The Impact of Cardio Renal Syndrome (CRS) in Renal Transplant Recipients: A Systematic Review

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Abstract

Cardiovascular disease is a major cause of morbidity and mortality in patients with CKD. This risk is increased fivefold in renal transplant patients when compared to an age-matched population. This study aims to explore and focus on the risk factors, management, and outcomes of cardiorenal syndrome in renal transplant recipients and to estimate its deleterious effect on the heart and renal allograft, opening the door for future randomized clinical trials to look at the problem in more depth. The current literature has little information and data on the impact of cardiorenal syndrome on the renal allograft and heart regardless of the specific type of cardiorenal syndrome. Renal transplant recipients can develop any one of the five types of the cardiorenal syndrome because of having both conventional and established risk factors for developing CRS. These risk factors particularly the established ones or best described as non-traditional risk factors such as immunosuppressive medications, acute renal allograft rejection, suboptimal renal allograft function, anemia, infections, proteinuria, and hyperparathyroidism are usually neglected after renal transplantation. Although the prevalence of CRS is low among renal transplant recipients, we believe that is due to under diagnosis and lack of clinical trials leading to a knowledge gap in this subject area.

Methodology: The present study conducted a systematic literature review and selected four Clinical trials of CRS in renal transplant recipients for datasets analysis to gain more knowledge about the risk factors contributing to CRS in renal transplant recipients and to produce a strategy to prevent CRS and manage such patients better.

Results: This systematic review of the current literature revealed that the presence of non-traditional risk factors post-renal transplantation when combined with traditional risk factors can significantly increase the risk of developing CRS where the prognosis is almost always poor in such patients. The study also showed no difference in the preventive measures and management of CRS between renal transplant recipients and non-renal transplant recipients.

Conclusion: Renal transplant recipients are at increased risk of developing CRS with poor outcomes compared to non-renal transplant recipients because of the additional non-traditional risk factors post-renal transplantation. However, the preventive measures and management of CRS in renal transplant recipients are similar to those used for the general population but more attention should be paid to the correction of non-traditional risk factors.

Keywords: Renal transplantation, Cardio renal syndrome, Systematic review, risk factors, Management options, potential outcomes, Clinical trials

Introduction

Patients with end-stage renal disease (ESRD) can have a significant reduction in individual life expectancy because of the high risks of CVD and other associated complications with either dialysis or renal transplantation. The life expectancy for an ESRD patient on dialysis is around five to ten years, though several patients may

survive for thirty years. Patients who undergo renal transplantation from a living donor may survive around fifteen to twenty years. Renal transplantation from deceased donors may last from fifteen to ten years before requiring to be replaced. Thus, ESRD can result in high social and hospital treatment costs. Patients diagnosed with ESRD are listed in the renal registries of their countries and although the data from these registries enables important observations on the health of the ESRD patients, the accuracy of the data is very variable when compared between countries. The international comparisons of data on patients with ESRD and the different modalities of renal replacement therapy may not, therefore, be valid because of the differences in acceptance of the treatment options, patient demographics, socioeconomic burdens, and national health care policy. Renal transplantation is considered a breakthrough of modern medicine and the best modality of renal replacement therapy which can provide years of good quality life to patients with end-stage renal failure worldwide. The limitations of access to renal transplantation are still a burden across the globe, particularly in developing countries, and patients with ESRD can remain on dialysis for an average period of 3 to 5 years or even longer. Patients on chronic maintenance dialysis waiting for a renal transplant are exposed to serious cardiovascular complications including heart failure in 20 to 30% of patients. There are high-quality cohort studies that have looked at the subject of cardiovascular disease in renal transplant recipients, but none have evaluated the incidence, risk factors, and prognosis of chronic heart failure in renal transplants (Ducloux D).

This systematic review focuses specifically on the cardiorenal syndrome among renal transplant recipients. Cardiorenal syndrome (CRS) was first described by the Working Group of the National Heart, Lung, and Blood Institute in 2004 which described CRS as the result of interactions between the kidneys and other circulatory compartments that increase circulating volume and worsens the symptoms of cardiac failure and disease progression. Since then, the term CRS was used without an accepted definition until a new classification of two major groups, cardiorenal and reno-cardiac syndromes, based on the initial disease process was presented by Ronco[1] This was further subdivided into five subtypes of CRS to reflect the pathophysiology, timeframe, and nature of the cardiac and renal impairment.

We believe that renal transplant recipients are at high risk of developing almost any type of CRS because of having two categories of risk factors which will be discussed later in detail.

1. Traditional risk factors such as age, hypertension, diabetes, dyslipidemia, smoking, anemia, and obesity.

2. Non-traditional risk factors such as history of heart failure with impaired left ventricular ejection fraction, prior myocardial infarction, elevated cardiac troponins, inadequate renal allograft function, chronic kidney disease, episodes of acute rejection, immunosuppressive medications, proteinuria, left ventricular hypertrophy, etc.

These factors can contribute to a reduction in glomerular filtration rate (GFR) in renal transplant recipients with heart failure. The major mechanisms that have been identified include neurohumoral adaptations, reduced renal perfusion, increased renal venous pressure, and right ventricular dysfunction. The risk of cardiovascular disease is significantly high reaching fivefold among renal transplant recipients when compared to the age-matched population. This study aims to explore and focus on the risk factors, management, and outcomes of cardiorenal syndrome in renal transplant recipients and to estimate its deleterious effect on the heart and renal allograft, opening the door for future randomized clinical trials to look at the problem in more depth. The current literature has little information and data on the impact of cardiorenal syndrome on the renal allograft and heart regardless of the specific type of cardiorenal syndrome. Renal transplant recipients can develop any one of the five types of the cardiorenal syndrome because of having bothtraditional and established non-traditional risk factors for developing CRS.

These risk factors particularly the established ones such as immunosuppressive medications, acute renal allograft rejection, suboptimal renal allograft function, anemia post renal transplantation, infections, proteinuria, hyperparathyroidism, and high flow AVFs are usually neglected after renal transplantation. Although the prevalence of CRS is low among renal transplant recipients, we believe that is due to underdiagnosis and lack of clinical trials which led to a knowledge gap in this subject area.

Methodology

The literature was thoroughly searched for the risk factors, management, and outcomes of CRS in renal transplant recipients. A literature search had been performed using Cochrane Library, PubMed, Google Scholar, and other trusted databases as well as the grey literature from 2005 to 2020 using keywords such as CRS, renal transplantation, heart failure diuretics, ultra filtration, hemodialysis, and peritoneal dialysis. Publications including renal transplant recipients with CRS in adult patients 18-year-old and above were selected.

Studies had been assessed according to the following:

- The population of interest is renal transplant recipients with CRS.

- The presence or absence of a comparator will not be used to determine study inclusion.

- The primary outcomes include:

- Identifying the potential risk factors for developing CRS in renal transplant recipients.

- The survival and mortality rate

- The secondary outcomes include:

- Management options

- Barriers and facilitators to diagnose and manage CRS in renal transplant recipients.

- Eligibility criteria:

- All study types about CRS in renal transplant recipients in the English language set in high-income, middle income, or low-income countries were included.

- Renal transplant recipients 18-year-old and above.

- Exclusion criteria

- Publications including patients with heart transplantation and Publications including patients with combined heart and renal transplantation.

Study Selection

The literature search included randomized controlled trials, prospective observational studies, retrospective observational studies, case series, and case reports. Studies with no renal transplant recipients, combined renal and heart transplant, renal transplant recipients with heart transplantation, review articles, and non-English publications were not selected as shown in Figure 2.

Literature Review

The prevalence of moderate to severe renal dysfunction is estimated to be around 30 to 60 percent in patients with cardiac failure (Smith GL). A systematic review of sixteen studies of more than 80,000 hospitalized and non-hospitalized patients with cardiac failure, moderate to severe renal dysfunction defined by the levels of serum creatinine and cystatin C was positive in 29 percent of patients (Smith GL). Database data from the acute decompensated heart failure national registry revealed that 30 percent of 100000 hospitalized patients with cardiac failure had a diagnosis of chronic renal disease (Heywood JT). To further understand the context of CRS and renal transplantation, one must understand the concept of CRS in non-renal transplant recipients. Therefore, the first part of this section is devoted to CRS in the general population and the second part is devoted to the systematic review results of CRS in renal transplant recipients.

CRS in non-renal transplant recipients

Several conventional risk factors contribute to the pathogenesis of CRS. These risk factors and outcomes are nicely described in a cross-sectional study made by (Maria Prothasis). The most common risk factors include hypertension, ischemic heart disease, and anemia. In addition, there are other risk factors associated with poor

outcomes (mortality) such as age more than sixty, high BMI, smoking, alcohol, dyslipidemia, diabetes mellitus, sepsis, chronic kidney disease (CKD), and cerebrovascular disease. Patients with different types of CRS were treated by either hemodialysis or conservative management but unfortunately, the mortality rate was high, only fifty-two patients out of 96 (54.16%) survived and went home in a stable condition whereas 44 patients died (45.83%). Thus, we can conclude from this study that the poor outcomes are significantly high in the CRS patients regardless of the type of CRS and modality of treatment used.

Diagnosis of the CRS is not always straightforward because the levels of serum creatinine used to evaluate GFR can sometimes be misleading particularly in patients who have a reduction in muscle mass and as a result in creatinine production, this condition is frequently seen in older and sick patients. Therefore, even if the serum creatinine is normal the GFR can be significantly low in such category of patients. When diagnosing CRS special attention should be paid to the differentiation between underlying renal disease and renal dysfunction due to the CRS. Some patients may have both underlying chronic kidney disease and CRS which can make it harder to distinguish between both conditions.

The prognosis of CRS depends significantly on the underlying cause. However, the baseline GFR is a strong indicator and a valuable predictor of mortality in the setting of either acute or chronic cardiac failure but as we explained earlier the levels of serum creatinine may not reflect the actual GFR. Thus, Serum cystatin C may be a better marker of GFR than serum creatinine particularly in patients with reduced muscle mass because cystatin C production is not influenced by muscle mass. In the systematic review of (Smith GL) where they looked at the outcomes of CRS in eighty thousand patients from 16 studies, they found that the mortality rate in patients with mild, moderate, and severe impaired renal function as manifested by reductions in eGFR was reaching 51% compared to 24% in patients with apparently normal GFR. The conclusion of this systematic review was the mortality had increased by 15% for every 10 mL/min reduction in eGFR showing a strong correlation between the baseline GFR and poor prognosis in patients admitted into hospital with cardiac failure.

Another report in the literature of 2680 patients with chronic cardiac failure that were followed up for three years by (Hillege HL) in the CHARM program to retest the hypothesis that the renal function can be used as a predictor of outcomes in patients with cardiac failure. This study demonstrated clearly when the baseline eGFR was below 75ml/min all-cause mortality raised dramatically. This study was of great significance because the effects took place when the eGFR is low regardless of the left ventricular ejection fraction. Another important prognostic study performed by (George LK) evaluated the poor renal outcomes in patients with a normal

renal function who had been diagnosed with cardiac failure. This study included 3,570,865 United States veterans and demonstrated a strong correlation between cardiac failure and a rapid decline of eGFR concluding that patients with cardiac failure have a significantly higher risk for developing incident chronic renal impairment and mortality compared to patients without cardiac failure.

Management options of CRS in the general population

Management of cardiorenal syndrome is based on the improvement of cardiac function because this is directly correlated with improvement in renal function particularly in patients with cardiorenal syndrome type one and two (CRS l and CRS ll). This statement was evidenced by a study of 4719 patients who had their cardiac function improved with continuous flow left ventricular assist devices (LVADs) throughout two years of follow-up (Kirklin JK). Investigators in this study found that the presence of renal dysfunction before the LVAD implant is associated with high mortality after LVAD implant. Therefore, LVAD implants should be considered before progression of the renal function decline during cardiorenal syndrome.

The management of CRS can be divided into three options or strategies

1. Conservative treatment includes the use of diuretics, ACE, ARB, angiotensin receptor neprilysin inhibitor (ARNI), vasodilators, inotropic drugs, and other agents such as sodium-glucose cotransporter two inhibitors (SGLT2i) and combined use of thiazide and acetazolamide (Collins SP).

2. Ultra filtration using continuous renal replacement therapy in the acute setting when patients are hemodynamically unstable, conventional sessions of hemodialysis and peritoneal dialysis.

3. Combined management with both conservative treatment and ultra filtration.

The most common clinical presentation of CRS is symptoms of fluid overload, shortness of breath, and lower limb swelling resulting from pulmonary and peripheral edema. Therefore, the use of loop diuretics has always been the first-line treatment for the management of patients with cardiac failure in the setting of CRS. Some physicians try to avoid the use of a loop diuretic in patients with CRS because of increased blood urea and nitrogen (BUN) and creatinine but this decision is not right when there is clear clinical evidence of fluid overload or congestion. It is well known from the medical practice that the administration of loop diuretics to patients with CRS can effectively induce diuresis and relieve the symptoms of fluid overload in several patients but the effects on the renal function are various. No one can predict the effects of loop diuretics on renal function (glomerular filtration rate) but there are three effects, each one of which can take place when a loop diuretic is given.

- Loop diuretics can decrease cardiac filling pressure and lower cardiac output. This mechanism can cause a decline in renal perfusion and hence some patients may have a significant rise in serum creatinine levels.

- When the cardiac output is well maintained, there will be no change in serum creatinine levels.

- Loop diuretics can decrease renal venous pressure, intraabdominal pressure, and right ventricular dilatation. These mechanisms can reduce serum creatinine levels in some patients.

It is essential to mention that patients with CRS due to decompensated cardiac failure may significantly benefit from aggressive fluid removal induced by a loop diuretic, even if at the expense of associated mild to moderate renal dysfunction. The current data support the strategy of aggressive fluid removal. The evaluation study of congestive cardiac failure and pulmonary artery catheterization effectiveness by Testani JM.[2]

The study evaluated 336 patients diagnosed with decompensated cardiac failure and examined the correlation between hemoconcentration induced by aggressive fluid removal, renal function, and mortality. Authors found that aggressive fluid removal can improve survival but is associated with deterioration of kidney function.

Renin angiotensin antagonists

The group of medications includes angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and angiotensin receptor neprilysin inhibitor (ARNI). Based on the current literature these are the currently used medications for the management of patients with cardiac failure and reduced ejection fraction. The use of such medications can improve symptoms associated with heart failure, reduce recurrent hospitalization with symptoms of cardiac insufficiency and reduce mortality. It is important to note that data from the current literature have focused mainly on the use of these medications in patients with cardiac failure without paying attention to cardiorenal syndrome. However, subgroup analysis of patients with renal dysfunction performed by (Anand IS, Eschalier R, Lesogor A) revealed that the use of RASS blocking agents is beneficial when used in patients with cardiac failure with reduced ejection fraction and chronic kidney disease (CKD) but with a higher risk of developing hyperkalemia and deterioration of renal function when compared to patients without CKD. Therefore, the 2013 ACCF/AHA guideline highly recommended keeping a close eye on the serum potassium and creatinine levels of patients with CRS.[3] Sacubitril/valsartan (ARNI) has similar clinical benefits to enalapril (ACEi) on cardiac failure mortality and hospitalization but has a slower rate of decline in renal function.[4]

Vasodilators

To evaluate the effects of vasodilators on the CRS a total of one hundred thousand patients with acute decompensated cardiac failure and deteriorating renal function were studied by (Costanzo MR). The data for this study were obtained from the database of the national registry of acute decompensated cardiac failure. The clinical trial revealed that the use of combined intravenous diuretics and vasodilators such as nitroglycerin is associated with worsening of the renal function compared to using intravenous diuretics alone, but this can just be a casual effect and not reflect the real scenario when combined therapy is required for management of patients with severe cardiac failure.

Inotropic agents

These agents include drugs such as dopamine, dobutamine, and milrinone. Their use is confined to patients with cardiogenic shock due to acute decompensated cardiac failure. It has been thought in the past that inotropic agents such as dopamine can improve renal function in patients with heart failure by decreasing renal venous pressure and increasing renal blood flow. However, little data are supporting this beneficial effect. Studies performed by (Ungar A and Elkayam U) showed the role of dopamine in improving renal function in a patient with decompensated cardiac failure, particularly when given at doses of 2 to 10mcg/kg/min by increasing the cardiac output and dilating the renal blood vessels. The clinical evidence of the benefits of using dopamine to improve renal function in the setting of decompensated heart failure has not been established because the loss of renal vasodilating adaptive mechanisms induced by severe decompensated cardiac failure is beyond the renal effects of dopamine. The combined use of a loop diuretic (furosemide) and dopamine was studied by (Giamouzis G). This study involved a total of sixty patients with decompensated cardiac failure, the use of furosemide 5mg/h continuous infusion combined with dopamine 5mcg/kg/min was compared with using a high dose of furosemide alone (20mg/h). The urine output was similar in both groups, but the risk of worsening renal function was reduced in the combined (furosemide and dopamine) group. When dopamine is combined with furosemide but at a lower dose (2mcg/kg/min), the improvement in renal function was not seen as demonstrated in the renal optimization strategies evaluation study by (CM Bonita RE).

Ultra filtration using renal replacement therapy

Ultra filtration is defined as the removal of excess fluid in patients with acute decompensated cardiac failure who do not respond to conservative treatment with diuretics (diuretic resistance) or those with advanced renal impairment. Three important randomized studies evaluated ultra filtration versus intravenous diuretics in patients with acute decompensated congestive cardiac failure and cardiorenal syndrome. These important randomized trials were performed by (Bart BA) (RAPID-CHF), (Costanzo MR) (Unload Trial) and Bart BA[3] (CARRESS-HF). The RAPID-HF was a controlled randomized study of forty patients admitted into hospital with volume overload secondary to chronic congestive cardiac failure, twenty patients were managed by a single session of ultra filtration of 8 hours duration and twenty patients were managed conservatively. This study proved that the early use of ultra filtration in patients with pulmonary edema secondary to chronic congestive cardiac failure is safe, effective, and well-tolerated. Then came the ULOAD trial in 2007 to retest the same hypothesis (safety and efficacy of ultra filtration) of the previous study. The UNLOAD trial was also a randomized study that evaluated the safety and effectiveness of ultra filtration by randomizing overloaded patients to either ultra filtration or intravenous loop diuretics. The results of the ULOAD trial were consistent with RAPID-HF in terms of efficacy and safety, it also added new knowledge to the literature that early ultra filtration can result in greater fluid loss without jeopardizing the renal function. In addition, early ultra filtration can significantly reduce hospital stay, rehospitalization rate, and unscheduled outpatient clinic visits at 90-day follow-up.

The third randomized trial was a study of great significance because it was devoted to patients with the cardiorenal syndrome (CARRESS-HF). This study compared the effect of ultra filtration with conservative stepped pharmacologic management. The stepped pharmacologic management is based on achieving a target urine output of 3 to 5 liters per day using the following guiding points:

- If the urine output target (3-5L/day) is not reached, use intravenous loop diuretics.

- If the urine output target is still not achieved, add metolazone up to 5 mg twice per day.

- If there is right ventricular systolic failure or EF less than 40% and systolic blood pressure is less than 110mm Hg, add dopamine or dobutamine or add nitroglycerin if systolic blood pressure is more than 120mm Hg regardless of EF%.

- If the urine output is still not achieved, consider adding a left ventricular assist device (LVAD).

- The ultimate step is dialysis or ultra filtration.

- The results of this study showed that managing CRS patients with a stepped pharmacologic therapy strategy was superior to management with ultra filtration for avoiding adverse effects on renal function at 96 hours. The amount of fluid removal was almost the same in both strategies. However, the ACC/AHA recommends the use of ultra filtration in patients with

refractory pulmonary edema not responding to conservative management (diuretics). Level of evidence B.

Investigational therapeutic strategies

These two classes of medications have been investigated in the management of patients with cardiorenal syndrome due to decompensated congestive cardiac failure but unfortunately with no beneficial effects on renal function. These two classes include vasopressin receptors antagonists (tolvaptan) and adenosine A1 receptors antagonists (rolofylline). A randomized controlled trial was performed by Konstam MA[5] evaluated the management of patients with deteriorating cardiac failure by using oral tolvaptan but failed to show any beneficial effects on long-term mortality and renal function. It was believed that adenosine acting on adenosine A1 receptors can decrease renal function by constricting the afferent glomerular arteriole and hence the use of adenosine A1 receptors antagonists can reverse this effect and improve renal function by increasing GFR and improved diuresis (Vallon V) and (Dohadwala MM). To test this hypothesis a multicenter double-blind placebo-controlled study evaluating the management of patients with acute decompensated congestive cardiac failure by using rolofylline was performed by (Massie BM), results showed no clinical benefits.

The use of erythropoiesis-stimulating drugs

It was found that there is no clinical benefit of increasing hemoglobin from 9g/dl to 13g/dl in patients with cardiac failure. However, it is recommended to follow the current KDIGO guidelines for the management of anemia in CKD patients.

Hypertonic saline with diuretics

It was hypothesized that using hypertonic saline with diuresis in non-oliguric patients with congestive cardiac failure can stimulate renal sodium extraction and improve renal function. This strategy is not routinely recommended because there are no confirmatory data.

The role of salt restriction

Further research is required to identify to the role of salt restriction in the management of CRS and acute decompensated cardiac failure.

Future strategies in the management of CRS

The current literature and guidelines have little information on how to use diuretics optimally in the management of congestive heart failure and CRS. Fortunately, several ongoing studies are attempting to address this issue. A large-scale randomized trial is evaluating the use of furosemide versus torsemide in decreasing all-cause mortality in patients with decompensated cardiac failure.

There is a pressing need for finding new techniques to assess volume status in patients with CRS because the correlation between clinical examination and clinical outcomes is weak.

CRS in renal transplant recipients (selected studies characteristics)

The current literature has been searched thoroughly to look for publications related to this topic but unfortunately, the data were scarce. After the application of the inclusion and exclusion criteria, four publications were included to be studied, analyzed, and discussed.

The first publication was a retro-prospective observational study conducted by Nikolina Basic.[6] Although the study was a retrospective and observational study but can be considered of great significance because it added knowledge to the current literature about the relevant topic. They evaluated the medical records of all renal transplant recipients over 20 years between 1999 to 2019. A total number of 1610 patients who received renal transplantation in this period were studied thoroughly to detect patients who developed CRS based on renal dysfunction and heart failure. Surprisingly, the prevalence of CRS among the studied population was not high as only nine patients were identified to have CRS out of 1610 renal transplant recipients (0.56%). The mean age of patients, gender, type of heart failure, modality of treatment used, and outcome are shown in Table 1. The main clinical presentation of patients obtained from the medical charts included shortness of breath and lower limb swelling. The management of patients involved different modalities of treatment to achieve ultra filtration (UF), hemodialysis, continuous renal replacement therapy in the form of CVVH (continuous venovenous hemofiltration) as shown in Table 1. The median basal GFR of all patients was 37ml/min which was declined at hospitalization to 24ml/min. all patients received diuretics to induce and relieve their symptoms, but five patients were resistant to diuretics and required hemodialysis to achieve ultra filtration and remove the fluid. Although the prevalence of CRS was low (0.5%), but the outcome was poor particularly in patients with heart failure and reduced ejection fraction where one died and two remained dialysis-dependent and lost their renal grafts. The overall mortality of CRS-diagnosed patients was 22%.

The second publication was a case series performed by Samarendra.[7] This study is unique because it shed light on a neglected area in the relevant topic of this systematic review, though in general, the level of evidence is low in case series studies. The authors of this work evaluated thirteen renal transplant recipients with a syndrome of high flow functioning AVF which was defined as having a functioning AVF with a flow rate of more than 2L/min post-renal transplantation. Patients in this study were extensively investigat-

ed by echocardiogram, right heart catheterization, cardiac MRI, and renal graft ultrasound. Patients presented clinically with shortness of breath, lower limb swelling, and renal allograft dysfunction 3-8 months post-renal transplantation. Lack of adequate response to conservative management with diuretics and ruling out of renal graft rejection led to the belief that ligation and partial closure of functioning AVF can be a potential meaningful change. AVF with a high flow rate can divert blood to a low resistance venous circuit reducing the systemic vascular resistance and causes arterial hypovolemia. This results in stimulation of the renin-angiotensin system and the sympathetic nervous system leading eventually to volume overload increased renal venous pressure, and the resul-

tant declined GFR and renal function. However, this is not the only mechanism that a high flow AVF can impact the function. A high flow AVF can also increase venous return to the right heart leading to increased right atrium pressure, right ventricular pressure, right atrium dilatation, right ventricular dilatation, high right ventricular output, raised pulmonary pressure, and increased renal venous pressure. The results of this pathway are declined renal function and high output heart failure (CRS type V). Patients who underwent ligation and partial closure of high flow functioning AVFs (more than 2l/min) had their symptoms completely resolved and the overall prognosis was good as shown in Figure 1 and Table 3.

Table 1: The overall results from the selected four studies are analyzed in the following.

Study design	No patients with CRS	M/F	Age (Mean)	HFpEF/HFrEF	Treatment	Renal graft loss	Mortality
Nikolina Basik Retrospective study (1) 2009 to 2019	9	7/2	71.8	4/5	3 Dialysis. 4 diuretics 2 CVVH	2 cases became dialysis-dependent and 2 cases died	7 survived/ 2 died
Samarendra[7] Case series (2) 2018	13	N/A	60	13 HFpEF due to functioning AVF	AVF ligation Diuretics	4 cases (Became dialysis-dependent)	8 recovered. 4 on dialysis 1 died.
Johannes Waiser Retrospective study (3) 2006 to 2011	7	N/A	61	2/5	Intermittent ultrafiltration. Diuretics. ACE/ARBs. Beta-blockers. Spironolactone	7 cases	1 survived/6 died
E hyrniewiecks A case report	1	M	44	HFrEF	Hemodialysis Diuretics AVR	No	Recovered

HFpEF: Heart Failure with Preserved Ejection Fraction; HFrEF: Heart Failure with Reduced Ejection Fraction; AVF: Arteriovenous Fistula; AVR: Aortic Valve Replacement

Type	Name	Mechanism	Clinical Conditions
I	Acute Cardiorenal Syndrome	Abrupt worsening of kidney function leading to Acute Kidney Injury (AKI)	Acute cardiogenic shock and acutely decompensated heart failure
II	Chronic Cardiorenal Syndrome	Chronic abnormalities in cardiac function causing progressive & potentially permanent kidney disease	Chronic congestive heart failure
III	Acute Renocardiac Syndrome	Abrupt worsening of kidney function causing acute cardiac disorder	Acute kidney ischemia & glomerulonephritis
IV	Chronic Renocardiac Syndrome	Chronic kidney disease causing cardiac dysfunction	Chronic kidney disease leading to heart failure
V	Secondary Cardiorenal Syndrome	Systemic condition causing both cardiac and renal dysfunction	Diabetes; Sepsis

Figure 1: Demonstrates the five types of CRS (Bataclan).

Table 2: Time from transplantation.

Studies included	CRS type	Time from transplantation
Study 1	4 cases CRS l 5 cases CRS ll	11 years (median)
Study 2	13 cases CRS V	3-8 months
Study 3	6 cases CRS ll 1 case CRS l	25 months (median)
Study 4	1 case CRS 1	6 years

CRS: Cardiorenal Syndrome

Table 3: Risk factor for CRS

Study	Risk factor for CRS	Mortality
1	HF 100% CAN 100% HTN 100%	22% (2/9 patients)
2	High flow AVF	7.6% (1/13 patients)
3	CAD 28% (2/7 patients) 71.4% PH and TR HFrEF 28% (2/7 patients) HTN 71% (5/7 patients) DM 14% (1/7 patients)	85.7% (6/7 patients)
4	HTN CKD HFrEF Sepsis	0%

CAD: Coronary Artery Disease; HTN: Hypertension; DM: Diabetes Mellitus; HF: Heart Failure; CAN: Chronic Allograft Nephropathy; PH: Pulmonary Hypertension; TR: Tricuspid Regurgitation

The third study was also a case series study performed and published by Johannes Waiser.[8] This study evaluated renal transplant recipients who had renal graft loss because of the cardiorenal syndrome (CRS) in the period between 2006 and 2011 from a single center. The authors investigated and evaluated the prevalence of CRS, the clinical picture, the underlying cause of cardiac pathogenesis, and the renal graft biopsy findings. A total number of 1137 renal transplant recipients were thoroughly investigated to identify patients with renal allograft loss cause by cardiorenal syndrome (CRS). 232 patients with renal graft loss were identified. Eighty patients out of the 323 had renal graft loss because of death. However, seven out of the 332 patients had their renal graft lost because of CRS accounting for 3% of all cases and 4.5% (7 out of 152 patients) after excluding death with function renal graft. Type l CRS was identified in one patient and CRS type ll in six patients Table 2. The median time for diagnosis of CRS post-transplantation was 25 months with a range of 3 to 73 months after renal transplantation. The renal graft survival after the diagnosis with CRS was 1 to 62 months (median, 6 months). Six patients died out of seven diagnosed with CRS (2 to 69 months) after diagnosis (median 31) and 4.5 months after renal graft loss Figure 1.

The fourth publication was a case report performed by E Hyrniewiecks.[9] This case report was a case presentation of a 44-year-old gentleman who presented with CRS and acute on top of chronic renal graft failure. This patient had the end-stage renal disease in 1994 secondary to hypertension and reflux nephropathy. The Patient had a history of bilateral nephrectomy because of severely infected hydronephrosis. After which he was maintained on regular dialysis for 6 years before he underwent renal transplantation in 1999 but no information was mentioned about the donor. Immunosuppressive medications post-renal transplantation included prednisolone, cyclosporine, and azathioprine.

In 2000 he was treated with pulses of methylprednisolone for Banff IA renal rejection and mycophenolate mofetil was given instead of azathioprine. The patient had a history of multiple infections, CMV viral infection in 2000, fungal encephalitis in 2008, and Hodgkin lymphoma lllA in 2014 (treated with eight courses of rituximab, doxorubicin, bleomycin, vinblastine, and dacarbazine). Mycophenolate mofetil was shifted to leflunomide because of resistant CMV and continued for four months from October 2014 to February 2015. In 2015 a renal graft biopsy was done and revealed chronic renal graft glomerulopathy with elements of mixed active and chronic antibody-mediated rejection. Thus, the patient had been maintained on cyclosporine 25mg two times per day and prednisolone 5mg daily without leflunomide. In the same year, the patient presented to the hospital with non-specific symptoms such

as general weakness and fever. The clinical and laboratory investigations revealed a systolic murmur of high intensity and increased level of CRP.

Severe aortic regurgitation and pulmonary hypertension were diagnosed and confirmed by echocardiography but fortunately, the ejection fraction was normal (EF 65%). The condition continued to deteriorate because of sepsis (staphylococcal), CMV reactivation, and labial herpes. The patient was clinically improved after receiving different classes of broad-spectrum antibiotics (ceftriaxone, clindamycin, vancomycin, and acyclovir) and an antifungal agent (fluconazole). After 6 months in 2015, the patient was a candidate for aortic surgery and placed on a waiting list but unfortunately while waiting for aortic valve replacement surgery, she developed severe symptoms of both right and left heart failure for which she was admitted into a specialist hospital and got diagnosed with bilateral pneumonia and infective endocarditis. The patient was given ciprofloxacin, ceftriaxone, and fluconazole. At this stage, the patient became anuric and developed acute on top of chronic renal failure, therefore hemodialysis was started, and the condition became stable after one week of management. The final diagnosis was acute on chronic CRS, cardiac failure class lV (NYHA), anemia, and CKD stage IV. Clinically the patient was dialysis-dependent and maintained on oxygen therapy for dyspnea. Other laboratory investigations showed increased white blood cells count (leukocytosis) and elevated inflammatory markers in addition to elevation of N-terminal pro-B-type natriuretic peptide. Repeated echocardiography revealed worsening of the ejection fraction from 65% to 50% and fibrosis with calcification of the aortic valve. The source of infection was not known so a computed tomography scan was performed and demonstrated pulmonary abscess. Bronchoscopy was also performed and showed a positive culture of staphylococcus which was sensitive to vancomycin only. Based on the clinical examination and the earlier mentioned findings the final diagnosis was bilateral lobar pneumonia with infected emphysematous bulla of the right lung, culture-negative infective endocarditis, severe aortic regurgitation, and decompensated biventricular cardiac failure overlapping with acute kidney injury on top of chronic kidney disease (chronic renal graft nephropathy) requiring hemodialysis. Meropenem, vancomycin, and fluconazole were given to that patient while being on regular hemodialysis. As the patient was thought to have reached ESRD, cyclosporine was stopped, and they started tapering prednisone. The infection had resolved after the antibiotic course and the patient was stable and fit to undergo aortic valve replacement surgery in December 2015. Surprisingly 15 days after the surgery renal function and diuresis started to improve dramatically and the patient became dialysis-free for 74 days postoperatively. Cyclosporine 25 mg twice per day was resumed with a small dose of prednisolone 5mg daily. Three months later the cardiac function was evaluated by echocardiography which showed improved ejection fraction (EF 62%) and for the renal function, the estimated GFR was 28ml/min (CKD stage IV). The renal function was evaluated again three years after the surgery; the estimated GFR was 22ml/min (CKD stage IV). The loss of 3 ml/min over three years is acceptable while the patient has still been maintained on cyclosporine 25mg twice daily and prednisolone 5mg daily. This case report is of great significance because it has several important educational points that will be discussed in the discussion section.

Risk of bias in each study

The quality of the two retrospective observational studies, case series, and the case report included in the systematic review was evaluated using the PRISMA checklist and the Newcastle-Ottawa scale (NOS). This tool has nine points to help to grade the risk of bias (4 points for selection of study subjects, two points for comparing between groups, and three points for establishing exposures and outcomes. Each one of these studies scored seven points. The overall risk of bias is low to medium.

Data analysis

The overall results from the selected four studies are analyzed in the following points:

• The prevalence of cardiorenal syndrome among renal transplant recipients is low, particularly in the first retrospective observational study which was performed over 10 years and evaluated a total number of 1610 renal transplant recipients. Only nine patients with CRS were identified between 2009 to 2019 (0.56 % of the studied population). The prevalence of CRS in the third retrospective study was also low as only seven out of 152 renal transplant patients were identified to have renal graft loss secondary to CRS (4.6%) as shown in Table 1. The prevalence from the second and fourth studies cannot be estimated because these studies were based on selected cases with CRS Table 1.

• The mean age for patients with CRS was highest in the first study (71.8-year-old), almost the same in the second and third studies (60- and 61-year-old respectively) and the fourth study was a case report (44-year-old). The studies identified more males than females with CRS.

• All renal transplant recipients with CRS from the first, third and fourth study shared similar risk factors such as hypertension, diabetes, coronary artery disease, chronic congestive heart failure (HFrEF and HFpEF), and chronic renal allograft nephropathy Table 3. Sepsis as a risk factor was confined to the fourth study and high outflow AVF was the main risk factor in the second study Table 3.

• Regarding types of CRS, the first and second types (CRS l and CRS ll) were the most common types in renal transplant recipients in the first, third and fourth study whereas in the third study it was CRS type V due to high flow functioning AVF Table 2.

• Management of renal transplant recipients with CRS included treatment with diuretics, ACEi/ARBs, spironolactone, beta-blockers, and in non-responding cases ultra filtration by frequent or continuous dialysis Table 1. In addition, specific surgical interventions were performed to correct the underlying cause of CRS such as high flow AVFs ligation in the second study and aortic valve replacement in the fourth study Table 1.

• The overall mortality among renal transplant recipients with CRS is high (30%), renal graft loss (36%), and 13% of patients remained dialysis dependent.

Figure 2: Demonstrates the study flow diagram.
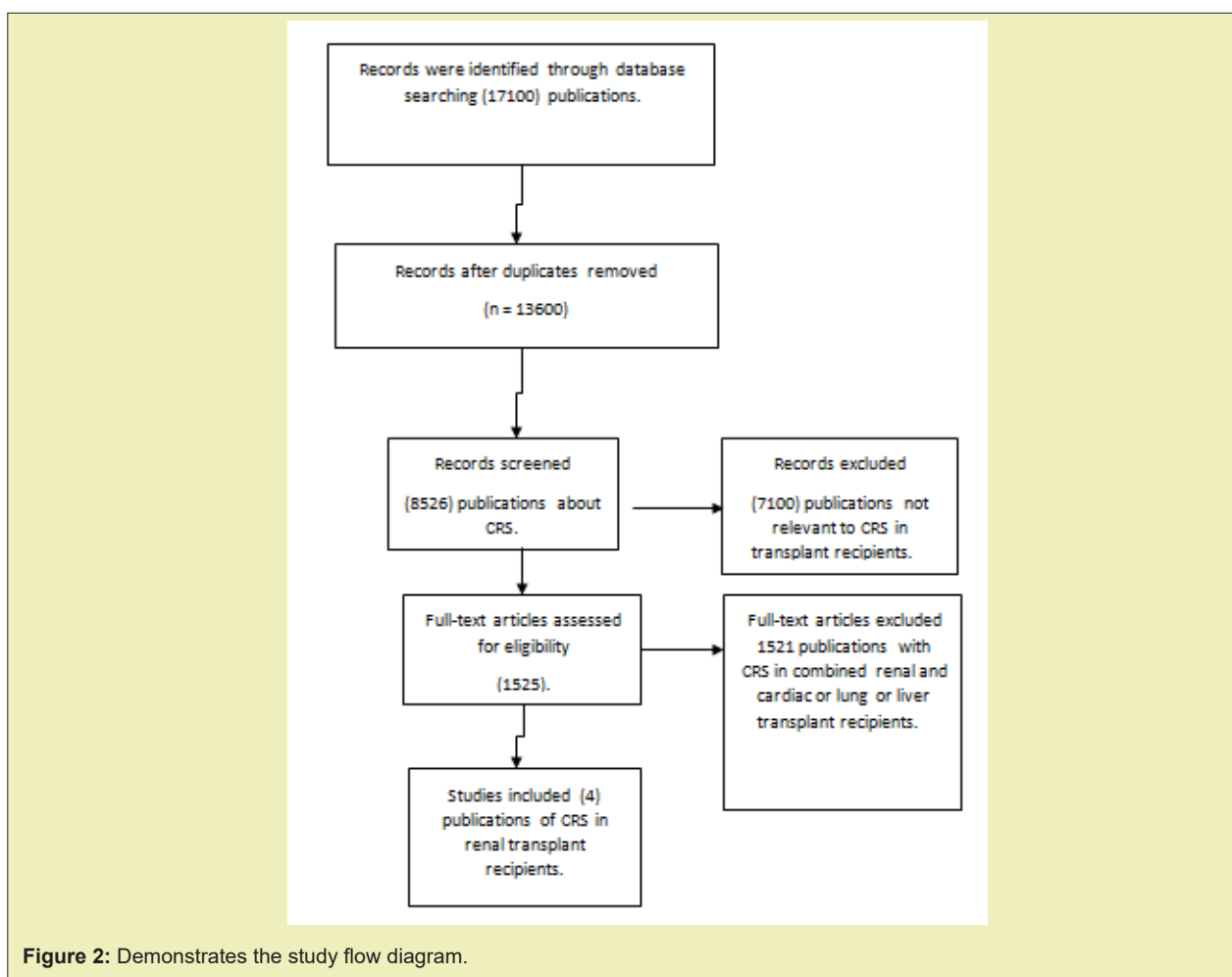
Discussion

The pathogenesis of increasing levels of serum creatinine in patients with acute cardiac failure and aggressive diuresis is still not clear. However, it is believed that the major key players in the pathogenesis of the CRS are neurohumoral adaptations (reduced stroke volume and cardiac output, arterial underfilling, increased atrial pressures, and venous congestion), reduced renal perfusion, rising renal venous pressure, and right ventricular impairment. Renal impairment may also be seen in patients with cardiac failure with preserved ejection fraction as well as with decreased ejection fraction (Eur J). Endothelial dysfunction and a pro-inflammatory condition are the main triggers of cardiorenal interactions. One study looked at 104 hospitalized patients with acute decompensated cardiac failure who developed renal impairment within 72 hours of hospitalization[10] and found that those who developed impaired renal function had markedly declined RV function and increased right ventricular free wall thickness. However, these are just associations and may not prove causality between renal dysfunction and right ventricular dysfunction.

The results from the four studies in the systematic review have shed light on the prevalence and types of CRS among renal transplant recipients, contributing risk factors, outcomes, and management approach. The retrospective observational studies performed by Nikolina Basik[6] and waiser[8] were extremely essential in the syn-

thesis of evidence for the systematic review. There are no specific data on the prevalence of CRS in the general population, but we know from the current literature that more cases with CRS will be seen in the future because of an increased incidence of acute and chronic cardiovascular pathologies worldwide.[11] The prevalence of CRS among renal transplant recipients from both retrospective studies was less than 5%, probably due to under diagnosis. Both studies shared common traditional risk factors, namely hypertension, diabetes mellitus, coronary artery disease, and chronic heart failure. Unfortunately, variables that represent non-traditional or established risk factors post-renal transplantation such as hyperparathyroidism, anemia, proteinuria, previous episodes of AKI, types of immunosuppressive medications used, left ventricular hypertrophy and acute rejection episodes were not included in patients' characteristics. However, both studies shared a common non-traditional risk factor which was chronic renal graft nephropathy. In both retrospective studies, the prevalent types of CRS were type one and type two Table 2. Management of patients focused on the typical use of diuretics, ACEi/ARBs, beta-blockers, hemodialysis, intermittent ultra filtration, and CVVH, though no details of how each patient was approached. The prognosis in the two retrospective studies in terms of survival and renal graft survival was poor. The mortality rate was 22% in the first study[6] and 85.7% in the third study[8] among renal transplant recipients diagnosed with CRS. The second study in the systematic review was a study of case series[7] that evaluated a specific and neglected cause of CRS in renal transplant recipients which is the presence of a high flow functioning AVF post-renal transplantation. This study revealed the role of a high flow AVF (more than 2L/min) post-renal transplantation in the early development of CRS 3 to 8 months Table 2 by the mechanisms explained earlier. Complete or partial closure of high flow AVFs in the studied cases had led to significant clinical improvement and resolved CRS in 8 patients, 4 patients remained on dialysis (renal graft loss) because of other added etiologies of pulmonary hypertension and one patient died because of lung cancer. The role of high flow AVFs post-renal transplantation was demonstrated in this study and proved by evidence using echocardiography techniques and cardiac catheterization before and after the procedure. This type of CRS should not be regarded as CRS type V but a separate type of CRS in renal transplant recipients because when managed early the prognosis is excellent. Therefore, high flow AVFs should be closed earlier in patients with an elevated risk of CVD. However, because there is no consensus and clear guidelines till the present time on how to deal with high flow AVFs, future randomized studies are needed to further explore the optimal way of prevention and management of the CRS secondary to a high flow functioning AVF. The last study was a case report about a renal transplant recipient who had several traditional and non-traditional risk factors for developing CRS such as hypertension, chronic renal graft nephrop-

athy, immunosuppressive medications, heart failure with reduced ejection fraction, recurrent infections, and sepsis. As a result of these complications and a sequence of events described earlier this patient developed CRS type 1 secondary to severe aortic valve regurgitation and was maintained on dialysis and considered to have complete renal graft loss and had his immunosuppressive medications stopped. However, when the aortic valve replacement surgery was performed, the renal function started to improve significantly, and dialysis was stopped with the resumption of immunosuppressive medications. This study showed the importance of treating the underlying causes of CRS before considering the renal graft is completely lost. Although this systematic review has excluded CRS in patients with either heart transplantation or combined renal and heart transplantation, it is essential to mention that this group of patients are at increased risk of CRS. CRS types two and three can develop after heart transplantation due to acute and chronic renal impairment caused by calcineurin inhibitors nephrotoxicity. Several strategies had been utilized in the past to decrease the risk of CRS post-heart transplantation such as minimization or avoidance of calcineurin inhibitors, but none proved to be effective.

However other preventive measures including alternative immunosuppressive agents such as rapamycin inhibitors (sirolimus or everolimus) or mycophenolate and the use of antithymocyte globulin as an induction agent are still under investigation (Daniel R). The diagnosis of CRS before heart transplantation is correlated with increased risk of renal function decline and progression to CKD.[12] Therefore, patients with CRS before cardiac transplantation need regular follow-up and aggressive management of both traditional and non-traditional risk factors.

The overall results from the selected studies in terms of risk factors, outcomes, and management can be explained in the following points:

• The most common traditional risk factors which were almost shared by all patients in the selected studies were hypertension followed by chronic heart failure, acute heart failure, CAD, DM, and sepsis. Unfortunately, the confounders for non-traditional or established risk factors post-renal transplantation such as hyperparathyroidism, anemia, duration on dialysis before renal transplantation, types of immunosuppressive medications used, proteinuria, lipids profile, and history of previous episodes of renal graft rejections were not taken into consideration. However, the results showed non-traditional risk factors such as chronic renal allograft nephropathy and high flow AVFs can play a significant role in the development of CRS in renal transplant recipients Table 3.

• There are no current guidelines for the management of CRS in renal transplant recipients, thus the same recommendations for non-renal transplant patients are applied. The selected studies

demonstrated that patients received diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and ultra filtration through hemodialysis. Definitive treatments to correct the underlying cause of CRS were delivered in the second and fourth studies with the closure of high flow AVFs and AVR respectively Table 1.

• The overall prognosis in terms of renal graft loss and mortality was generally poor and consistent with the current literature data about CRS in non-renal transplant recipients, particularly in patients with CRS l and ll. We expect the length of hospital stay, re-hospitalization, and cost to be higher among renal transplant recipients, though these variables were not included in the studies. The prognosis of type V CRS in renal transplant patients caused by a high flow functioning AVF can be favorable if managed by AVF closure once diagnosed or can even be prevented by early closure post-renal transplantation.

Review limitations

The present systematic review has several limitations because it included retrospective, case series, and a case report, studies which can provide only a low level of evidence because of lack of randomization and each study has a limited number of patients. The risk of selection and information bias cannot be ruled out, particularly in retrospective studies. Thus, the final findings cannot be generalized to the entire population of renal transplant recipients with CRS.

Recommendations based on the current synthesized evidence

Based on the knowledge we obtained from the current literature review and the systematic review about CRS in renal transplant recipients the following points can be recommended to address the contributing risk factors to the development of CRS and management of such patients to have a better prognosis:

• Hypertension is a common traditional risk factor to develop CRS in renal transplant recipients and it can be present before renal transplantation or develop after renal transplantation (post-transplant hypertension). Post-transplant hypertension is defined as constantly increased blood pressure or normal blood pressure while on blood pressure-lowering agents, possibly secondary to the use of immunosuppressive medications such as cyclosporine (Zeier M), prednisolone, and tacrolimus. Unfortunately, there is no consensus of a blood pressure target post-renal transplantation; the American society of transplantation recommends blood pressure of less than 140/90mm Hg while the British renal Association recommends less than 130/80mm Hg. Until the role of hypertension is well defined in the future on the progression of CKD and CVD, post-renal transplant recipients should not have

their BP elevated more than 130/80mm Hg. Other traditional modifiable risk factors such as dyslipidemia, obesity, smoking, vitamin D deficiency, uncontrolled DM should be corrected accordingly with regular follow-ups. Special attention should be paid to non-traditional or established risk factors in renal transplant recipients such as repeated episodes of acute renal graft rejections, chronic renal graft nephropathy (CKD), drug-induced DM (tacrolimus), anemia, infections, hyperparathyroidism, and proteinuria. Repeated episodes of acute rejections can be prevented by early detection and optimization of immunosuppressive medications after renal biopsy, antimicrobial prophylaxis, and vaccinations against early and late infections post-renal transplantation can help avoid repeated episodes of AKI and progression to CKD as well as can reduce the progression of CKD in chronic renal allograft nephropathy, reduce risk of CVD and CKD by treating proteinuria, monitoring of cyclosporine level to avoid renal toxic effects, avoid nephrotoxic medications and dehydration.

• Diagnosis of the CRS can be challenging in renal transplant recipients because as mentioned earlier such patients can develop any type of the five types of CRS. CRS should be suspected in renal transplant recipients who present with unexplained acute kidney injury, unexplained accelerated progression of chronic renal allograft nephropathy, refractory pulmonary edema not responding to conservative treatment with loop diuretics, history of advanced cardiovascular disease, elevated levels of cardiac BNP, and a renal biopsy without obvious histopathological signs of rejection. It should be noted that cachectic patients with chronic cardiac failure may have misleading serum levels of creatinine and GFR, thus biomarkers such as cystatin C, KIM-1, and NGAL are not affected by patients' weight can be considered.

• The optimal management of CRS in renal transplant recipients can be extremely complex and needs further studies in the future to be defined. However, the optimal management should include early identification of renal transplant recipients with CRS to avoid delay of treatment and progression of renal function decline, optimization of anti-heart failure medications in CHF, and monitoring of response to treatment to avoid episodes of acute decompensated heart failure and renal impairment, adequate treatment of reversible underlying causes of cardiac failure (cardiac valvular disease) as well as reversible causes of renal dysfunction (renal allograft rejection and AKI) and treatment of underlying conditions causing both renal and cardiac failure such as a high flow AVF, post-renal transplant infections, and sepsis. According to the current guidelines and evidence-based medicine, the management of CRS in renal transplant recipients is not different from in non-renal transplant patients. The stepped pharmacologic therapy protocol is the cornerstone and first line in the conservative management of CRS but when patients fail to respond to it, ultra filtration through

dialysis will automatically be the second option of treatment. The current evidence regarding ultra filtration was derived from clinical trials which used only hemodialysis modalities. The role of peritoneal dialysis was not fully explored in the management of CRS. Theoretically, peritoneal dialysis can have several benefits in renal transplant recipients with CRS who require ultra filtration and failed to respond to the pharmacologic stepped therapy. These benefits include maintaining hemodynamic stability, preservation of renal residual function, no risk of line infections, and maximum anti-heart failure medications can be given once peritoneal dialysis is initiated. Several clinical trials reported the effectiveness and safety of PD in the management of acute and chronic CRS (Bourne L).

• Sodium-glucose cotransporter two inhibitors such as dapagliflozin may play a key role in the prevention of CRS in renal transplant recipients with DM or established CVD. Several studies had shown the benefits of SGLT2 inhibitors in reducing the risks of CVD, HF, hospitalization due to HF, and renal dysfunction.[13,14] However further studies are needed to explore if the same benefits can be achieved in renal transplant recipients with DM and established non-traditional risk factors for CVD.

Suggestions to improve the current CRS guidelines

A high flow functioning AVF is another unique non-traditional risk factor that has a significant role in the development of CRS post-renal transplantation over a short period (less than 6 months), though further studies are needed in the future to confirm this correlation with a high level of evidence.

However, this type of CRS should not be simply regarded as type V and can be considered as a separate entity and added to the current classification of CRS as the sixth class of CRS (high flow functioning AVF more than 2L/min causing renal and cardiac failure post-renal transplantation). Based on the current evidence the closure of high flow AVFs should be suggested before renal transplantation.

Conclusion

The prevalence and incidence of CRS among renal transplant recipients are still underestimated, though the prevalence is surprisingly low in the present systematic review. Non-traditional risk factors in renal transplant recipients combined with traditional risk factors can significantly increase the risk of developing any type of CRS. Thus, modification of both types of risk factors is essential to reduce the risk of CRS. The management of CRS in renal transplant recipients should be individualized to meet the need of each patient to treat the underlying causes particularly in patients with curable conditions such as cardiac valves replacement, acute renal allograft rejection, and adequate treatment of CHF and chronic renal graft nephropathy. High flow AVFs have a significant role in the early development of CRS post-renal transplantation and therefore should be closely monitored after renal transplantation or better be closed in patients with high risks of CVD. When the conventional therapy for cardiac failure is failed or renal transplant recipients with CRS become resistant to conservative management, PD as an option of ultra filtration may be more beneficial than other hemodialysis modalities, though more studies and randomized trials are needed in the future to confirm this hypothesis.

Conflicts of Interest

Authors declares that there is no conflicts of interest.

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