

PSYCHOSOCIAL ASSESSMENT OF HEART TRANSPLANT REJECTION

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Abstract: The assessment of the diagnosis and prognosis of cardiac allograft rejection correlates directly with the success rate of heart transplantation. Cardiac allograft viability is influenced both by treatment-related biomedical variables and by the neuro-psychic and social status of the recipients. Thus, a personal history of depression, anxiety, mental retardation, or substance abuse is associated with a higher risk of chronic rejection, responsible for the increase in overall morbidity and mortality. The comprehensive psychosocial analysis of all forms of cardiac rejection reveals the intervention and synergistic action of such social factors as patient education, family and social support, marital status, along with his/her cultural and religious profile. All these psychosocial predictors of compliance have a particular impact on the risk stratification of all transplant candidates. In this respect, it is necessary to identify and describe some objective methods for monitoring the main psychosocial factors in order to streamline the standardization of international protocols. The dynamics of translational research supports the importance of early identification of psychosocial rejection as a key factor in improving survival and quality of life after heart transplantation.

Keywords: cardiac allograft rejection; heart transplantation; psychosocial predictors.

INTRODUCTION

The patterns of heart disease etiopathogenesis, clinical manifestations, and disease course are equally influenced by the intervention of biological, behavioral and psychosocial risk factors [1].

Since 1967, heart transplantation has been one of the great hopes of modern medicine in streamlining the treatment of end-stage heart disease [2].

At present, although it is unanimously acknowledged that the long-term results are quite satisfactory, the International Society for Heart and Lung Transplantation's (ISHLT) indication of the need for a multidisciplinary approach in the selection of patients eligible for cardiac allograft transplantation is supported [3]. This way, pre-transplant screening, performed correctly and thoroughly, will improve post-transplant prognosis [1].

In the last decade, the assessment of functional status and care of cardiac transplant recipients have changed significantly, a shift towards patient-centered approach being noticed [4]. Similarly, various

hypotheses have been suggested according to which post-transplant survival of 81-87% at 1 year, 69-72% at 5 years, and 55-60% at 10 years, can be greatly improved by identifying and correcting all the factors involved in organ preservation, regardless of the action of comorbidities [5, 6].

Also, similar to other transplantation types, the long-term survival of cardiac allograft recipients is correlated with the early identification of the factors contributing to transplant rejection [7]. In this regard, it is extremely important to assess adherence/non-adherence to immunosuppressive therapy, therapy with a crucial role in all solid organ transplant recipients. Moreover, recent studies are focused on identifying tools for the specific quantification of this parameter [8].

Cardiac allograft rejection is defined variably by different centers and in different studies using various protocols involving few identifiable risk factors [5]. Consequently, by using the current working tools, there are enough cases of asymptomatic or unexplained rejection, which results in a delayed diagnosis in the

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end-stage when the allograft is compromised [9]. Therefore, the best diagnostic strategy must include both somatic and biological and psychological and social information [1].

Unlike acute cardiac allograft rejection, diagnosed quickly and frequently in the first 3-6 months after transplantation, the chronic one, identified during the next 3-5 years, is associated with serious complications with a negative impact on morbidity and mortality [6]. At the same time, it is considered that many predisposing and/or favoring factors of chronic cardiac allograft rejection are expressed since the early stages of post-transplant recovery [10]. Etiopathogenic assessment and early recognition of all signs and symptoms suggestive of cardiac allograft rejection lesions are largely influenced by the patient's ability to understand the vital role of adherence to all recommendations by health professionals [11].

In 2018, ISHLT developed in collaboration with the American Society of Transplantation an international guideline that included among the specific recommendations for heart transplantation key points for psychometric assessment defining the preservation of cardiac allograft viability [12]. Both general and individual psychosocial variables interfere with the follow-up care plan of transplant patients, which draws attention to the use of all resources specific to heart transplantation [7]. On the other hand, some experts believe that the best solution for post-transplant bioclinical improvement is to develop their protocols including both the basic general ISHLT recommendations and new elements essential and specific to a medical procedure [13].

Over the years, several types of tools have been devised to find the best formula for standardizing pre- and post-transplant psychosocial assessment [14]. Some of the main factors used in this psychometric mechanism are mental stability, psychological and psychiatric history, patient ability to understand the occurrence and progression of the disease, willingness

to cooperate in correcting his/her lifestyle, and last but not least the available and functional social support systems [5].

Given that one of the main challenges in quantifying the rejection risk is the psychosocial one [10], the main goal of this study was to identify the correlations between the clinical expression of the main neuropsychiatric/mental health and social checkpoints, predictors of cardiac allograft rejection, with the prognosis and survival after heart transplantation.

Variability of the neuropsychiatric context

For all recipients of cardiac allografts, and not only, the challenging emotional amalgam renders this experience a very stressful one [11].

To date, no relevant studies investigating the perception of heart transplant recipients regarding the importance and benefits of this procedure have been identified [8].

From one year to the next, the synergistic role of psychologists in the team diagnosing and monitoring of pre- and posttransplant heart diseases is increasingly outlined through the implementation of specific tools for assessing the risk of cardiac rejection as objectively as possible [14] (Table 1).

Globally, assessing the functional status of patients at high cardiovascular risk eligible for heart transplantation requires screening for depression, anxiety and/or posttraumatic symptoms [5]. Under these circumstances, psychometric assessment uses questionnaires to record useful information for identifying organic and nonorganic psychotic disorders relevant to prognosis [1].

Numerous surveys conducted in various specialized clinics indicate active schizophrenia, suicide attempts, suicidal ideation, and dementia as absolute contraindications to heart transplantation [10].

Although there are few data to correlate both moderate and severe psychiatric disorders with posttransplant cardiac survival, daily practice suspects

Table 1. Variability of the neuropsychiatric context

Assessed criterion	Mental health impact		Reference
	Type of heart transplant rejection Acute	Chronic	
Cognitive dysfunction	negative	negative	Bui <i>et al.</i> ,2019
Depression	negative/neutral	negative	Sponga <i>et al.</i> ,2016
Anxiety	negative/neutral	negative	Forsberg <i>et al.</i> ,2021
Intellectual disability	neutral	neutral	Dipchand,2018
Schizophrenia	negative	negative	Albus <i>et al.</i> ,2019
Bipolar disorder	neutral/negative	negative	Dew <i>et al.</i> ,2019
History of psychological/psychiatric disorders	neutral/positive	positive	Sponga <i>et al.</i> ,2016
Neurological disorders	neutral	negative	Trevizan <i>et al.</i> ,2017

their synergistic action on quality of life [2]. Therefore, identifying and properly treating mental disorders is considered to be of the utmost importance [1].

Cardiac allograft transplantation can induce and maintain a stressful situation that can trigger depression (36% of cases) and anxiety (33% of cases), both in the early period, corresponding to the first year after transplantation, and later, after several years of adaptation to the new conditions [5]. Thus, the patient can experience a very deep feeling of guilt [6].

In literature, the evidence pointing to the role of depression is much stronger than that discussing the involvement / presence of anxiety [15]. As to the impact and mechanisms of action of other psychiatric disorders, such as bipolar disorder, psychoses and personality disorders, evidence is very rare and irrelevant [12]. However, it can be stated that the presence of personality disorders can affect the availability of social and family support resources with a negative impact on adherence to treatment [15].

Acute cardiac allograft rejection

The chronicity of heart diseases favors the emergence of major behavioral and emotional changes, which in the presence of mental disorders makes both the determination of transplant feasibility and the monitoring of its effectiveness quite challenging [16]. Immediately after transplantation, it is necessary to make an inventory of all aspects that allow the psycho-behavioral adaptation of the patient to the new situation [17].

In the first six to twelve months after transplantation, there is a sequence of three phases during which, until the total incorporation of the transplanted organ, discordant states from persecution anxiety to idealization and rationalization are identified [18].

Until recently, intellectual disability diagnosed in both the pediatric and adult populations was considered a relative contraindication to solid organ transplantation, such as the cardiac one [2]. However, some comparative studies based on the analysis of pediatric posttransplant outcomes did not reveal significant differences in terms of survival or acute rejection in the two groups with and without intellectual disabilities [9].

The prevalence of Axis 1 psychiatric diagnoses - mood disorders and anxiety - among the transplanted population is about 60% [10].

The paradoxical results of some clinical trials in which the risk of acute cardiac allograft rejection

is inversely associated with depression and anxiety disorders [10] were refuted four years later by much more sensitive and specific studies. They showed the importance of intrusive anxiety as a determinant of the patient's overall mental wellbeing. This anxiety manifests itself as fear related to the performance of the transplanted heart [6]. It is estimated that approximately 24% of cardiac transplant candidates face anxiety and depression before and after cardiac transplantation [3]. Moreover, the association of depression with demoralization is a much better predictor of acute rejection episodes compared to any of these two alone [5].

Most often the prognostic role of frailty in patients with heart failure can be quantified by using various tools for measuring cognitive capacity and depression. This frailty, defined as overall fatigue, reduced muscle mass, and low physical activity, is associated with an approximately 25% decreased survival in the first posttransplant year [4].

The advanced, end-stages of heart diseases that require heart transplantation are often characterized by reduced cardiac output resulting in a significant decrease in cerebral blood flow. Finally, brain lesions are detected by neuroimaging, lesions that have as a frequent clinical expression the cognitive dysfunction also known as cardiogenic dementia [7]. Cardiogenic dementia affect attention and perception, memory and practical skills, with a defining role on the ability of patients to take care of themselves and adhere to treatment for as long as possible [11].

Chronic cardiac allograft rejection

A 15-year analysis did not report negative influences on the incidence and prevalence of posttransplant complications in the population with mental disorders because these patients are considered to be closely monitored in specialized services [10]. However, the medical team must correctly and thoroughly assess the patient's perception of the received organ [11]. Therefore, it is often found that irritability, anger and hostility shown by patients in relation to the steps of the diagnostic and therapeutic algorithm are potential predictors of modest medical outcomes by reducing the therapeutic value of heart transplantation. On the contrary, optimism is associated with a good general condition and improved prognosis [5].

The controversial results obtained by correlating the degree of depression with mortality 6 years after heart transplantation draw attention to the need of using more reliable scores in identifying the

specific mechanisms [12]. At the same time, we must not ignore the increasingly common situation in which the transplant itself can be a trigger and favoring factor of depression in the medium and long term [15].

Over time, depressive symptoms may persist or get worse depending on the action of associated comorbidities, negatively influencing patients' quality of life [19]. Their exacerbation can be directly correlated with decreased motivation, compliance, and adherence to treatment [5,12].

Depending on the operational methods for defining and measuring adherence to immunosuppressive treatment, essential for posttransplant survival, heart transplant recipients exhibited a non-adherence rate ranging from 4.6 to 39.2% [20]. Most of the time, the emphasis is on personal medical history while family history is somewhat ignored [12]. It should also be ignored that the potency of these clinical manifestations is limited over time [21].

The presence of mental disorders has direct negative repercussions on the recovery and rehabilitation of allograft cardiac recipients, making it impossible for them to adapt to this new situation and to make the necessary lifestyle changes [17].

Variability of the social context

Over the years, complex ethical principles have limited the identification and specifically quantification of cardiac allograft donors, with a particular impact

on the therapeutic measures [10]. At the same time, another important factor influencing the efficacy of heart transplantation is represented by the adequate screening of such social factors as social isolation, marital status, socioeconomic status, stress at work [12].

Most literature studies investigating the profile of patients undergoing heart transplantation noticed the preponderance of male recipients, with an average age of 53, retirees, with limited education, and living in cohabitation [17].

In addition to somatic and psychological information suggested as important by various international therapeutic protocols, social history is often defining in the management of medium to long-term clinical symptoms after heart transplantation. On the other hand, social factors reduce the mental barriers to the development of a preventive behavior (Table 2).

One key pillar of optimal posttransplant care is compliance and/or adherence to treatment. According to the World Health Organization (WHO), the latter is defined as "the extent to which a person's behavior corresponds with agreed recommendations from a health care provider" [20]. In this sense, when an objective assessment of the degree of adherence is desired, three large areas and / or compartments are delimited and followed, namely - adherence to immunosuppressive drugs, vital for transplant patients, adherence to clinical visits and laboratory tests, and periodic self-monitoring [5]. This way, the doctor-

Table 2. Variability of the social context

Assessed criterion		Social impact		Reference
		Type of heart transplant rejection Acute	Chronic	
Age	< 70 years	neutral	positive	Cooper <i>et al.</i> , 2016
	>70 years	neutral	negative	
Sex	male	neutral/positive	positive	Trevizan <i>et al.</i> , 2017
	female	neutral/negative	negative	
Drug and illicit substance use Alcohol consumption		negative	negative	Sponga S <i>et al.</i> , 2016 Sponga S <i>et al.</i> , 2016
		neutral/negative	negative	
Smoking		negative	negative	Sponga <i>et al.</i> , 2016; Dew <i>et al.</i> , 2019
Public/private health insurance	present	neutral/neutral	negative/positive	Sponga <i>et al.</i> , 2016; Breathett <i>et al.</i> , 2017
	absent	neutral	negative	
Marital status	married/partners	neutral/negative	neutral/negative	Colignase <i>et al.</i> , 2015
	single	neutral/positive	neutral/positive	
Educational level	primary and/or secondary school	neutral/negative	positive	Dew <i>et al.</i> , 2019
	higher education	negative	negative	
Distance to the transplant center	0-500km	neutral	positive	Sponga <i>et al.</i> , 2016; Maldonado <i>et al.</i> , 2019
	over 500km	neutral/negative	negative	
Socioeconomic status	low	neutral	negative	Tumin <i>et al.</i> , 2017
	high	neutral	positive	

patient relationship can be anticipated and quantified. It was found that non-adherence before transplantation will continue after transplantation, favoring the occurrence of such medical complications as vascular thrombosis [12].

The development of an adaptive behavior to the received new organ depends on adequate social support [2]. The availability of the latter, either in the form of advice or in the form of medical and / or financial assistance, is a perspective that predicts the risk of rejection, ignoring the individual characteristic [22].

Acute cardiac allograft rejection

Acute rejection directly correlates with morbidity and mortality after transplantation, causing it to decrease long-term survival [9].

As to the availability and quality of transplanted organs, some retrospective cohort studies support the age factor as an important factor in obtaining optimal results [11].

According to the latest multicenter studies using ISHLT and United Network of Organ Sharing (UNOS) data, three-quarters of all transplants recorded worldwide involve the pediatric population. The percentage of pediatric transplantation has remained stable since the mid-1990s, and the age distribution is influenced by the geographical area. Thus, whereas in Europe there are less than 10 transplants per year, mostly in adolescents, in North America there are over 10 transplants per year, with a higher frequency among infants [9].

Using the Lansky score in children who survive at least one year after transplantation, a very good functional status is identified, independent of the associated organic or non-organic co-morbidities [9].

The older the patient, the higher the prevalence of comorbidities. Thus, for example, age over 70 years is considered a relative contraindication, with no significant differences in post-transplant prognosis in this age group [4]. Compared to people in their sixties with a median survival of 9.8 years, people over 70 have a survival of 8.5 years. However, in the first post-transplant year, elderly recipients did not need longer or more hospitalizations. Moreover, the rejection episodes were rarer [23].

In the selection of transplant candidates, there is a unanimous consensus on which substance abuse is an absolute exclusion criterion [10]. Lately, special emphasis is placed on the therapeutic role and legalization of marijuana, making it increasingly

difficult to delimit the boundary between legal and illegal, positive and negative [12].

Immediately after transplantation, an increase in treatment non-adherence is demonstrated among the population with higher education [10]. It is assumed that this population category frequently develops behaviors dominated by tension, distrust in the therapeutic value of the heart transplant [6].

The impact of social factors on the risk of acute cardiac rejection is difficult to quantify. Globally, public health systems make every effort to encourage transplant patients to use quality health services as often as needed in order to establish and continue appropriate therapeutic and prophylactic management [10].

Frequently, tobacco exposure is associated with an increase in the incidence of acute rejection even if not immediately resumed [10].

Another factor that strongly influences the adherence / nonadherence to treatment, with a significant impact on the biological response in the first year, is marital status. In the married recipients better posttransplant outcomes with a lower incidence and prevalence of cardiac allo-graft rejection in the first six to twelve months have been demonstrated [5].

Chronic cardiac allograft rejection

Socioeconomic status, defined by education, occupation, income and place of residence, along with environmental factors - low quality housing, high crime rates, traffic noise, pollution - is a significant predictor of cardiovascular morbidity and mortality [22].

As to the chronic complications of transplantation in the pediatric population, there is a significant reduction in survival among adolescents, directly proportional to the reduction in adherence to treatment [24]. For them, biomedical applications are continuously developed and implemented to combat the challenges of adolescents in improving the ability to monitor and care after heart transplantation. Long-term outcomes depend on the coordinated approaches between transplant teams, adolescents, and their families, approaches that must anticipate the particularities of care specific to the transition from one age group to another [25]. This complex and uninterrupted process is planned taking into account both the medical aspects and psychoemotional characteristics of adolescents and young adults and their educational and sociobehavioral needs [9].

Age-based stratification of cases reported in

literature revealed that the risk of rejection, with negative impact on long-term morbidity and mortality, increases exponentially after the age of 70 [26]. Some studies have found that the reduction in 5-year survival in the elderly is comparable to that of other age groups [23]. However, according to The Canadian Cardiovascular Society, strategies related to the selection of elderly patients also require the use of other criteria such as the presence and/or severity of comorbidities [4].

Over time, the strong effect of excessive alcohol use (6%) on cardiomyopathy and coronary artery disease negatively influences the occurrence of chronic cardiac allograft rejection. Moreover, all comorbidities induced or amplified by this abusive behavior reduce the survival and quality of life of these patients [10].

The association of smoking (56% of cases) correlates with an increase in the incidence of vasculopathy, a formidable complication associated with chronic rejection. Therefore, heart transplant candidates are recommended to quit smoking for at least 6 months prior to transplantation and abstinence should be assessed in the long term given that at least 24% of former smokers relapse, depending on favorable environmental factors [10].

In view of achieving favorable clinical outcomes, hospitalization of rejection cases needs additional funding [26]. Most often, in developing countries, where the socioeconomic status is low, health insurance does not cover all medical services required by heart transplant protocols, reflected in a significant reduction in treatment compliance [22]. In this respect, both the access to specialist healthcare professionals and to immunosuppressive treatment, as well as to regular check-up visits are the decisive factors in health preservation [11].

Population studies have shown a directly proportional correlation of survival after heart transplantation with the level of education. In addition, absolute increases of 7% at 10 years were found in patients with higher education [10]. At the same time, this social factor influences patients' perception of cardiac allograft performance.

Analyzing more closely the relationship between long-term survival and chronic cardiac rejection and the marital status of the heart transplant recipient, a hypothesis emerges that marriage does not always have positive effects on the course and monitoring after cardiac allograft cardiac transplantation. In addition, marital quality and not just being married is regarded as very important by both males and females [27].

In conclusion, assessing the benefits of a heart transplant involves identifying the survival rate and the degree of quality of life improvement. These are strongly influenced by the modeling of cognitive-behavioral strategies, which approaches in a multidisciplinary manner the management of biomedical and psychosocial resources.

Individual vulnerability has a particular impact on the strategies used to help the patient to adapt to the new situation. Modulation of this vulnerability by family, demographic, social and confessional factors plays a major role in the full recovery of the patient both physically and mentally, and socio-culturally.

Awareness of the active involvement of psychosocial factors in the pathophysiology of cardiac allograft rejection will change the protocol adopted in post-cardiac transplantation clinical care. Under these conditions, high quality care relies on the most accurate and personalized quantification of these factors.

The dynamics of translational research indicates the need for the implementation of specific and standardized algorithms in monitoring and correcting the entire biopsychosocial spectrum that influences the results of cardiac allograft transplantation. Fulfilling this goal will lead to a decrease in the prevalence and incidence of the so-called "psychogenic cardiac rejection", whose profile has been incompletely defined worldwide.

Recommendations

By carefully analyzing the data reported by the studies on the management of cardiac allograft rejection published in the past five years, several study perspectives can be formulated:

1) comprehensive assessment of the risk of cardiac rejection realizing that transplant-specific surgery involves the concomitant use of an organic and emotional graft;

2) compliance with the general recommendations regarding the protocol for monitoring the viability of the transplanted organ, with the identification and ongoing follow-up of the individual conditions favoring rejection;

3) intensifying research aimed at establishing the role of biopsychosocial interdependence in quantifying the overall risk of rejection.

Conflict of interest

The authors declare that they have no conflict of interest.

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