx patients require more time for follow-up than patients in primary care settings. In addition, our findings shed light on the "dose" of time needed during consultations. Yet, further research on aspects contributing to trust during consultation is required.

In fact, the positive association of CIM and trust seems not surprising, when considering relevant components of CCM based CIM programs [10]. Largely overlapping with aspects increasing interpersonal trust, those components include availability of standards and training for clinicians (e.g., communication), patient-centered care, i.e., well informed and activated patients making their own choices, as well as care coordination of and advocacy for patients [33]. Another relevant aspect of CIM and driver of health outcomes include healthcare teams' multidisciplinarity in HTx follow-up. In the BRIGHT study, the majority of included transplant centers (80.6%) involve multidisciplinary teams in HTx follow-up with no significant variability in the type of professionals within the HTx teams across HTx centers [34]. However, larger, multidisciplinary teams run the risk of individual healthcare providers working in silos and responsibilities for a patient not being clearly defined. To enable trust in multidisciplinary teams, care concepts based on CCM are needed in HTx centers to ensure, for example, continuity in care of the patient and support for self-management [35].

Second, we found trust significantly independently associated with diet adherence, even after controlling for potential confounders. In general, the association of trust in healthcare professionals and behavioral outcomes such as adherence (medication, exercise, diet), self-care activities, preventive care (r = 0.14, 95% CI 0.10–0.19, $p < 0.001$) was already described in Birkhäuer et al.'s [4] meta-analysis on 21 studies including a total of 26′642 patients. Further studies highlighted a positive influence of interpersonal trust on following physicians` recommendations (e.g., diet, lifestyle) [5, 8], use of services (e.g., screening) [6, 8] and adhering to medication and treatment [2, 6–8]. However, these studies only focused on trust in individual professionals, whereas our study takes a broader perspective and focusses on trust in the HTx team, reflecting current HTx practice. Our findings indicate CIM, trust and patient outcomes are closely related. While only one behavioral outcome was significantly associated with trust in our multivariate analysis, CIM itself can have a positive effect on behavioral and health outcomes (e.g., patient survival one-year post-Tx) [15]. Further, studies in renal Tx research show associations of CIM with increased medication adherence [36], improved quality of life [36], fewer emergency room visits [37], fewer hospital admissions [37, 38] and reduced mortality [38]. To enhance HTx patients' behavioral and health outcomes, a systems perspective is needed, with not only focusing on interventions at patient-level, but also at re-engineering care processes in HTx follow-up towards CIM. This includes leadership accounting for trust as an important factor in HTx care, development of standards, best practices and training (e.g., communication and relationships skills) for the multidisciplinary HTx team, measuring, monitoring and reporting patient trust [33]. Further measures relevant to increasing patient's trust in their HTx team include working towards an ecosystem that provides continuity of care and care

coordination and allows patient centeredness and shared decision making within a CIM model [33, 39, 40]. The SMILe care model (Integrated Care Model (ICM) for SteM cell transplantatIon faciLitated by eHealth), for example, is one such care model that could potentially serve as a blueprint also for the care of HTx patients. Based on CIM building blocks, the SMILe-ICM aims to reengineer follow-up care of allogeneic stem cell transplanted patients and consists of four intervention modules to support patient self-management and health behaviors (i.e., monitoring & follow-up of vital signs, symptoms and health behavior; infection prevention; physical activity; medication adherence) [41–44].

However, the successful and sustainable implementation of complex interventions based on CIM principles and supporting trust into clinical practice is challenging due to healthcare, organizational, social, economic, and policy related barriers, among others [35, 45]. Implementation science supports the uptake of such interventions into routine practice and thus improves both health care services' quality and effectiveness [46]. Further, core and adaptable components of complex interventions can be adapted and fitted to the local context in which they will be delivered. Key implementation science elements supporting a shift towards CCM entail contextual analysis, stakeholder involvement, the use of strategies supporting implementation as well as research designs focusing on both implementation and effectiveness outcomes (i.e., hybrid designs) [47].

Limitations

Our study has several limitations. First, the cross-sectional study design does not allow causal inferences to be drawn. Second, a longitudinal analysis of trust over time could not be performed. Trust has to be understood as a continuum and may change over time. Since HTx patients usually receive life-long follow-up, changes in interpersonal trust relationships could point to aspects of CIM that are specifically relevant for patients' trust throughout the transplant continuum. Those specific measures could be taken to support trust relationships in practice over time. Third, most data analyzed in this study rely on self-reports from patients and clinicians, introducing a potential for inaccuracies, which could be mitigated by incorporating routine data, for example. Fourth, since we included Tx survivors beyond one-year post-Tx, outcome events in the first year were not considered. These outcomes should be also included in further studies. Further, the fact that 86% of the patients were white limits the assessment of social and cultural differences in perceptions of interpersonal trust. Fifth, the majority of clinicians involved in this study (90%) were nurses. Nurses and other transplant clinicians might differ in their evaluation on the level of chronic illness management as nurses are typically more involved in patient self-management and also typically have a higher sensitivity of psychological issues. Finally, given the limitation due to using secondary data, we did not assess the link of trust on clinical outcomes moderated by service outcomes. Moreover, other potentially important factors such as use of eHealth, distance from Tx-center, health outcomes (e.g., acute rejection, survival) or emotional moderators such as the patient`s mental health concerns could not be examined given the nature of this study.

Conclusion

To our knowledge, this is the first study linking CIM and interpersonal trust to service-level outcomes. We observed significant associations between CIM levels and trust in the HTx team moderated by consultation time, and a significant association between trust and diet adherence. Our findings highlight the need to consider trust and CIM in the HTx follow-up ecosystem as important factors as a basis for optimal transplant outcomes. Thus, further investment in re-engineering of HTx follow-up toward CIM, as well as allowing sufficient time for consultations, is required. Using longitudinal study designs, further research should focus on changes in trust over the transplant continuum and its influences on behavioral and clinical outcomes.

DATA AVAILABILITY STATEMENT

Original datasets are not openly available due to reasons of privacy and are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The studies involving humans were approved by the Ethics committee of the University Hospital Leuven, Belgium and the ethics committees of each participating center. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SD, CR, FD, SV, KD, MC, and JM had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. MC and JM contributed equally to this work. Concept and design of this secondary analysis: SD, JM, MC, and KD; Acquisition, analysis, or interpretation of data: MC and KD; Drafting of the manuscript: JM, MC, and KD; Statistical analysis: MC and KD; Critical revision of the manuscript for important intellectual content: SD, CR, FD, SV, KD, MC, and JM. Supervision: SD. All authors contributed to the article and approved the submitted version.

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CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontierspartnerships.org/articles/10.3389/ti.2024.11704/full#supplementary-material

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