

# Psychosocial challenges before and after organ transplantation

Karl-Heinz Schulz<sup>1,2</sup>  
Sylvia Kroencke<sup>1,2</sup>

<sup>1</sup>Department of Medical Psychology,

<sup>2</sup>University Transplant Center,  
University Medical Center Hamburg-  
Eppendorf, Hamburg, Germany

**Abstract:** This review addresses psychosocial challenges before and after solid organ transplantation. Stressors, corresponding psychosocial changes of the recipient, and psychological interventions in the different phases of the transplant process are described. Furthermore, important aspects of the preoperative psychosocial evaluation are presented with a special focus on living donors and patients with alcoholic liver disease. For the postoperative period, adherence, quality of life, and return to work are highlighted. Finally, research and clinical implications are presented.

**Keywords:** adherence, alcoholic liver disease, evaluation, living donation, quality of life, return to work

## Introduction

Organ transplantation has become an established treatment in end-stage organ failure. Even though it is now a routine procedure in many countries worldwide, patients are faced with various challenges. This review addresses psychosocial challenges and relevant psychological aspects in the different phases of the transplant process.

## Stressors before transplantation

Chronic illnesses are not only accompanied by somatic changes and functional limitations but also by emotional, cognitive, and social changes requiring extensive adjustments and considerable coping skills (Table 1). These psychosocial changes should not be considered as secondary, since they are as much part of the illness as pathological blood parameters and somatic symptoms. From the first symptoms and diagnosis to the very acceptance of having to live with a chronic condition, the process of the growing realization of being chronically ill is accompanied by emotional crises and destabilization. Depressiveness and hopelessness, anxiety, aggression, hope, and confidence vary in an unpredictable pattern, representing the gradual process of adaptation. Various coping strategies are utilized. Their functionality is less determined by a specific strategy but rather by its flexible and adequate use. The internal adaptation process is accompanied by an increasing loss of autonomy, social roles (family and occupational), contacts, and activities. Furthermore, occupational and financial problems might cause existential worries. In end-stage organ failure, the patient has to face his/her limited life expectancy and the need for organ transplantation. Fear of death, inner conflicts, and the uncertainty of a timely transplantation are prevailing emotional stressors in this stage of the illness. In the case of kidney disease, dialysis

Correspondence: Karl-Heinz Schulz  
Department of Medical Psychology,  
University Medical Center Hamburg-  
Eppendorf, Martinistrasse 52, W26,  
20246 Hamburg, Germany  
Tel +49 40 7410 54132  
Fax +49 40 7410 54965  
Email khschulz@uke.de

**Table I** Generic course of a chronic disease before and after transplantation, patients' coping demands, and psychological interventions

Disease course	Patients' psychological reactions and coping demands	Psychological interventions
<b>First symptoms</b>	Adaptation to crisis	Crisis intervention
<b>Diagnosis</b>	Attribution of meaning (subjective illness theory)	Supportive therapy to facilitate illness acceptance and illness coping
<b>Living with a chronic illness</b>	Attempting to maintain personal autonomy	Facilitate adherence and knowledge/understanding of illness (illness education)
Persistent symptoms	Accepting changes in occupational and family roles	Facilitate formation of new role perceptions and life goals
Frequent doctor visits and hospital stays	Developing new life goals	Family counseling
Medical treatment	Acquiring new coping strategies and activating resources (eg, social support)	Mediate contact to patient support groups and targeted treatment measures (eg, detoxification therapy)
<b>Preoperative stage</b>	Decisional conflicts	Psychosocial evaluation
Transplant evaluation	Uncertainty	Facilitate decision-making and adherence
Waiting list	Helplessness, hopelessness	Facilitate coping with uncertainty and stress reduction
Medical crises	Preoperative fear	Facilitate processing of fear, grief, depressiveness, and aggression
Hospitalization	Fear of death	Family counseling
	Acute stress reaction (shock)	Crisis intervention
<b>Perioperative stage</b>	Postoperative delirium (acute organic brain syndrome)	Facilitate processing of delirium/psychotic symptoms
Complications	Organ integration	Facilitate organ integration and processing of "donor fantasies"
Acute rejection	Traumatic experiences	Facilitate processing of traumatic reactions, fear, and pain
	Fear of rejection	Support/encouragement in case of somatic crises
	Coping with complications	
<b>Postoperative stage</b>	Fear of organ failure/loss	Facilitate fear processing and emotional stabilization
Convalescence	Fear of infections and other comorbidities (eg, cancer)	Facilitate adherence and readjustment
New medical treatments	Coping with medical problems	Crisis intervention
Immunosuppressive medication	Readjustment and adherence problems	Supportive therapy
Side effects, associated comorbidities	In case of graft failure:	Cognitive and behavioral interventions
Rehospitalization	Hopelessness, depressiveness	Family counseling
Chronic rejection	Feelings of guilt	Mediate contact to patient support groups
Retransplantation	Increased fear of retransplantation and organ failure	

is available as an alternative treatment. It is, however, associated with diverse and severe limitations, especially regarding quality of life (QOL) and life expectancy.<sup>1,2</sup>

## Stressors after transplantation

In the perioperative period, the focus is on the patient's physical recovery, with possible rejection episodes and other medical complications causing anxiety and emotional strain. Within the first days after transplantation, a postoperative delirium (acute organic brain syndrome) might occur. The accompanying symptoms of mental confusion, language disturbances, and occasional hallucinations and delusions are often a frightening experience to patients and their families. Acute brain dysfunction is common in intensive care patients and patients after surgery.<sup>3-6</sup> In transplant patients,

the immunosuppressive medication, especially corticosteroids, is known to contribute to this syndrome.<sup>7</sup> Although the symptoms are reversible in the majority of transplant patients, their occurrence is associated with longer hospital stay and higher mortality.<sup>8-10</sup> Some patients experience problems accepting the new organ and suffer feelings of guilt toward the donor which, in turn, can increase psychological stress and nonadherence.<sup>11</sup> In addition, the transplant and intensive care unit experience may cause symptoms of post-traumatic stress disorder or reactivate preexisting traumata.<sup>7</sup>

In the long-term postoperative period, medication side effects and associated comorbidities become central stressors impeding patients' QOL. Frequent comorbidities are infections, diabetes mellitus, hypertension, lipometabolic disorders, adipositas, cardiovascular diseases, oncologi-

cal diseases, osteoporosis, and chronic kidney failure.<sup>12,13</sup> Furthermore, psychiatric symptoms (eg, depression, anxiety, agitation, psychosis) and neurological symptoms (eg, sleep disturbances, cognitive impairment, delirium) can occur as neurotoxic side effects in patients receiving immunosuppressive drugs.<sup>7,14</sup> In most cases, episodes of acute rejection can be treated effectively, especially in the early postoperative period, whereas chronic rejection still constitutes a serious problem. Organ failure can be caused by the recurrence of the underlying disease (eg, hepatitis C following liver transplantation) or by chronic rejection and other immune-mediated as well as non-immunological factors (eg, hypertension, smoking, nonadherence) leading to irreversible organ damage (chronic allograft nephropathy in kidney transplantation, cardiac allograft vasculopathy in heart transplantation, bronchiolitis obliterans syndrome in lung transplantation, chronic liver allograft failure in liver transplantation). Graft failure along with infections is the leading cause of long-term mortality in heart and lung transplantation,<sup>15,16</sup> while patients after liver and kidney transplantation more often die of cardiovascular diseases.<sup>12,17</sup> Graft failure in kidney transplant recipients is primarily caused by chronic allograft nephropathy,<sup>18</sup> whereas in liver transplant recipients, disease recurrence and biliary problems are the most common causes of graft dysfunction.<sup>12</sup> Furthermore, the need for kidney transplantation can also arise in heart, liver, and lung transplant patients, mainly due to the nephrotoxic effects of the immunosuppressive medication.<sup>19</sup> In all transplant patients, cancer presents an increasing mortality risk in the long-term postoperative period.<sup>12,15–17</sup>

Faced with these multiple health risks, patients often continue to experience anxiety and worries regarding possible retransplantation, serious comorbidities, and death. It could be demonstrated that, irrespective of their health status, lung transplant patients' transplant-associated worries are correlated with increased chronic stress.<sup>20</sup> Should retransplantation actually become necessary, emotional strain increases further. But even patients in good physical health are confronted with severe challenges, for example, regaining their previously lost or restricted social roles as family members and partners (including sexual activity) and returning to work or taking up other meaningful activities.<sup>21,22</sup> Financial problems and legal disputes with health or pension insurance agencies constitute other possible sources of psychological strain. In a study assessing patients 5 years and 10 years after heart transplantation, the most bothersome stressors concerned work, school, and financial issues.<sup>23</sup> Furthermore, patients might feel stressed by the need for a

healthy lifestyle (eg, regular physical activity, weight control, alcohol and tobacco abstinence) and the strict adherence to the medical regimen (eg, punctual intake of medication, frequent follow-up appointments, dietary restrictions, and infection prophylaxis). This, in turn, might compromise their adherence after transplantation.

## Psychosocial adaptation and psychological disorders

After transplantation, the psychosocial burden is usually less severe than during the preoperative period. Nevertheless, patients must still be regarded as chronically ill and have to demonstrate considerable coping skills. In the best case, transplant patients learn to adapt to their new situation, often by reevaluating life goals and by focusing on more positive consequences, for example, personal growth.<sup>24</sup> On the other hand, unsuccessful readjustment is associated with lower QOL and psychiatric morbidity.<sup>14,25,26</sup> The most common psychological disorders among patients before and after transplantation are affective and anxiety disorders.<sup>7,14</sup>

Comprehensive literature reviews demonstrate a prevalence of depression in 20%–25% of cases before and after kidney transplantation.<sup>27–29</sup> Less information is available concerning patients receiving other organs. Prior to and following lung transplantation, depression seems to be prevalent in approximately 30% of patients.<sup>30,31</sup> Furthermore, lung transplant patients are more likely to suffer from anxiety disorders, especially panic disorder.<sup>7,31</sup> In heart and liver transplantation, most studies find symptoms of depression and anxiety in at least 30% and up to 60% of patients.<sup>7,32–41</sup> A recent cross-sectional study of patients after liver transplantation relates the different rates of depressive and anxiety symptoms to the time elapsed since transplantation, with symptoms being more prevalent in the first 2 years and beyond 15 years after transplantation. Post-traumatic stress symptoms were more prevalent within the first 5 years after transplantation.<sup>42</sup>

The extent of the perceived psychosocial burden is moderated by personal and social resources (resilience factors), that is, favorable coping skills, self-efficacy, sense of coherence, optimism, and social support.<sup>23,24,31,43–47</sup> Furthermore, associations of psychosocial variables with medical outcome and even mortality in transplant patients could be demonstrated.<sup>14,25,29,32,48–52</sup> DiMartini et al<sup>52</sup> identified three different trajectories of depressive symptoms within the first postoperative year in a cohort of 167 liver transplant patients with alcoholic liver disease (ALD): group 1 with consistently low depression levels, group 2 with initially low depression

levels that increased over time, and group 3 with consistently high depression levels. Groups 2 and 3 showed significantly higher mortality within the subsequent years (controlling for age and medical variables commonly associated with mortality). The strongest predictors of mortality were depression scores and number and severity of comorbidities. Rogal et al<sup>35</sup> found untreated depression as the factor most strongly linked to long-term mortality after liver transplantation.

## Psychological care

Psychological consultation can be helpful in all disease stages enabling patients to better cope with their extraordinarily stressful situation (Table 1). A need for psychological care was found in up to 50% of transplant patients.<sup>53,54</sup> Of particular importance are educational and supportive therapy elements but also cognitive-behavioral interventions including relaxation techniques.<sup>55–57</sup> Less common methods like hypnotherapy<sup>58</sup> and “Quality of Life Therapy”<sup>59</sup> have also been utilized. Gross et al<sup>60</sup> were able to demonstrate a positive effect of “Mindfulness-Based Stress Reduction” on transplant patients’ depression, anxiety, and sleep quality. Dew and DiMartini<sup>40</sup> advise a multicomponent interventional approach focused on risk factor reduction and the enhancement of personal coping resources. However, interventional studies are still rare, and further research is necessary regarding the effectiveness of interventions in order to develop evidence-based therapy strategies.

Moreover, family members and caregivers of transplant patients show increased psychological strain before and after transplantation.<sup>61</sup> Family counseling, and if necessary,

psychotherapeutic support, can help reduce psychological strain, thus also maintaining the valuable social support provided by caregiving family members of the transplant patient. In this context, the issue of possible conflicts due to changing family roles may also be addressed.

## Psychosocial evaluation

In the preoperative period, the psychosocial evaluation of transplant patients is an important psychological task, particularly in view of the prevailing organ shortage. Similar to the medical evaluation, the psychosocial evaluation should be evidence-based and avoid any moral judgment. The procedure should aim at identifying factors likely to have a negative impact on the postoperative prognosis. The goal should not be the exclusion of patients from transplantation but rather the recommendation of supportive or therapeutic measures which, upon successful completion, enable access to the waiting list (at a later date). Final exclusion is to be considered only if cooperation with the patient cannot be achieved in the long term, thus making graft loss highly probable.

A psychosocial evaluation should be part of every transplant program. In its course, cognitive, behavioral, emotional, and social factors that might impair coping or adherence should be explored, and the patient and his/her family should be prepared as best as possible for transplantation. Table 2 shows evaluation criteria as well as critical results. In most cases, problematic evaluation results need not be considered as contraindications for transplantation, since modification is possible, for example, education in case of inadequate knowledge, counseling or psychotherapy in case

**Table 2** Psychosocial evaluation criteria and critical results

Evaluation criteria	Critical results
Disease acceptance	Denial/lack of acceptance of illness or necessity for transplantation
Knowledge regarding disease and transplantation	Lack of knowledge
Transplant motivation	Lack of motivation to receive a transplant
Expectations regarding transplant outcome	Unrealistic expectations
Past and present coping behavior	Inadequate coping behavior
Past and present adherence	Inadequate adherence
Health behavior	Inadequate health behavior
Substance use (alcohol, tobacco, illicit drugs)	Substance abuse
Past and present addictive behavior	Substance dependence
Past and present psychiatric disorders	Active psychiatric disorder
Symptoms of anxiety, depression	Severe symptoms of anxiety/depression
Cognitive status, capacity to give consent and adhere to the medical regimen	Cognitive deficits, inability to give consent/adhere
Social anamnesis (living arrangements, relationships, social support)	Unstable/problematic relationships, lack of social support
Occupational situation and post-transplant expectations/goals, economic situation	Occupational and/or financial problems, unrealistic goals (under- or overstated)
Other psychosocial stressors	High psychosocial burden

of psychiatric disorders, and inadequate coping, activation of family support, or outpatient care for patients needing help taking their medication. A history of psychiatric disorders is not to be considered as absolute contraindication for transplantation.<sup>14</sup>

As opposed to post-transplant psychological disorders, pretransplant psychopathology does not seem to be as strongly associated with the medical outcome of transplantation.<sup>50,62</sup> Even in case of psychotic or major depressive disorders, a favorable long-term outcome can be achieved with specialized treatment, good social support, and regular follow-up visits.<sup>50</sup> Regarding cognitive disorders, it is important to attempt a differentiation between potentially reversible deficits due to organ dysfunction (eg, hepatic encephalopathy, uremic encephalopathy) and more persistent deficits that might be due to preexisting dementia or a static cognitive impairment.<sup>7</sup> While the restoration of normal organ function may most likely correct the reversible cognitive impairments, there is growing evidence that some patients continue experiencing cognitive deficits after transplantation.<sup>63–66</sup> Special attention is necessary regarding substance-induced disorders leading directly (eg, alcoholic liver or heart disease, acute liver failure due to acetaminophen poisoning) or indirectly (eg, hepatitis B/C cirrhosis due to intravenous drug abuse) to transplantation.<sup>67</sup>

Jowsey et al<sup>68</sup> listed the following risk factors for poor transplant outcome:

- Weak or absent support systems
- History of nonadherence
- Active psychiatric pathology
- Significant cognitive impairment or moderate/severe mental retardation or dementia
- Personality disorders with impulsivity.

Whether or not these criteria should be taken as contraindications for transplantation, however, should be decided on a case-by-case basis by an interdisciplinary team considering all available medical and psychosocial information.

## Psychosocial evaluation in living organ donation

In kidney and liver transplantation, living donation has become a routine procedure in many centers worldwide with the majority of donors showing good QOL outcomes.<sup>69–72</sup> In some countries, the majority of transplanted organs are procured from living donors.<sup>73</sup> Psychosocial evaluation of living donors has to consider national legal prerequisites. Whereas, in some countries, a close genetic or emotional relationship between donor and recipient is required, others permit unrelated or even anonymous (unspecified) donation.<sup>74</sup>

A systematic literature review assessing guidelines, consensus statements, and clinical protocols describing the psychosocial evaluation of living donors concludes that the current evidence base of psychosocial evaluation criteria is weak and there is a wide variation of methods used to evaluate donors.<sup>75</sup> Most authors recommend the use of a structured or semistructured interview providing a framework for comprehensive assessments. Several propose additional psychometric testing. Psychosocial domains frequently addressed in donor evaluation are the following:

- Motivation to donate, decision-making process, ambivalence, expectations
- Voluntariness of the decision
- Cognitive status, competence to give informed consent
- Knowledge regarding own and recipient's risks
- Sociodemographic characteristics, family-related issues, social support
- Donor–recipient relationship
- Current and past psychiatric disorders, psychological stability
- Current stressors, critical life events, coping
- Adherence with the medical regimen, health behavior including substance use
- Financial issues, for example, economic risks of donation, possible financial inducements (prohibition of organ trafficking)
- Employment-related issues, for example, occupational risks of donation.

The recipient interview in case of living donation should also include an exploration of the relationship with the donor as well as the recipient's attitude toward living donation and possible associated expectations.

## Psychosocial evaluation of patients with ALD

Even though alcohol-related liver disease has become one of the most common indications for liver transplantation in Europe and the USA, it remains the most controversially discussed indication.<sup>76–78</sup> Compared to patients with other disease etiologies, survival of patients with alcoholic liver cirrhosis is similar<sup>78,79</sup> or even better.<sup>80</sup>

Liver damage from alcohol varies from asymptomatic, and in most cases, reversible steatosis to cirrhosis with subsequent risk of hepatocellular carcinoma. Factors influencing disease development include the dose, duration, and type of alcohol consumption, drinking patterns, sex, ethnicity, and associated risk factors including obesity, iron overload, concomitant infection with viral hepatitis, and genetic factors.<sup>81,82</sup>



The medical diagnosis of ALD is to be differentiated from the psychiatric diagnoses of “alcohol abuse” or “alcohol dependence”. ALD diagnosis is based on histological and laboratory markers along with the patient’s admission of having consumed excessive amounts of alcohol. Patients, however, will often downplay or even deny alcohol consumption, and the other diagnostic criteria lack specificity, especially if considered individually. Even without pathophysiological evidence of organ damage, severe addictive behavior can be present. At the same time, alcohol-induced organ damage is not necessarily accompanied by addictive behavior, and only approximately 30% of patients with continued alcohol consumption (>40 g/day) progress from steatosis to liver cirrhosis.<sup>83</sup> The percentage declines to 15% if abstinence can be achieved.<sup>81</sup>

The importance of differentiating between ALD and alcohol abuse/dependence is demonstrated in a retrospective study by Rowley et al.<sup>84</sup> With a median follow-up time of 6 years, the authors assessed  $n=358$  liver transplant recipients, 22% of whom had a transplant indication of ALD. In ten out of these 77 patients, clinical psychologists could not ascertain a psychiatric diagnosis of alcohol dependence or alcohol abuse (according to Diagnostic and Statistical Manual of Mental Disorders IV - Text Revision criteria), whereas in 54 patients without ALD diagnosis, alcohol abuse or dependence could be diagnosed. This newly defined group of  $n=121$  patients included 34% of the study sample, overlapping approximately by half with the ALD group. While ALD diagnosis did not predict survival, patients classified according to psychiatric diagnosis had significantly poorer survival rates than patients without psychiatric diagnosis (7.3 years, 95% confidence interval: 6.3–8.3 versus 9.4 years, 95% confidence interval: 8.7–10.1). No significant difference was found between patients with alcohol dependence and alcohol abuse. Thus, psychiatric diagnostic criteria appear to have greater utility in predicting survival than the pathophysiologically defined ALD diagnosis. This might be due to harmful behavioral consequences of substance addiction (ie, impaired sleep, unhealthy eating habits, low social support, nonadherence to the immunosuppressive regimen) having a negative impact on long-term survival as “... transplant surgery is not considered a cure for maladaptive behavior” (p 202).<sup>84</sup> In fact, drug addiction was found to be another independent predictor of mortality in this study. In addition, more frequent comorbidities (cardiovascular diseases, de novo neoplasms) in patients with substance misuse as well as alcohol relapse and tobacco consumption are associated with reduced postoperative survival.<sup>79,80,85–87</sup> A literature

review concludes that excessive drinking after transplantation is associated with worse patient outcomes regardless of primary transplant indication.<sup>88</sup> In a study comparing survival of patients with and without alcohol relapse, 5-year and 10-year survival was 70% and 20%, respectively, in patients with excessive alcohol consumption versus 90% and 82%, respectively, in abstinent patients.<sup>89</sup> Thus, especially, long-term survival is reduced.

Alcohol relapse rates after transplantation vary widely between 10% and 50%,<sup>79</sup> depending on preoperative selection, postoperative care, methods used to assess alcohol relapse, and the definition of what constitutes a relapse (eg, any consumption versus harmful drinking). Approximately 20% return to harmful drinking after transplantation.<sup>78</sup> A major challenge of the preoperative evaluation is to assess the probability of relapse after transplantation. The predictive value of the duration of preoperative abstinence is still under discussion, but evidence of newer studies assessing large samples suggests that a longer period of abstinence is associated with lower relapse rates.<sup>89–92</sup> In most centers, a minimum of 6 months is determined as an adequate length of sobriety (“6-month rule”). However, exceptions can be justified in case of patients with predicted survival of <6 months, especially if other prognostic factors are in favor of the patients’ abstinence. There is even evidence that selected patients with acute severe alcohol hepatitis receiving a transplant without observing a period of abstinence derive a benefit from transplantation similar to that achieved for other indications.<sup>76,88,93</sup> Thus, some authors argue against the 6-month rule being used as a major selection criterion.<sup>88,94</sup> Apart from a shorter duration of preoperative sobriety, literature reviews<sup>95–98</sup> found the following predictors relevant to the prognosis of post-transplant alcohol relapse: family history of alcohol abuse/dependence, other substance misuse, abuse versus dependence, psychiatric comorbidity, younger age, lack of social support, preoperative drinking pattern (eg, high frequency, large amounts of alcohol), repeated treatment failures, and nonadherence with medical care. The preoperative evaluation is based on these criteria, along with other emerging predictors, such as nonacceptance of having an alcohol problem, low motivation for change, and lack of self-esteem.<sup>82,99</sup> Thus, psychosocial evaluation in case of ALD should include the following:

- Individual and family history of alcohol consumption
- Drinking patterns (type and amount of alcohol, frequency)
- Withdrawal treatments
- Diagnosis of abuse versus dependence
- Duration of abstinence

- Nonalcohol-related substitute activities
- Negative social consequences in case of relapse
- Social support/stability (vocational situation, family, friends, relationship with husband/wife/partner, living conditions)
- Other substance use
- History of adherence (regarding substance use and medical treatment)
- Acceptance of alcoholic disease etiology
- Motivation for change
- Self-esteem, hope, and confidence.

Failure to meet these criteria, however, should not lead to ultimate exclusion but rather to a diagnosis of deficits to develop treatment recommendations.<sup>100</sup> With a careful preoperative psychosocial evaluation and life-long medical and psychological follow-up, including regular monitoring of alcohol consumption and early treatment of relapse, good long-term results can be achieved<sup>76</sup> with relapse rates lower than or similar to intense inpatient relapse prevention treatment.<sup>101</sup>

## Adherence

For the long-term success of transplantation, adherence is an essential prerequisite as nonadherence can lead to graft rejection, graft loss, and even death. Prior to transplantation, continued nonadherence is considered a contraindication for transplantation. This constitutes an ethical dilemma of patient autonomy and the right to receive treatment versus the necessity to limit access to transplantation due to the scarcity of donor organs. Thus, the evaluation and promotion of adherence is a key objective in transplant psychology.

Nonadherence means “not taking medications, missing medications, taking too much, not taking enough, wrong timing, wrong dose and/or wrong pill, but may also refer to missing appointments, not booking appointments, not doing blood work, not returning calls and/or refusal to follow the treatment regimen” (p 27).<sup>102</sup> Furthermore, adherence in transplant patients also refers to observing hygiene rules and specific dietary regimens as well as adequate health behavior and substance use. Compared to the common term “compliance”, adherence is of less instructive character and focuses more on doctor–patient cooperation and the jointly negotiated treatment plan. Accordingly, the reasons for nonadherence not only reside in the patient but also within the physician’s behavior and the doctor–patient relationship. In addition, treatment characteristics like the number, intake frequency, and (perceived) side effects of drugs influence adherence behavior.

It can be estimated that approximately 50% of late acute rejections and 15% of graft losses are associated with non-adherence.<sup>103</sup> Along with medication nonadherence, tobacco consumption seems to be a contributing factor which further increases the postoperative risk of developing comorbidities.<sup>104</sup> According to a meta-analysis, approximately 23 out of 100 adult transplant patients per year fail to take their immunosuppressants correctly.<sup>105</sup> The authors found similarly high nonadherence rates regarding diet, exercise, and other health care requirements. However, rates vary between patient groups and depending on age. Medication nonadherence is highest in kidney recipients<sup>105</sup> and in adolescent transplant patients with estimated rates of >50%.<sup>106</sup> With respect to substance use, it was found that approximately ten out of 100 adult patients per year resume smoking, six out of 100 take up drinking alcohol again, and four out of 100 experience illicit drug relapse.<sup>107</sup> The variety of methods used to quantify adherence also contribute to the wide range of reported nonadherence rates, with De Bleser et al<sup>108</sup> reporting immunosuppressive medication nonadherence rates of 24%–70% depending on the measurement method.

Despite the clinical relevance of adherence with respect to the long-term outcome of transplantation, there currently exists no single method considered as the gold standard to assess medication nonadherence.<sup>109</sup> Electronic monitoring with microdevices recording each opening of the pill bottle gives the most accurate insight into patient behavior and is recommended for research studies.<sup>110</sup> It is, however, too cost-intensive and usually not available in clinical practice. Methods like pill counts and prescription refill rates are difficult to monitor in clinical practice and reveal nothing about the timing of ingestion.<sup>111</sup> Patient self-reporting by interview, diary, or questionnaire, and proxy reports by clinicians or family members are inexpensive and feasible in most clinical settings, but these methods are prone to recall and social desirability response bias. Proxy reports depend on the familiarity with the patient.<sup>112</sup> Butler et al<sup>113</sup> found that clinicians’ rating yielded even more inaccurate results compared to electronic monitoring than self-report at a confidential interview. However, high specificity can be reached with collateral reports of at least three clinicians.<sup>112</sup> Self-report questionnaires have been developed which can be useful in detecting nonadherence; however, further validation of these measures is needed in transplant populations.<sup>109</sup> No conclusive biological markers of medication nonadherence have yet been identified. Blood-level monitoring of immunosuppressive medication did not prove useful when only single measurements were considered. More reliable results can be

achieved by assessing the variability in immunosuppressant trough levels over a longer period of time.<sup>114,115</sup> In clinical practice, combining different assessment methods, such as self-reporting, clinical judgment, and variability in immunosuppressant blood levels, is advised.<sup>109,111,112</sup>

Studies have identified a variety of variables predicting nonadherence, but reviews are inconclusive. The best predictor of postoperative nonadherence seems to be preoperative adherence behavior.<sup>105,116</sup> Furthermore, an association was found between medication nonadherence and a high perceived symptom burden due to the immunosuppressive medication<sup>117</sup> as well as negative attitudes toward the immunosuppressive medication.<sup>118</sup> Other frequently identified predictors of nonadherence are age (adolescence and very old age), psychiatric disorders, substance abuse, and a lack of social support.<sup>118–120</sup> Dew et al<sup>121</sup> found that the probability of nonadherence increases with the number of risk factors or predictors present: with 0–1 risk factors, the probability was 30%, increasing to 50% with 2–3 risk factors and to 80% with  $\geq 4$  risk factors.

A small number of intervention studies show that post-transplant adherence can be improved, but the available data are inconsistent with only five out of 12 studies reviewed by De Bleser et al<sup>103</sup> showing significant improvement in at least one medication adherence outcome. Most interventions include a combination of patient-focused cognitive/educational, behavioral, emotion-centered, and social support-activating dimensions. The most promising approach is seen in a paradigm shift from cure to prevention, with a continuous routine assessment of nonadherence focusing on its individual reasons, followed by a combination of tailored interventions addressing the underlying causes of the problematic behavior in an interdisciplinary setting.<sup>103,106</sup> Future studies should also explore the communication skills of physicians, nurses, and other transplant professionals with respect to promoting adherence and whether improving their adherence management skills can improve transplant patients' outcome.<sup>106</sup>

## Quality of life

The term “health-related quality of life” describes the extent to which the habitual or expected physical, emotional, and social well-being is affected by a medical condition or its treatment. In former years, transplantation medicine was primarily oriented toward patient survival, that is, the quantity of life years gained. With the improvement of long-term outcomes, the focus has shifted to the quality of the years gained and the perception from a patient point of view.

Today, QOL is acknowledged as a main outcome parameter in transplantation medicine, the aim being to restore patients' physical, psychological, and social functioning. Some studies even identified QOL as a significant predictor of mortality and graft failure after transplantation.<sup>51,122</sup>

A considerable number of prospective and retrospective studies with large samples have been published along with >20 literature reviews summarizing results across either different types of organs or organ-specific procedures. Systematic reviews and meta-analyses<sup>123–132</sup> mostly assessed QOL in liver and kidney recipients (including combined pancreas transplantation), but overviews are also available for heart and lung transplantation<sup>49,133–136</sup> and even for small intestine transplantation.<sup>137</sup> Anthony et al<sup>138</sup> reviewed QOL in pediatric patients across all organ types, while Kniepeiss et al<sup>139</sup> focused on QOL in elderly patients. Other reviews considering QOL across different organ types are available from Burra and De Bona,<sup>140</sup> Ortega et al,<sup>141</sup> Feurer et al,<sup>142</sup> Schulz et al,<sup>143</sup> Dew et al,<sup>123</sup> and Molzahn.<sup>144</sup> It should be noted that especially in early studies, the definition of QOL and its measurement differed considerably. Until today, there is no gold standard for measuring QOL. Instead, a variety of generic and disease-specific instruments have been applied.<sup>145,146</sup> The most commonly used QOL instrument in transplantation medicine is the 36-Item Short-Form Health Survey by Ware and Sherbourne.<sup>147</sup> However, as a generic instrument, its possible shortcomings to capture aspects of health relevant and specific to transplantation should be kept in mind.

Current evidence suggests that postoperative QOL is clearly superior to preoperative QOL. The gain is larger in scales affected by physical health, whereas improvements are less distinctive in areas affected by psychosocial functioning.<sup>140</sup> In single dimensions, like sexual function and occupational rehabilitation, deficits appear to persist after transplantation.<sup>21,49,148,149</sup> QOL was found to be significantly better compared to specific reference groups of chronically ill patients not receiving a transplant. In contrast, results comparing transplant patients to the general population or healthy controls are inconsistent, with studies finding worse, similar, or even better QOL scores. The latter, however, might be attributed to a change in patients' appraisal of QOL and to selection effects. In conclusion, QOL in transplant patients is probably lower than within the general population.<sup>143</sup> Nevertheless, even in the long term ( $\geq 10$  years after transplantation), a good QOL can be achieved.<sup>38,150–153</sup> Yet, organ-specific or disease-specific factors may negatively influence postoperative QOL.<sup>49,123,154,155</sup> Furthermore, studies



often are limited by methodological problems as there is no correction for confounding variables, such as age, sex, and other potential biases (eg, socioeconomic and educational status, hemoglobin concentration, diabetes mellitus, renal function).<sup>141</sup>

Other factors possibly influencing postoperative QOL are specific complications, the immunosuppressive treatment and its adverse effects, comorbidities, and the disease course prior to and after transplantation, especially disease recurrence and graft failure.<sup>143</sup> Strong associations with physical and mental QOL could also be demonstrated for distinct coping strategies, anxiety, depression, and employment. These psychosocial factors were far more relevant to QOL than purely somatic variables, such as the number of postoperative complications or length of hospital stay.<sup>156</sup> As determinants predicting a higher QOL, the following variables were found: lower burden of immunosuppressive treatment, better social integration, higher income/education, employment after transplantation, younger age for physical QOL, and older age for mental QOL.<sup>157,158</sup> The type of transplanted organ appears to be less relevant in terms of QOL. In some studies, organ-specific differences were found, but not all of these are consistent. Prior to transplantation, Pinson et al<sup>155</sup> and Ortega et al<sup>141</sup> demonstrated the best QOL in kidney patients, followed by liver, heart, and lung patients. Ten years after transplantation, Karam et al<sup>153</sup> reported the best QOL in liver transplant recipients, a medium QOL in heart recipients, and the lowest in kidney recipients. Kugler et al,<sup>159</sup> on the other hand, found the smallest QOL benefit in liver transplant recipients within 2 years after transplantation. Ortega et al<sup>141</sup> reported the best QOL in kidney recipients 3 months post-transplant, followed by heart recipients, and then liver recipients, with lung transplant patients showing the worst QOL. At 1 year, however, lung recipients had the best QOL. It can be summarized that improvements were found for all types of transplants, but the trajectories were not the same. Because of their superior preoperative QOL, kidney recipients seem to experience the smallest benefit,<sup>141,153,155</sup> while lung recipients have the largest benefit in terms of QOL.<sup>141,159–161</sup>

In conclusion, postoperative QOL is associated with demographic, clinical, and psychosocial variables. Depending on the age group, different predictors may be relevant.<sup>162</sup> Studies comparing QOL in different samples should therefore always correct the results for confounding variables, especially age and sex. Moreover, predictors may change within the postoperative course.<sup>154</sup> To explore these complex interrelations, more research, especially prospective studies, is needed with the aim of developing a model

to better understand risk factors for inferior QOL outcomes and determine interventions that positively influence these factors. Furthermore, previous research has been mostly deficit-oriented, while future studies should, instead, focus on resources and conditions for a better QOL.

## Return to work

Enabling patients to take up productive employment constitutes a main goal of transplantation<sup>55</sup> and is regarded as an indicator of societal participation.<sup>163</sup> Prevalence rates of patients actually returning to work or finding new employment show a wide range between 18% and 86%.<sup>22,163–165</sup> The heterogeneous results can be attributed to differing sociodemographic and clinical characteristics, length of follow-up time, definition of “work” (whether part-time employment or housework is included), assessment methods, and inclusion criteria (eg, whether retirees are categorized as nonworking) as well as national legal and social framework of health care, social security, and the labor market. Furthermore, although patients more frequently report feeling able to work, fewer actually do work.<sup>166,167</sup> On the other hand, patients may have to take up employment, even though they do not feel able to work. In a Belgian study, the employment rate was highest in kidney transplant recipients with 59%. Employment rates in heart and liver transplant recipients were 44% and 38%, respectively. The lowest rate of 28% was found in lung transplant patients.<sup>21</sup>

As a strong predictor of return to work, a shorter duration of previous unemployment/disability was identified.<sup>21,22,163,165,167</sup> Associations with return to work were also found for sociodemographic variables like younger age, male sex, and higher education<sup>21,22,165</sup> as well as for the postoperative health status (complications and comorbidities, eg, diabetes) of transplant patients.<sup>167–169</sup> Barriers keeping patients from returning to work include not only the fear of losing insurance coverage and financial support but also a lack of information and/or tools on how to realize their goals, for example, inadequate vocational rehabilitation, skills training, job placement assistance,<sup>170</sup> and a lack of support from employers.<sup>165</sup> Furthermore, a number of patients reported low subjective motivation or ability to work<sup>167</sup> and a lack of confidence<sup>171</sup> as reasons for not taking up employment after transplantation. Patients’ subjective health perception relating to their perceived ability or inability to work appears to be a significant predictor of return to work.<sup>166,167,170</sup> In a study by Slakey and Rosner,<sup>166</sup> kidney transplant patients considered their disability status more related to having received a transplant than to any specific physical limitation. This might be

due to the often prolonged period of preoperative disability with frequent severe physical impairment. The modification of patients' perception of disability after transplantation is, therefore, seen as an important goal in enhancing employment rates.<sup>170</sup> However, it is difficult to differentiate between perceived disability and actual impairments. Van der Mei et al<sup>172</sup> found high levels of fatigue and physical impairment even in employed kidney transplant recipients, while, with a substantial variation among patients, in liver transplantation, poor health or health problems are cited as the most common reason for nonemployment.<sup>165</sup>

A number of studies have shown that more patients could take up employment than actually do return to work, and Huda et al<sup>165</sup> conclude that "social rehabilitation ... lags behind the medical results of transplantation" (p 238). Important requirements for return to work are improvement of health status, patients' own motivation, and social support at the workplace. It has been demonstrated that patients employed after transplantation showed better QOL<sup>22,165,173</sup> and less depression<sup>174</sup> than patients not working. Due to the mainly cross-sectional study design, it remains unclear whether better well-being is cause or consequence of employment. Evidence exists, however, that, with targeted interventions, return to work can be facilitated.<sup>170</sup>

## Perspective

Although knowledge concerning psychosocial aspects of transplantation has considerably increased over the last decades, the evidence base in most areas of research still does not permit definitive conclusions. This article gives an overview of the current evidence regarding some of the most relevant topics. More in-depth information regarding these and other topics is available.<sup>7,14,48,55,67,68,175,176</sup> Furthermore, the scope of this review is limited to adult transplant recipients as priorities in pediatric transplantation are different in a number of areas.<sup>177–180</sup> Future research should focus on factors influencing long-term outcomes and methods to assess and promote adherence as a main and modifiable determinant of transplant outcome. In many transplant centers, a lot of effort and resources are spent on preoperative evaluation and perioperative management, while during long-term follow-up, the attention patients receive is comparably low. Medical follow-up should be more easily available and complemented with routine psychosocial monitoring and interventions to assist patients in coping with the numerous demands they are faced with. Continuous attention seems warranted in order to optimize long-term success of transplantation.

## Disclosure

The authors report no conflicts of interest in this work.

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