Managing Cardiovascular Risk in the Post Solid Organ Transplant Recipient

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KEYWORDS

- Solid organ transplant Cardiovascular disease Risk factors
- Immunosuppression Survival

KEY POINTS

- Overall mortality among solid organ transplant recipients has improved owing to advances in surgical techniques and immunosuppressive therapy.
- Although short-term survival rates have improved significantly, long-term survival rates are suffering secondary to enhanced cardiovascular mortality.
- Identifying comorbidities that contribute to enhanced cardiovascular risk and modifying these risks while awaiting transplantation and after transplantation are imperative to improve long-term graft and patient survivals.

INTRODUCTION

Solid organ transplantation has become the standard of care for patients with end-stage liver, kidney, lung, and heart diseases and has significantly improved the survival and quality of life for successful recipients. A mean of 4.3 life years per solid organ transplant recipient (SOTR) are saved based on retrospective analysis of data from the United Network for Organ Sharing for solid organ transplants over a 25-year period by Rana and colleagues.[1] Despite improvements in overall graft and patient survival rates that have followed the major advances in the management of transplant recipients and improvements in cardiovascular health that follow successful transplantation, cardiovascular disease (CVD) remains the leading cause of posttransplant mortality.[2–5] The prevalence of CVD is high among kidney and liver transplant recipients compared with the general population, which has been attributed to metabolic and systemic derangements that are associated with end-stage organ disease processes and exacerbations of these processes with immunosuppression, as well as

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the added risks of infection and rejection with transplantation. CVD in SOTR can be categorized primarily into atherosclerotic heart disease/ischemic heart disease, which manifests secondary to abnormality in cardiac perfusion, disorders of cardiac function (left ventricular hypertrophy, left ventricular systolic and diastolic dysfunction), which typically present as congestive heart failure and cardiac arrhythmias. Despite the high prevalence and mortality associated with CVD in SOTRs, there is limited evidence available for management of risk factors and prevention. CVD is the most frequent cause of death with functioning graft in kidney transplant recipients (KTRs) and thus the leading cause of graft loss. This review summarizes the risk factors contributing to cardiovascular mortality and therapeutic strategies to address these risk factors in SOTRs. In this review, we discuss CVD risk factors in KTRs that can then be extrapolated to other SOTRs.

EPIDEMIOLOGY OF CARDIOVASCULAR DISEASE IN SOLID ORGAN TRANSPLANT RECIPIENTS

SOTRs are at increased risk for premature CVD and cardiovascular mortality. Although the risk of CVD improves after kidney transplantation when compared with patients with end-stage kidney disease awaiting transplantation, CVD risk remains significantly greater in KTRs when weighed against the age- and sex-matched general population.[6,7] Several variables contribute to the CVD risk in SOTRs including recipient's pretransplant disease process, traditional and nontraditional risk factors and transplant related risk factors such as exposure to immunosuppression.[8] Fig. 1 depicts the various risk factors contributing to CVD risk in SOTRs. There are also organ-related risk factors, such as pretransplant uremic cardiomyopathy and dialysis vintage in KTRs, and pulmonary hypertension (HTN) and cirrhotic cardiomyopathy[9] in liver transplant recipients. Detailed discussion of organ-specific and donor-specific cardiovascular risk factors is beyond the scope of this article.

The United States Renal Data System 2014 annual data report system revealed that mortality from CVD among KTRs is approximately twice as frequent when compared

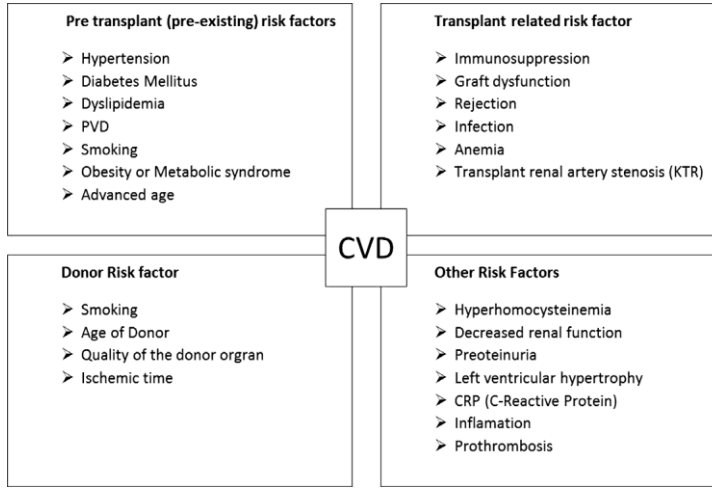

Fig. 1. Risk factors contributing to cardiovascular mortality in solid organ transplant recipients. CVD, cardiovascular disease; KTR, kidney transplant recipient; PVD, peripheral vascular disease.

with malignancy and infection.[10] Many of the end-stage organ disease patients would have been exposed to various risk factors for CVD and may have covert disease and pretransplant cardiovascular event is a strong predictor of posttransplant cardiac events.[11] Hence, the risk factor modification should begin before transplantation.

Striking rates of acute myocardial infarction were noted early after kidney transplantation by Kasiske and colleagues[12] in an observational study. Lentine and colleagues[13] concluded that approximately 11.1% of KTRs experience myocardial infarction by 3 years posttransplantation. The magnitude of CVD in SOTRs may be difficult to capture accurately owing to the significant number of nonfatal events. Congestive heart failure is associated with a poor prognosis in patients with end- stage renal disease and improvement of left ventricular systolic function after transplantation is noted in some studies. However, congestive heart failure is one of the frequent causes of hospitalization in KTRs and de novo congestive heart failure is noted to be a potent predictor of subsequent mortality in KTRs.[14]

TRADITIONAL AND NONTRADITIONAL RISK FACTORS

Conventional risk factors for coronary artery disease (CAD) include advanced age, HTN, elevated low-density lipoprotein cholesterol, low high-density lipoprotein cholesterol, diabetes mellitus (DM) and smoking,[15,16] and presence of peripheral vascular disease is considered to be CAD equivalent. Various risk factors for CAD have been identified both in the general population and SOTRs.[4,7,17,18] Many clinical and laboratory parameters have been described as predictors of CAD, but the clinical usefulness and cost effectiveness of screening to recommend their routine use is insufficient at this time. Both traditional and nontraditional risk factors are more prevalent in the transplant population compared with the general population even after adjusting for age and sex. This high prevalence of cardiovascular risk factors in SOTRs is attributed to frequent association of these risk factors in patients with end-stage organ disease along with exacerbation of preexisting systemic and metabolic conditions after transplantation owing to use of immunosuppression therapy. Some of these risk factors are modifiable with lifestyle changes and pharmacotherapy (Table 1).

Hypertension

HTN is a strong predictor of CVD in SOTRs. HTN is a risk factor for CVD and also is an independent risk for graft failure in KTRs.[19–21] HTN is associated with left ventricular hypertrophy before and after transplantation, and left ventricular hypertrophy is an independent risk factor for cardiovascular mortality.[22,23] HTN in renal transplant

Table 1
Risk factors for cardiovascular diseases

Modifiable	Nonmodifiable
HTN	Age (men >45 y and women >55 y)
Diabetes mellitus	Gender
Dyslipidemia (low HDL and high LDL cholesterol level)	Race/ethnic factors
Smoking	Family history of premature CAD (<55 y of age in male first-degree relative or <65 in female first-degree relative)
Obesity (BMI 30 kg/m^2) or the metabolic syndrome	
Elevated HDL 60 mg/dL (positive risk factor)	

Abbreviations: BMI, body mass index; CAD, coronary artery disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

recipients is defined as a blood pressure (BP) of greater than 130/80 mm Hg by Kidney Disease Improving Global Outcome (KDIGO) guidelines. HTN in SOTRs is usually multifactorial, including preexisting disease process, donor factors, and effects of immunosuppression. Exposure to immunosuppression is a major contributor to post-transplant HTN and effects are dose dependent. Steroids cause fluid retention and calcineurin inhibitors (CNIs) cause HTN through vasoconstrictive and nephrotoxic effects.

BP control in SOTRs is challenging. KDIGO guidelines recommended achieving a goal BP of less than 130/80 mm Hg regardless of proteinuria in KTRs. The Collaborative Transplant Study, an observational study, showed that achieving lower systolic BPs even within the normal ranges has incremental benefit. Patients with systolic BPs in the range of 120 mm Hg have better outcomes than the group with 130 mm Hg.[20,24] Opelz and Dohler[25] stated that approximately 55% of KTRs with HTN did not attain their goal BP in the examined group. This study also demonstrated that even delayed control of HTN as late as 3 years after the transplantation could still contribute to improved outcomes and mortality. Ambulatory BP monitoring is sug- gested to uncover HTN and assist in the management of HTN.[26] Fig. 2 summarizes the HTN evaluation and monitoring in SOTRs.

Although there are reported advantages with lower BP targets[20,24] in the past, Eighth Joint National Committee recommended a goal systolic BP of less than 140 mm Hg and diastolic BP of less than 90 mm Hg for all age patients with CKD.[27] There is insufficient evidence to assert any additional cardiovascular, cerebrovascular, or mortality benefit with lower BP targets, but lower BP (<130/80 mm Hg) goals are recommended for CKD patients with proteinuria. Goal BP in SOTRs is a topic of

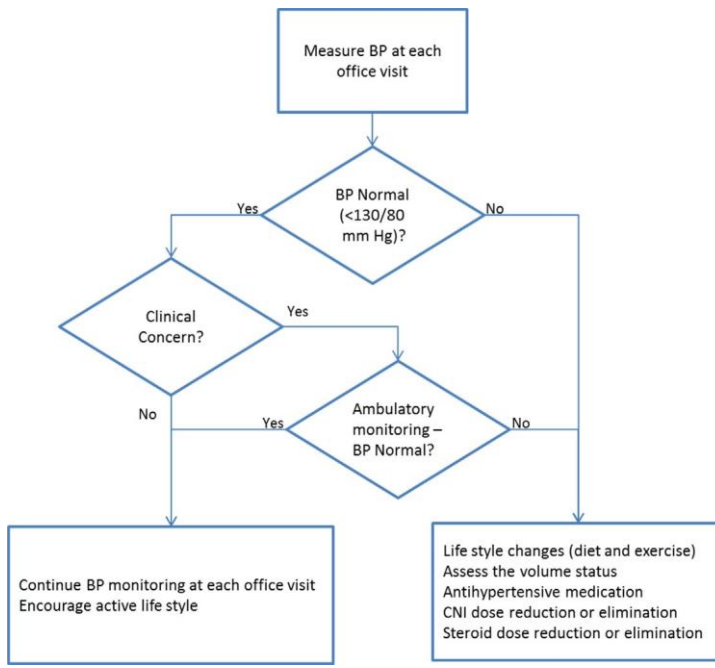

Fig. 2. Algorithm of hypertension evaluation and management in solid organ transplant recipients. BP, blood pressure; CNI, calcineurin inhibitor.