Chapter

Hepatorenal Syndrome

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Abstract

Hepatorenal Syndrome (HRS) is an important condition for clinicians to be aware of in the presence of cirrhosis. In simple terms, HRS is defined as a relative rise in creatinine and relative drop in serum glomerular filtration rate (GFR) alongside renal plasma flow (RPF) in the absence of other competing etiologies of acute kidney injury (AKI) in patients with hepatic cirrhosis. It represents the end stage complication of decompensated cirrhosis in the presence of severe portal hypertension, in the absence of prerenal azotemia, acute tubular necrosis or others. It is a diagnosis of exclusion. The recognition of HRS is of paramount importance for clinicians as it carries a high mortality rate and is an indication for transplantation. Recent advances in understanding the pathophysiology of the disease improved treatment approaches, but the overall prognosis remains poor, with Type I HRS having an average survival under 2 weeks. Generally speaking, AKI and renal failure in cirrhotic patients carry a very high mortality rate, with up to 60% mortality rate for patients with renal failure and cirrhosis and 86.6% of overall mortality rates of patients admitted to the intensive care unit. Of the various etiologies of renal failure in cirrhosis, HRS carries a poor prognosis among cirrhotic patients with acute kidney injury. HRS continues to pose a diagnostic challenge. AKI can be either pre-renal, intrarenal or postrenal. Prerenal causes include hypovolemia, infection, use of vasodilators and functional due to decreased blood flow to the kidney, intra-renal such as glomerulopathy, acute tubular necrosis and post-renal such as obstruction. Patients with cirrhosis are susceptible to developing renal impairment. HRS may be classified as Type 1 or rapidly progressive disease, and Type 2 or slowly progressive disease. There are other types of HRS, but this chapter will focus on Type 1 HRS and Type 2 HRS. HRS is considered a functional etiology of acute kidney injury as there is an apparent lack of nephrological parenchymal damage. It is one several possibilities for acute kidney injury in patients with both acute and chronic liver disease. Acute kidney injury (AKI) is one of the most severe complications that could occur with cirrhosis. Up to 50% of hospitalized patients with cirrhosis can suffer from acute kidney injury, and as mentioned earlier an AKI in the presence of cirrhosis in a hospitalized patient has been associated with nearly a 3.5-fold increase in mortality. The definition of HRS will be discussed in this chapter, but it is characterized specifically as a form of acute kidney injury that occurs in patients with advanced liver cirrhosis which results in a reduction in renal blood flow, unresponsive to fluids this occurs in the setting of portal hypertension and splanchnic vasodilation. This chapter will discuss the incidence of HRS, recognizing HRS, focusing mainly on HRS Type I and Type II, recognizing competing etiologies of renal impairment in cirrhotic patients, and the management HRS.

Keywords: Hepatorenal Syndrome, Cirrhosis, Kidney Injury

1. Introduction

Hepatorenal Syndrome (HRS) is an important condition for clinicians to be aware of in the presence of cirrhosis. In simple terms, HRS is defined as a relative rise in creatinine and relative drop in serum glomerular filtration rate (GFR) alongside renal plasma flow (RPF) in the absence of other competing etiologies of acute kidney injury (AKI) in patients with hepatic cirrhosis [1–7]. It represents the end stage complication of decompensated cirrhosis in the presence of severe portal hypertension, in the absence of prerenal azotemia, acute tubular necrosis or others. It is a diagnosis of exclusion [2]. The recognition of HRS is of paramount importance for clinicians as it carries a high mortality rate. Recent advances in understanding the pathophysiology of the disease improved treatment approaches, but the overall prognosis remains poor, with Type I HRS having an average survival under 2 weeks [3]. Generally speaking, AKI and renal failure in cirrhotic patients carry a very high mortality rate, with up to 60% mortality rate for patients with renal failure and cirrhosis and 86.6% of overall mortality rates of patients admitted to the intensive care unit [4, 5]. Of the various etiologies of renal failure in cirrhosis, HRS carries a poor prognosis among cirrhotic patients with AKI.

HRS continues to pose a diagnostic challenge. AKI is relatively frequent, seen in about 20% of patients with cirrhosis [8]. AKI can be either pre-renal, intrarenal or postrenal. Prerenal causes include hypovolemia, infection, use of vasodilators and functional due to decreased blood flow to the kidney, intra-renal such as glomerulopathy, acute tubular necrosis and post-renal such as obstruction. Patients with cirrhosis are susceptible to developing renal impairment. HRS may be classified as type 1 or rapidly progressive disease, and type 2 or slowly progressive disease. There are other types of HRS [9], but this chapter will focus on type 1 HRS and type 2 HRS. HRS is considered a functional etiology of AKI as there is an apparent lack of nephrological parenchymal damage. This is one of several possibilities of AKI in patients with both acute and chronic liver disease.

AKI is one of the most severe complications that could occur with cirrhosis. Up to 50% of hospitalized patients with cirrhosis can suffer from AKI, and as mentioned earlier an AKI in the presence of cirrhosis in a hospitalized patient has been associated with nearly a 3.5-fold increase in mortality [6].

The definition of HRS will be discussed in this chapter, but it is characterized specifically as a form of AKI that occurs in patients with advanced liver cirrhosis which results in a reduction in renal blood flow, unresponsive to fluids this occurs in the setting of portal hypertension and splanchnic vasodilation [7].

This chapter will discuss the incidence, definitions and management of HRS, focusing mainly on HRS type I and type II.

2. Frequency of acute kidney injury in cirrhosis

AKI is a common entity in cirrhotic patients at baseline. It is also commonly seen in general hospitalized patients, both with and without cirrhosis. This fundamentally means that a clinician should be able to distinguish various etiologies of AKI establish the reason for AKI in each cirrhotic patient so that management can be conducted appropriately.

As mentioned before, the frequency of AKI in patients with underlying liver pathology can be as high as 50%. One study looked at hospitalized patients with

cirrhosis. Of these patients, 19% found to have an AKI, out of these 23% found to have HRS [10]. "The AKI was divided into pre-renal, intrinsic, and post-renal. Pre-renal injury was the most common form of AKI which represented 68% of patients with AKI. The pre-renal injury was usually volume responsive, while HRS is non-volume responsive. In most cases, the injury was volume responsive and therefore less likely HRS [11, 12]. Although HRS is not always the most common cause of renal impairment in cirrhosis; renal impairment itself is commonly seen as the frequency of AKI in cirrhosis can vary in the literature from approximately 15–40% [13–15].

The etiologies of AKI in cirrhosis vary, and the prognosis that each etiology carries also varies. One large prospective study found that hypovolemia and infections were in fact the most common culprits of AKI in cirrhosis, with HRS being identified in 13% of cases [16]. The definition of HRS is important as it can guide clinicians into decision making. For instance, if the etiology of an AKI in cirrhosis is reversible and will not cause significant long-term impairment, the urgency for immediate transplantation dissipates. Conversely, if there is the development of HRS, there may be urgent indication for transplantation.

While there are varying figures reported in the literature on the frequency of AKI in the cirrhotic population, it is evident that it is a common entity. Not all AKI in cirrhosis is considered HRS and defining HRS as the specific cause of renal impairment in cirrhosis represents another challenge for clinicians.

3. Defining hepato-renal syndrome

As stated previously, HRS is defined as renal impairment that occurs in patients who have clinically established cirrhosis or have significant liver impairment. The most widely used definition is the relative rise in creatinine and the relative drop in serum GFR and renal plasma flow in the absence of other causes of AKI like prerenal, renal or post-renal. Given its poor prognosis, HRS was formerly associated with the term terminal functional renal failure [17]. In theory, since there is no intrinsic kidney pathology, upon reversing the hepatic dysfunction either medically or via transplantation, there should be resolution of HRS. In intrinsic renal pathologies, this would not be the case. Before considering HRS, clinicians should rule out other competing etiologies.

4. Competing etiologies of hepatorenal syndrome

Differentiating HRS from other etiologies of AKI in cirrhotic patients is clinically of high importance because of the pronounced difference in management and prognosis. Patients with liver cirrhosis are prone to have acute, subacute and chronic kidney disease through a variety of mechanisms. Clinicians should have a broad differential diagnosis when approaching patients with AKI as there is no definitive test for HRS yet [18]. It is therefore necessary to rule out other differential diagnosis before a diagnosis of HRS is made. Identification of risk factors and careful assessment of the renal system are the mainstay to make such a diagnosis.

Cirrhotic patients may have a certain level of renal insufficiency at baseline since some etiologies of cirrhosis can directly or indirectly lead to renal insufficiency. For instance, patients with non-alcoholic fatty liver disease have higher incidence of obesity and associated diabetes and diabetic nephropathy. Also, both glomerulonephritis and vasculitis can occur in patients with liver cirrhosis secondary to viral

hepatitis [2]. These are just a few examples of how one pathology can affect both the hepatic and renal system.

Given the wide spectrum of possibilities, when approaching a renal impairment in a patient with cirrhosis, a systematic approach can be of benefit to clinicians to assess the nature of renal impairment. Causes of AKI and renal failure in cirrhotic patients can be summarized in four main categories.

4.1 Hypovolemia-induced renal failure

This is usually due to hemorrhage related to gastrointestinal bleed or fluid loss associated with excessive diuresis or diarrhea induced by excessive laxatives use [19]. Also, can be secondary to different infectious etiologies including spontaneous bacterial peritonitis. In any of these cases, renal failure will occur soon after any of the mentioned hypovolemic events [16, 19]. Due to the fact that patients with worsening liver cirrhosis will have decreased intravascular volume and mean arterial resistance [17], hypovolemia should be considered as a frequent component of AKI in those patients [16]. The management of hypovolemia induced renal failure is to address the volume status.

4.2 Parenchymal renal disease

By definition HRS is a purely functional disease and it does not induce renal parenchymal damage. However, any parenchymal renal disease can occur in both cirrhotic patients and non-cirrhotic patients. The presence of proteinuria, hematuria or both is associated with glomerular disease. Differentiating HRS from acute Tubular Necrosis (ATN) remains difficult. While the presence of muddy brown casts favors ATN, other urinary indexes like fractional excretion of sodium (FeNa) can be misleading due to the prolonged use of diuretics in cirrhotic patients. Granular casts can be seen in both ATN and HRS [19].

4.3 Drug induced renal disease

Drug-induced tubular/tubulointerstitial injury is a common cause of AKI especially with the consideration ill patients such as those with cirrhosis will inevitably need medications. There are various pathways and in which a drug can cause renal injury [20]. Some examples can include aminoglycosides, vancomycin, and even administration of contrast needed for imaging studies.

4.4 Hepatorenal syndrome

HRS is a diagnosis of exclusion based on the previously mentioned criteria. This chart simplifies the definition based on the criteria set forth by the International Ascites Club [21, 22].

The key factor in diagnosing HRS is the absence of improvement of kidney function despite discontinuation of potential nephrotoxic agents, and a trial of fluid repletion. Essentially HRS appears as a non-volume responsive pre-renal injury. This is why it is essential to rule out all other possible AKI systematically (**Table 1**).

4.4.1 Diagnosis

AKI stage 1 is defined as the increase in serum creatinine (sCr) of >0.3 mg/dl within 48 hours or a > 50% percentage increase in sCr from a known or presumed

Defining hepatorenal syndrome
• Chronic or acute liver failure with signs of portal hypertension
• Low GFR
• Exclusion of shock
• Protienuria less than 0.5 grams per day with exclusion of obsrtuvtive uropathy and exclusion of parecnyhmal disease
• Failure of renal function improve with 1.5 liter isotonic volume - exapnsion and/or with discontiuation of diuretic
Additional criteria
• Urine volume less than 0.5 liters per day
• Low urine sodium (<10mmol/l), serum sodium <130mmol/l
• Less than 50 red blood cells per hpf on urine microscopy

Table 1.
Defining Hepatorenal Syndrome. Adopted from International Ascites Club and in [21, 22].

baseline in the past 3 months which occurred within the past 7 days or urine volume < 0.5 cc/kg for 6 hours.

Changes in the definition of AKI in patients with cirrhosis has changed over time and has been replaced by the ICA (International Club of Ascites) AKI criteria [4, 23]. One of the most important changes was the removal of cutoff values of sCr for diagnosis of HRS in the setting of AKI, allowing earlier recognition and treatment of HRS.

Major diagnostic criteria include cirrhosis with ascites, presence of renal failure which helps differentiate HRS type I and HRS type II.

4.4.1.1 HRS type I

HRS type 1, renal failure is acute based on the KDIGO guidelines, increase in serum creatinine by ≥0.3 mg/dL within 48 hours; Increase in serum creatinine to ≥1.5 times baseline (i.e. 50% above baseline), which is known or presumed to have occurred within the prior 7 days; or urine volume < 0.5 mL/kg/h over a 6-hour period [23].

4.4.1.2 HRS type II

Type 2 HRS renal failure decline in renal function progresses more slowly, usually Cr >1.5. Diagnosis of HRS-type 2 be made either in the context of chronic kidney disease (CKD), that is, in a patient with cirrhosis and a GFR <60 ml/min per 1.73 m2 for >3 months (HRS-CKD) in whom other causes have been excluded, or in the context of AKI, defined as a renal dysfunction that does not meet criteria for AKI and lasts for less than 90 days.

KDIGO guidelines define CKD as abnormalities in kidney structure or function (GFR <60 ml/min/1.72 m2) that persist for more than 90 days, and acute kidney disease (AKD), as AKI or as abnormalities in kidney structure or function that persist for more than 90 days [9, 23].

A recent proposal in the European association for the study of the liver guidelines suggested that HRS-2 should be referred to as HRS-NAKI (hepato-renal syndrome non-acute kidney injury) [24]. This is due to many reasons. HRS 2 is poorly defined and is more of an assumption that chronic abnormalities in serum creatinine without a definite timeline, thus arriving at a new definition of HRS-2 is more challenging than expected.

It is proposed that the diagnosis of HRS-NAKI be made either in the context of CKD, that is in a patient with cirrhosis and a decrease in GFR greater than 3 months (HRS-CKD) or in the context of AKD, defined as a renal dysfunction that does not meet criteria for AKI and lasts for less than 90 days underlying factors such as diabetes, arterial hypertension causing nonalcoholic steatohepatitis which eventually lead to cirrhosis can simultaneously affect the kidneys causing CKD as well [23].

The new nomenclature may enable clinicians to define the presence of HRS-AKI superimposed on CKD in a patient with structural damage of the kidney, as evidenced by previous abnormal biopsy, renal ultrasonography or by significant proteinuria.

In the context of the new definition of HRS-AKI on CKD: HRS-AKI, there would be no evidence of chronic structural damage. For HRS-AKI on CKD in which there would be evidence of chronic structural damage such as chronic proteinuria and/or abnormal renal ultrasonography but with a high suspicion of HRS-AKI.

Other diagnostic criteria for hepatorenal syndrome include:

1. Failure of response to 48-hour volume expansion with albumin and discontinuation of diuretics.

2. Absence of current use of nephrotoxic medications.

3. Absence of macroscopic indication of structural kidney injury such as of proteinuria less than 500 mg per day, microhematuria (less than 50 red blood cells per high powered field) and normal kidney ultrasound [9, 21, 23] (**Table 2**).

4.4.2 Challenges in diagnosing hepatorenal syndrome

Although the definition of HRS appears straightforward, there are many clinical challenges to consider when making a diagnosis. For instance, the usefulness of creatinine measurement in patients with cirrhosis may be limited for many reasons such as assay interference with bilirubin, reduced creatinine production in liver failure patients, muscle wasting and malnutrition [25].

Also using the urine output in patients with cirrhosis is limited as it can affected by other factors, for example decreased urine can be a normal in hypovolemic patients as they retain sodium or it can be simply increased secondary to the use of diuretics, [26, 27] despite that urine output remain a factor to look for, as was demonstrated by, Amathieu et al. who showed that reduction in urine output is associated with worse prognosis and 3-fold increased in hospital mortality [28].

These are just a few examples of how clinicians must use sound judgment when attempting to make a diagnosis of HRS. As mentioned earlier, it is important to stratify causes as it would impact both management and possibly the urgency for transplantation.

4.5 ATN versus HRS

Differentiating ATN and HRS can also pose a challenge to clinicians. Pre-renal azotemia represents the leading cause of AKI in patients with cirrhosis, good history and physical examination of patients warranted to exclude causes of hypovolemia as discussed above.

Urine studies have been also sought to be helpful, with structural etiologies such as ATN, tubular injury limits sodium reabsorption and fraction excretion of sodium (FENa) is increased, typically by greater than 2–3%, using these cutoffs has been challenging owing to the fact that all patients with advanced cirrhosis have chronic

Hepatorenal syndrome type 1	Hepatorenal syndrome type II
Rapid, progressive	Insidious
Median survival <2 weeks	Median survival 6 months

Table 2.
Comparing Types of Hepatorenal Syndrome. Adopted from KDIGO guidelines [9, 21, 23].

renal hypoperfusion and have an FENa less than 1%, even in the absence of AKI [29]. Other studies such as urinary sodium (less than 40 milliequivalents per liter), low urine osmolality are suggestive of ATN although their use in HRS has been limited.

The fraction excretion of urea (FEUrea) is superior to FeNA in differentiating AKI-HRS from ATN, obtaining such tests is very important in HRS as most patients with HRS are on diuretics. Urinary sodium is known to be affected by use of diuretic which can falsely elevate the urine sodium. That is one main reason why FeNa has been excluded from HRS definitions.

4.6 The role of biomarkers in diagnosing HRS

Novel urine biomarkers of tubular injury have long been sought to differentiate AKI-HRS and ATN in patients with cirrhosis [30].

There are many biomarkers released by tubular injury. Among these, NGAL has been the most widely studied biomarker in patients with cirrhosis and showed the greatest diagnostic accuracy in differentiating ATN from AKI-HRS [9]. Cut-off of 0.2% has been widely used in distinguishing HRS from ATN [9]. Urinary NGAL seems to be superior to plasma concentrations and performs better when measured after the two-day volume challenge recommended in the management of any AKI including HRS [31].

At the current time human studies rely on expert adjudication for differentiating ATN from AKI-HRS owing to the limited availability of renal biomarkers and restricted use of kidney biopsies in such a high risk population.

5. Management of hepatorenal syndrome

HRS is one of the many causes of AKI in individuals with both acute and chronic liver disease. After correctly making a diagnosis of HRS, clinicians must address the underlying etiology of HRS. Patients that develop usually have cirrhosis, alcoholic hepatitis, liver failure, or fulminant hepatic failure from any etiology. Management of HRS is usually supportive, with the definitive treatment being reversal of the underlying liver pathology. In several patients, this means liver transplantation.

First line treatment of supportive management for HRS is using vasoconstrictors in combination with albumin to combat splanchnic arterial vasodilation [32]. The goal of treatment is to improve hemodynamic dysfunction by combatting the decreased circulating volume and increasing mean arterial pressure. The most common vasoconstrictors used are vasopressin analogues (terlipressin), norepinephrine, and somatostatin analogues such as octreotide and midodrine.

6. Vasopressin analogues (terlipressin)

The vasopressin analogue Terilpressin is noted to have a greater affinity for the vasopressin 1 receptors in the splanchnic bed, it has been found to improve kidney

function in patients with HRS with a decreased incidence of ischemia as compared to vasopressin [33]. Studies have demonstrated that continuous administration of Terlipressin is better tolerated and associated with fewer adverse effects as compared to intermittent bolus administration [34]. Continuous infusion of terlipressin in an outpatient setting has also been reported to be an effective, safe option of HRS treatment as a bridge to transplant [35, 36]. Terlipressin is considered as the first treatment of choice of HRS in Europe. Despite this fact, it is not currently approved by the Food and Drug Administration for use in the United States and Canada as a clear benefit of treatment in HSR has not been established.

Terlipressin was proven to be more effective than placebo in treating HRS type 1 although terlipressin use was associated with more adverse events such abdominal pain, nausea, diarrhea and respiratory failure [37].

7. Norepinephrine

While Terilpressin is the traditional first choice for HRS, norepinephrine is another option clinician can use as vasoconstrictive therapy. One large meta-analysis looking at randomized control trials in HRS compared the efficacy of various constrictive therapies. Terlipressin did demonstrate the most effective pressor to reverse HRS, but had an increased risk of adverse events. Norepinephrine was nearly as efficacious as Terlipressin, and although it was not able to provide the survival benefit as Terlipressin did have a better safety profile [38, 39].

8. Role of albumin

Albumin has a role in maintaining plasma oncotic pressure and detoxification. One of the few indications for albumin administration is HRS; with existing studies in the literature that report the efficacy of albumin in the treatment of HRS [40]. Although albumin has been proven to help in HRS, the optimal treatment dose has not yet been established in guidelines. One large meta-analysis study did demonstrate a benefit with albumin, but optimal treatment dose with albumin has yet to be established. The study did demonstrate that a cumulative dose predicts a successful response to therapy [41].

Current recommendation is to use both albumin with Terlipressin as it has been shown that it improves its beneficial effect when compared to using terlipressin alone or placebo [34, 42].

9. Transjugular intrahepatic portosystemic shunt

Transjugular intrahepatic portosystemic shunt (TIPS) is a treatment option for those patients who fail to respond to pharmacologic therapy. TIPS reduces portal pressures by placing a stent between the portal and hepatic vein. This decreases portal pressure and vascular resistance by reducing endothelin-1 [43, 44]. This procedure has shown to improve kidney function in patients with HRS with a reduction in serum blood urea nitrogen, serum creatinine, and urinary sodium excretion [45, 46]. Although the TIPS procedure does improve elements of HRS, it was shown that there is limited evidence of survival benefit in patients with HRS [47] in addition to risk of development of hepatic encephalopathy which remains the greatest concern for clinicians. This is due to the portosystemic bypass shunt which results in bypassing the livers detoxifying function.

10. Renal replacement therapy

Renal replacement therapy (RRT) is an option for patients with HRS who progress to kidney failure and is most commonly done in patients awaiting liver transplant, or those with an acute reversible event. The role of RRT remains unclear due to lack of survival benefits as similar short term and long-term survival rates have been demonstrated as compared with non RRT treated patients [48].

11. Liver transplantation

HRS is an important entity in liver transplantation. Firstly, many patients waiting for liver transplant will develop HRS. This is owing to the fact that the indication for liver transplant is often advanced cirrhosis or decompensated cirrhosis with ascites. These conditions may also predispose for HRS. The 1-year probability of developing HRS in the presence of ascites is 20%, and the 5-year probability is 40%. The patient population at highest risk of complications are those with fluid retention, which is seen in advanced and decompensated cirrhosis [49, 50].

Secondly, in patients who have HRS the therapies mentioned above such as vasoconstrictors are used often as a bridge to transplantation. Therapies discussed above including vasoconstrictors may help, but the definitive treatment in HRS patients is often a transplant. Aggressive supportive care is unable to improve the recovery of kidney function in less than 50% of patients with HRS [50].

12. Simultaneous liver and kidney transplant

The concept of addressing HRS with a Simultaneous Liver and Kidney Transplant (SLKT) would seem to address both organ dysfunctions. However, HRS has the potential to be reversed by liver transplantation alone, and thus SLKT is not routinely considered in HRS. As mentioned in earlier sections, HRS is associated with many renal pathologies and it is possible for patients with HRS to develop end-stage renal disease after liver transplant alone. Long wait times for liver transplantation has led to a rise in the incidence of pre-transplantation renal dysfunction. The prolonged HRS and long-term RRT can lead to permanent renal damage. The permanent renal injury may lead to a decline in renal function that may not be adequate after liver transplant alone [42, 50].

13. Conclusion

HRS is not an uncommon entity in cirrhotic patients. It remains a challenge both diagnostically and in terms of management. Although there are many causes of renal impairment in the setting of cirrhosis, HRS is unique as the kidneys do not have an organic injury; rather they are a victim of poor circulation seen in advanced liver disease. Any renal impairment has the potential to increase mortality in the cirrhosis population, but HRS in particular is endangering to patients. There are two common forms of HRS, type 1 and type 2, and they can be generally distinguished based on acuity. There appears to be promise in the ease of diagnosis, with the advent of possible biomarkers; however, the present diagnosis is one of exclusion and can often be of challenge for clinicians. The management is mostly supportive care, with albumin and pressor playing a prominent role. The definitive treatment is addressing the underlying liver pathology, which often

means liver transplantation. In some instances, there may be a simultaneous transplantation of the kidney and liver.

Abbreviations

HRS	hepatorenal syndrome
GFR	glomerular filtration rate
AKI	acute kidney injury
ATN	acute tubular necrosis
CKD	chronic kidney disease
HRS-NAKI	hepato-renal syndrome non-acute kidney injury
AKD	acute kidney disease
FENa	fraction excretion of sodium
FEUrea	The fraction excretion of urea
RRT	Renal replacement therapy
SLKT	Simultaneous Liver and Kidney Transplant

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