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EDITORIAL

Tacrolimus-induced posterior reversible encephalopathy syndrome following liver transplantation

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Abstract

In this editorial, we talk about a compelling case focusing on posterior reversible encephalopathy syndrome (PRES) as a complication in patients undergoing liver transplantation and treated with Tacrolimus. Tacrolimus (FK 506), derived from *Streptomyces tsukubaensis*, is a potent immunosuppressive macrolide. It inhibits T-cell transcription by binding to FK-binding protein, and is able to amplify glucocorticoid and progesterone effects. Tacrolimus effectively prevents allograft rejection in transplant patients but has adverse effects such as Tacrolimus-related PRES. PRES presents with various neurological symptoms alongside elevated blood pressure, and is primarily characterized by vasogenic edema on neuroimaging. While computed tomography detects initial lesions, magnetic resonance imaging, especially the Fluid-Attenuated Inversion Recovery sequence, is superior for diagnosing cortical and subcortical edema. Our discussion centers on the incidence of PRES in solid organ transplant recipients, which ranges between 0.5 to 5 +ACU-, with varying presentations, from seizures to visual disturbances. The case of a 66-year-old male status post liver transplantation highlights the diagnostic and management challenges associated with Tacrolimus-related PRES. Radiographically evident in the parietal and occipital lobes, PRES underlines the need for heightened vigilance among healthcare providers. This editorial

emphasizes the importance of early recognition, accurate diagnosis, and effective management of PRES to optimize outcomes in liver transplant patients. The case further explores the balance between the efficacy of immunosuppression with Tacrolimus and its potential neurological risks, underlining the necessity for careful monitoring and intervention strategies in this patient population.

Key Words: Posterior reversible encephalopathy syndrome; Liver transplantation; Tacrolimus; Immunocompromised patients; Neurological complications; Solid organ transplant

Core Tip: Tacrolimus, a crucial immunosuppressant in liver transplantation, is associated with the rare but serious complication of posterior reversible encephalopathy syndrome (PRES). Although the incidence is relatively low (0.5%-5%) in solid organ transplant recipients, the presentation of PRES can vary significantly, including seizures and visual disturbances. This condition, primarily affecting the parietal and occipital lobes, underscores the need for diligent monitoring and early intervention in liver transplant patients undergoing Tacrolimus therapy. The case presented highlights the complexities in diagnosing and managing Tacrolimus-related PRES, emphasizing the critical balance between adequate immunosuppression and the risk of severe neurological adverse effects.

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INTRODUCTION

Tacrolimus, also known as FK 506, is a potent macrolide antibiotic originating from *Streptomyces tsukubaensis*, recognized for its robust immunosuppressive capabilities[1]. Its immunosuppressive mechanisms closely mirror those of cyclosporine, a calcineurin inhibitor (CNI). Cyclosporine impedes T cell transcription of nuclear factor of activated T-cells by binding to the immunophilin FK-binding protein (FKBP). This interaction forms a complex that effectively inhibits IL-2 transcription, Calcineurin phosphatase, T-lymphocyte signal transduction, and Calcium-dependent events[2]. Tacrolimus further enhances its immunomodulatory and anti-inflammatory effects by amplifying the effectiveness of glucocorticoids and progesterone. This augmentation occurs through its binding to FKBPs within the hormone receptor complex, effectively hindering the degradation process[3].

Notably, Tacrolimus has demonstrated remarkable success in preventing allograft rejection, especially in patients unresponsive to cyclosporine, thereby catalyzing a paradigm shift in the landscape of solid organ transplant management. It is crucial to note that the drug displays a substantial pharmacokinetic and pharmacodynamic variability. Following oral administration, the drug undergoes rapid absorption and exhibits extensive binding to erythrocytes in the blood, leading to significantly higher concentrations in blood compared to plasma (estimated to be 20:1). In the plasma, 99% of the drug is bound to proteins[4]. Tacrolimus undergoes systemic metabolism primarily in the liver, predominantly mediated by cytochrome P450 3A4 (CYP3A4) and CYP3A5 enzyme system. However, there is also evidence of presystemic gastrointestinal metabolism occurring in the intestinal wall *via* CYP3A4 and CYP3A5, contributing to a decrease in the oral bioavailability of tacrolimus. Additionally, it serves as a substrate for the efflux transporter P-glycoprotein, influencing gastrointestinal absorption and cellular distribution. The variability in pharmacokinetics has been attributed to polymorphisms of CYP3A5 enzymes, P-glycoprotein, and other factors like age, race, gender, hepatic dysfunction, organ transplanted and time post transplantation[5,6]. The primary pathway for eliminating tacrolimus metabolites is through biliary excretion, with a minor portion excreted in the urine[7]. Tacrolimus exhibits a terminal elimination half-life of approximately 12 h, encompassing a range from 3.5 to 40.5 h[8]. The clinical application of tacrolimus is not without potential drawbacks. The principal adverse effects associated with tacrolimus include neurotoxicity, nephrotoxicity, alterations in glucose metabolism, heightened susceptibility to infections or malignancies, and the infrequent yet severe complication known as Tacrolimus-related posterior reversible encephalopathy syndrome (PRES)[1,9-11].

PRES encompasses a range of neuroradiological symptoms initially described in 1996 by Hinchey and colleagues[12]. Its presentation includes headaches, visual disturbances, altered consciousness, seizures, and focal neurological deficits, and is often accompanied by elevated blood pressure, leading to hypertensive emergencies in many cases. The term PRES was coined after studying the neuroradiological manifestations in the posterior occipital circulation in a case of vasogenic edema. It can affect individuals from as young as two years old to older individuals[13], with a female predominance [14]. While its name suggests reversible etiology, that may not always be true. It has a strong association with hypertensive states; however, a broad spectrum of diseases can lead to PRES, namely preeclampsia, post-stem cell transplantation, autoimmune disorder, and use of cytotoxic medications, among others[15].

The incidence of PRES following solid organ transplantation is reported to range from 0.5%-5%[16], contingent on the specific organ transplanted. While hypertension is a prevalent condition in this population and may lead to the development of PRES, other contributing factors include the administration of immunosuppressive medications like CNI and long-term corticosteroids, use of antibiotics, reperfusion injury post-surgery, and so on. CNI, such as Tacrolimus, is commonly used post-transplant to avoid rejection and help sustain graft function. Elevated levels of circulating CNI have been linked with the development of PRES. The most common presenting symptoms in such patients include seizures followed by encephalopathy and headaches. However, the duration of occurrence of PRES varies based on the solid organ transplanted. In the case of liver transplants, it could manifest as early as 2 months post-transplant[17].

CNI most commonly causes PRES in post-transplant patients. However, the exact pathophysiology behind the same has yet to be elucidated entirely. CNI, particularly Tacrolimus, disrupts the cell membrane, leading to increased cytoplasmic calcium influx and apoptosis of the brain's capillary endothelium. This leads to damage to the blood-brain barrier and downregulation of P-glycoprotein, essential for membrane integrity. These mechanisms have been postulated in the development of PRES secondary to CNI use[18,19].

Vasogenic edema of the subcortical white matter, rather than cytotoxic edema, primarily influences the neuroimaging features of Tacrolimus-associated PRES. However, cases of both coexisting types indicating irreversible damage have been reported[20,21]. Primarily, there is symmetric involvement of the parietal and posterior areas of cerebral circulation with occasional involvement of the frontal lobe[22].

Computed tomography (CT) is the initial method for detecting hypodense lesions in posterior encephalopathy. However, magnetic resonance imaging (MRI), especially the Fluid-Attenuated Inversion Recovery (FLAIR) sequence, is a superior diagnostic tool, demonstrating higher sensitivity in detecting cortical and subcortical edema with more pronounced hyperintense signal changes than conventional sequences[10]. Recent advancements in imaging technologies, namely magnetic spectrography, susceptibility-weighted imaging, and positron emission tomography (PET), have significantly contributed to diagnosing more complex cases[23,24]. Additionally, there is compelling data for the utility of fluorodeoxyglucose (FDG)-PET scan in the diagnosis of PRES, especially as it aids in differentiating it from low-grade tumors. In PRES, the affected areas exhibit decreased FDG uptake, indicating reduced metabolism (associated with increased cerebral circulation). In contrast, brain tumors typically display increased FDG uptake attributable to their elevated metabolic rate[23,25]. This sophisticated imaging tool plays a crucial role in diagnostics, as both PRES and malignancy are potential complications observed in solid-organ transplant patients undergoing immunosuppressive therapy [26].

A 66-year-old male with a pertinent history of orthotopic liver transplantation (OLT) for hepatocellular carcinoma, Immunocompromised on chronic immunosuppression, end-stage renal disease (ESRD) on hemodialysis presented to the emergency department (ED) *via* emergency medical services after sustaining a mechanical fall.

Collateral information obtained from the patient's spouse reports worsening mental status and gait instability over the last month before the presentation. The patient was reported to have hit his head from the fall but did not lose consciousness. The spouse also reported a tremor-like movement of his right lower extremity following the fall, but she denies observing whole-body tonic-clonic activity. There was no tongue biting, bowel incontinence, or urinary incontinence (however, the patient is anuric at baseline, given ESRD status).

In the ED, the patient was found to be hemodynamically stable. Given the patient's altered state with a Glasgow coma scale score of 10, a full neurological exam could not be performed, but he was observed to have right-hand high-amplitude intention tremors. His labs were pertinent for hyperglycemia, normocytic anemia, mild thrombocytopenia, mild hyponatremia, and elevated creatinine, consistent with his ESRD (Table 1). CT head was done and did not show any evidence of acute territorial infarct, intracranial hemorrhage or mass effect. There were nonspecific areas of white matter hypodensity and generalized parenchymal volume loss, otherwise, it was generally unremarkable.

Further workup for acute toxic metabolic encephalopathy with liver function tests, thyroid function tests, venous blood gas, ammonia levels, and blood culture was within normal limits. The patient was subsequently admitted to the Internal Medicine service for further evaluation of his encephalopathy. A review of his home medication list included amlodipine 10 mg daily, Carvedilol 6.25 mg twice daily, hydralazine 10 mg three times daily, losartan 100 mg daily, paroxetine 20 mg every morning, basal insulin degludec 15 units daily, Insulin lispro 7 units three times daily after meals, entecavir 0.5 mg every Monday, levetiracetam 500 mg twice daily, tacrolimus 4 mg every morning and 3 mg at night. His blood toxicology report was generally unremarkable. He had mildly elevated troponins which peaked at 0.05, however he denied any chest pain or dyspnea and electrocardiography did not show any ischemic changes.

Of note, patient underwent OLT in May 2013 for hepatocellular carcinoma secondary to underlying chronic hepatitis C and alcoholic cirrhosis. He was placed on chronic immunosuppression with tacrolimus monotherapy with a goal trough level of 3-5 ng/mL in the late post-transplant phase. His post-transplant course was complicated by ESRD, likely related to multiple risk factors and comorbidities including tacrolimus toxicity, Hypertension and uncontrolled diabetes. A random tacrolimus trough level done on day 1 of admission was found to be 20.6 ng/mL. Nephrology, neurology and transplant hepatology were consulted and his tacrolimus was temporarily held due to suspicion of Tacrolimus neurotoxicity.

MRI of the brain was done which showed bilateral cortical and subcortical hyperintense lesions (arrows) involving occipital lobes and parietal lobes on Axial FLAIR sequence imaging (Figure 1).

His workup excluded seizures and any infectious or metabolic causes. Given his markedly elevated tacrolimus trough levels, clinical presentation and impressive MRI findings, PRES secondary to tacrolimus toxicity was the most probable diagnosis. Patient's mental status returned to baseline, and his tacrolimus twice daily (4 mg in the morning and 3 mg at night) was resumed prior to discharge, with follow-up with a transplant hepatology clinic set up to review alternatives for immunosuppressive regimen.

Table 1 Relevant laboratory data

Variable	Results on arrival	Reference range
White blood cell count (k/uL)	6.45	4.50-11.00
Red blood cell count (M/uL)	3.21	4.40-5.90 (male); 3.80-5.20 (female)
Hemoglobin (g/dL)	8.4	13.0-18.0 (male); 12.0-16.0 (female)
Hematocrit (%)	24.7	40.0-52.0 (male); 35.0-47.0 (female)
MCV (fL)	82.3	80.0-100.0
Platelet count (k/uL)	131	150-440
ESR (mm/h)	16	< 20
CRP (mg/L)	2.1	< 5.0
Sodium (mEq/L)	132	136-145
Potassium (mEq/L)	4.4	3.4-4.4
Chloride (mEq/L)	89	98-107
Bicarbonate (mEq/L)	33	22-29
BUN (mg/dL)	33	8-26
Creatinine (mg/dL)	6.63	0.72-1.25
Ammonia (umol/L)	12	18-72
Hemoglobin A1C (%)	11.4	4.3-5.7
Tacrolimus level (ng/mL)	20.6 (on admission)	3-5 (goal therapeutic trough level in the late post-transplant phase)

BUN: Blood urea nitrogen; MCV: Mean corpuscular volume; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein.

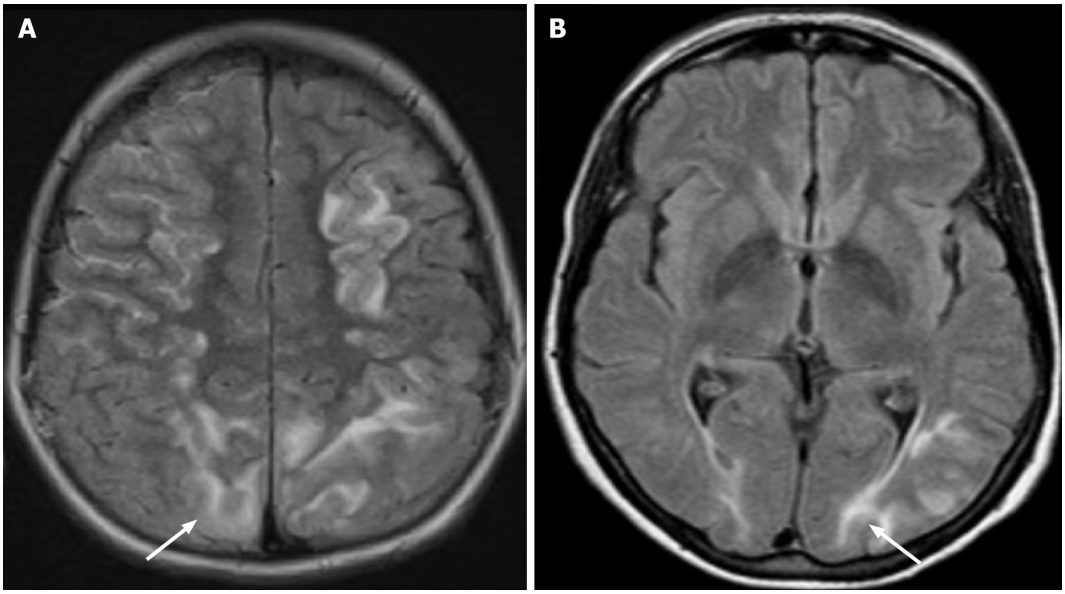

Figure 1 Magnetic resonance imaging of the brain (Axial Fluid-Attenuated Inversion Recovery sequence imaging) showing bilateral cortical and subcortical hyperintense lesions (arrows) involving occipital lobes and parietal lobes. A: Hyperintense lesions in the parietooccipital sulcus (white arrow); B: Hyperintense lesions at the transverse occipital fasciculi (white arrow).

MECHANISMS OF PRES DUE TO TACROLIMUS

The use of tacrolimus in solid-organ transplant patients has been associated with various complications, including a rare but critical neurological disorder known as PRES[9-11]. Tacrolimus related PRES can present with a wide range of clinical symptoms, including tremors, headaches, seizures, gait instability and incoordination, altered mental status, visual disturbances, nausea and vomiting. The most common presentation is usually seizures and altered mental status[27]. Due

to its nonspecific symptoms, PRES should always be considered in the appropriate patient subset as early recognition and timely intervention are crucial for reversing PRES and preventing long-term clinical sequelae.

Various theories aim to elucidate the pathophysiology of PRES, yet its exact cause remains elusive, and no single mechanism explains the development of PRES in all cases. The association between severe hypertension and PRES is well established in the extant literature[12,28]. The suggested mechanism posits that a rapid surge in blood pressure triggers the acute disruption of the blood-brain barrier, causing the failure of cerebral autoregulation. Consequently, cerebral arterioles dilate, resulting in the interstitial extravasation of serum protein and fluid, ultimately leading to vasogenic edema. Given that autoregulatory mechanisms rely on the neurogenic response, areas with poorer innervation in the posterior circulation become more susceptible to heightened blood pressure. The less adaptive mechanism in the posterior circulation of the brain for dealing with increasing pressures and preventing blood-brain barrier disruption when compared to the anterior circulation makes it more prone to vasogenic edema[29-32], hence the name 'Posterior' reversible encephalopathy syndrome.

While hypertension remains a prevalent theory, it is contested because PRES has also been observed in normotensive patients and our patient is a prime example. Similarly, a retrospective study by Liman *et al*[33] also revealed that 50% of PRES patients did not exhibit severe hypertension before presentation. This disparity in blood pressure findings in patients found to have PRES suggests that there are probably other factors at play in how PRES develops and which patients are prone to having PRES. Another postulated mechanism is through direct cytotoxicity by exogenous toxins. These toxigenic substances cause direct endothelial damage, leading to blood-brain barrier disruption. This is likely the mechanism through which tacrolimus causes PRES[34,35].

CNI, notably tacrolimus, disrupt the cell membrane, triggering an increase in cytoplasmic calcium influx and the apoptosis of the brain's capillary endothelium. This process results in damage to the blood-brain barrier, downregulation of P-glycoprotein, a loss of membrane integrity and ultimately vasogenic edema. However, as previously highlighted, there is evidence to suggest that beyond vasogenic edema, there is sometimes concurrent cytotoxic edema especially if left untreated suggesting progression to irreversible damage[20,21,36]. In such instances, utilizing diffusion-weighted MRI and assessing the apparent diffusion coefficient can be beneficial for distinguishing between conditions[36]. Brain MRI stands out as the most sensitive diagnostic tool, revealing predominantly posterior subcortical white matter and gray matter lesions consistent with PRES, while excluding differential diagnoses, such as infective encephalitis, sinus thrombosis, and cerebral ischemia.

Interestingly, while our patient was found to have supratherapeutic tacrolimus trough levels (20.6 ng/mL), numerous studies have shown that elevated tacrolimus levels beyond the therapeutic range are not necessary to trigger neurological complications or a PRES event[37-39]. Therefore, the serum drug level is not a sensitive diagnostic indicator for neurotoxicity induced by tacrolimus. There are suggestions that the cerebrospinal fluid (CSF) level could offer better utility than the serum level, hypothesizing that the drug may accumulate in the central nervous system after crossing the blood–brain barrier, resulting in a CSF level that significantly surpasses the corresponding serum tacrolimus levels[40]. However, there is currently limited data on this, necessitating further research into this claim.

In our case, the diagnosis of Tacrolimus-associated PRES was established based on the following criteria: The emergence of new-onset neurological symptoms, including altered mental status, headaches, and newly developed tremors; confirmed compliance with tacrolimus, indicated by elevated drug levels in our patient; distinctive brain MRI findings revealing posterior vasogenic edema; and a comprehensive workup ruling out infectious, metabolic, structural, and other medications that could potentially account for the patient's symptoms.

CLINICAL IMPLICATIONS

The management of PRES primarily adopts a symptomatic approach, with a key emphasis on regulating blood pressure. Additionally, when feasible, discontinuation of the causative drug is recommended. In cases where immediate cessation is impractical, considering dose reduction becomes a viable alternative. For individuals presenting with seizures, the administration of anti-seizure medications (ASMs) may be necessary. A standard practice involves tapering ASMs as symptoms alleviate, and MRI findings show resolution, a trend observed in the majority of patients.

Our diagnostic approach was further substantiated when the patient's symptoms exhibited resolution after tacrolimus was withheld for several days. This underscores the pivotal role of identifying and addressing the causative agent in PRES management, highlighting the potential reversibility of symptoms upon intervention. These observations contribute valuable insights to the broader understanding of PRES and its therapeutic strategies.

CONCLUSION

Tacrolimus-related PRES represents a significant and potentially severe complication in transplant patients undergoing immunosuppressive therapy with Tacrolimus. This neurological disorder manifests with cognitive and neuropsychiatric symptoms, presenting complex challenges for both patients and healthcare providers. Achieving a delicate balance between maintaining sufficient immunosuppression and averting neurotoxicity is pivotal for successful management. Timely recognition and intervention are of utmost importance, necessitating healthcare teams to remain vigilant in identifying subtle signs indicative of Tacrolimus-related PRES. Swift adjustments to Tacrolimus doses or consideration of alternative immunosuppressive regimens may be essential to mitigate the progression of this condition. Ongoing research plays a crucial role in deepening our understanding of the pathophysiological mechanisms involved and identifying

predisposing risk factors associated with Tacrolimus-related PRES. Despite the inherent challenges posed by this condition, healthcare providers can effectively manage and reduce the impact of Tacrolimus-related PRES. By adopting a proactive approach, healthcare teams contribute to improved outcomes and enhanced quality of life for transplant recipients. This comprehensive perspective underscores the importance of continued research and clinical vigilance in refining our strategies for the prevention, recognition, and management of Tacrolimus-related PRES in the context of immunosuppressive therapy.

FOOTNOTES

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EDITORIAL

Critical considerations for the management of acute abdomen in transplant patients

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Abstract

The number of solid organ transplantations performed annually is increasing and are increasing in the following order: Kidney, liver, heart, lung, pancreas, small bowel, and uterine transplants. However, the outcomes of transplants are improving (organ survival > 90% after the 1st year). Therefore, there is a high probability that a general surgeon will be faced with the management of a transplant patient with acute abdomen. Surgical problems in immunocompromised patients may not only include graft-related problems but also nongraft-related problems. The perioperative regulation of immunosuppression, the treatment of accompanying problems of immunosuppression, the administration of cortisol and, above all, the realization of a rapidly deteriorating situation and the accurate evaluation and interpretation of clinical manifestations are particularly important in these patients. The perioperative assessment and preparation includes evaluation of the patient's cardiovascular system and determining if the patient has hypertension or suppression of the hypothalamic-pituitary-adrenal axis, or if the patient has had any coagulation mechanism abnormalities or thromboembolic episodes. Immunosuppression in transplant patients is associated with the use of calcineurin inhibitors, corticosteroids, and antiproliferation agents. Many times, the clinical picture is atypical, resulting in delays in diagnosis and treatment and leading to increased morbidity and mortality. Multidetector computed tomography is of utmost importance for early diagnosis and management. Transplant recipients are prone to infections, especially specific infections caused by cytomegalovirus and *Clostridium difficile*, and they are predisposed to intraoperative or postoperative complications that require great care and vigilance. It is

necessary to follow evidence-based therapeutic protocols. Thus, it is required that the clinician choose the correct therapeutic plan for the patient (conservative, emergency open surgery or minimally invasive surgery, including laparoscopic or even robotic surgery).

Key Words: Acute abdomen; Abdominal emergency surgery; Transplantation; Immunocompromised patients; Immunosuppression; Posttransplantation surgery

Core Tip: Adequate caution should be taken with patients with acute abdomen after transplantation, and these patients need constant attention because of the altered clinical course of their disease due to existing immunosuppression. Computed tomography may be valuable in diagnosis. The management of these patients must be personalized, but urgent surgical intervention is commonly needed. Specific care must be applied during the perioperative period.

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INTRODUCTION

There is an increasing number of solid organ transplantations performed annually worldwide, and these transplants include, in order of frequency, kidney, liver, heart, lung, pancreas, and, less commonly, small bowel and uterus transplantations. The increase in the number of these procedures has been accompanied by improved results, leading to a graft survival rate of more than 90% in the first year[1]. Therefore, there is a high probability that a general surgeon will be faced with the management of a transplant patient with acute abdomen[1-3].

The clinical presentation may not be similar to that of patients in the general population with acute abdomen who have not undergone transplantation; thus, a misdiagnosis or severity underestimation could occur[1]. Surgical problems in immunocompromised patients may be related to the graft, which will require referral of the patient to a transplant center [4,5] but may also not be related to the graft, allowing the patient to be treated at a nontransplant surgical department[4,6].

Particular attention must be paid to the perioperative use of immunosuppressants, and the treatment of the patient should include the correction of immunosuppression with its accompanying problems and the administration of cortisol to cope effectively with the operative stress. However, the rapid progression of acute abdomen in transplant patients and the need for specific evaluation and different interpretations of its clinical manifestations should be anticipated[1,3].

The indications for emergency abdominal surgery include gallbladder diseases (80.3%), gastrointestinal perforation (9.2%), complicated acute diverticulitis (6.2%), obstructive ileus (2%), and acute appendicitis (2%)[1].

Immunosuppression is caused by various pharmaceutical agents, such as calcineurin inhibitors (ciclosporin, voclosporin, tacrolimus, and pimecrolimus), corticosteroids (prednisone), mTOR inhibitors (sirolimus), and antiproliferative agents (mycophenolate mofetil), which are used in solid organ transplantation to prevent graft rejection. Subsequently, transplant recipients are prone to both specific infections [cytomegalovirus (CMV), *Clostridium difficile* (*C. difficile*), and neutropenic enterocolitis] and intraoperative or postoperative complications that require great caution and constant vigilance. Care must be taken during every operative procedure to completely preserve the functional capacity of the transplanted organ. Thus, it is important to avoid episodes of hypotension that may have a negative impact on the graft situation because of reduction of the graft's blood supply[1].

The treatment of acute abdomen in immunocompromised patients, including patients who have had solid organ or bone marrow transplantation, constitutes a challenge that requires specific evidence-based medicine and adequate understanding of the new directions in the treatment of these patients[2]. The sensation of pain, the main manifestation of peritonitis, in such patients is often not perceived adequately, leading to delays in early diagnosis and proper management and subsequent severe deterioration of patients, leading to severe sepsis. Thus, meticulous evaluation of the clinical course and physical examination of the abdomen are highly important. Furthermore, it is well known that emergency abdominal surgery causes more intense postoperative pain than elective surgery, affecting the patient's clinical and psychological status, which may ultimately influence surgical outcomes[7].

Moreover, immunosuppression increases the morbidity and mortality of emergency surgery[3,6,8,9].

DIAGNOSIS

A misdiagnosis of acute abdomen that causes an immunocompromised patient to undergo an emergency surgical

intervention is associated with high morbidity and mortality rates; therefore a diagnosis based on a multidisciplinary discussion is recommended[3]. Transplant patients do not exhibit the usual symptoms or clinical signs of acute abdomen because the symptoms are alleviated by immunosuppression. Additionally, a sufficient diagnostic accuracy cannot be achieved by using the clinical signs of peritonitis, the laboratory tests, or the plain abdominal radiogram and ultrasound findings. The most reliable imaging method for a definitive diagnosis is contrast-enhanced multidetector computed tomography, and thus, it should always be performed in these patients[3,10,11].

In transplant patients, the most common intraperitoneal infections include[3]: (1) Acute cholecystitis, which is the most common and occurs mainly after heart (72%), lung and kidney (30%) transplantations; (2) acute diverticulitis, which occurs mainly after kidney and liver transplantation and exhibits a more severe course than in otherwise healthy people; (3) perforation of the gastrointestinal tract (gastroduodenal ulcer, diverticulitis, acute mesenteric ischemia, severe colitis)[1,12]; (4) acute appendicitis, which is usually complicated[13,14]; (5) obstructive ileus, which is caused mainly by lymphoproliferative disorders related to immunosuppression after transplantation or intraperitoneal adhesions[1,15]; (6) acute pancreatitis, which is attributed to tacrolimus and is rare[16,17]; and (7) Meckel's diverticulum perforation[18] or acute pseudoobstruction (Ogilvie's syndrome), which are rare[19]. Additionally, a rare case of ectopic pregnancy rupture after simultaneous pancreas and kidney transplantation has been reported[20]. In addition, specific intraperitoneal infections, such as neutropenic enterocolitis, CMV colitis[8,21,22] and *Clostridium difficile* (*C. difficile*) colitis, have been reported[3].

MANAGEMENT

The perioperative assessment and preparation involve the management and correction of cardiovascular system abnormalities, hypertension, any coagulation mechanism abnormalities, thromboembolic episodes and any cortico-adrenal insufficiencies caused by the suppression of the hypothalamic pituitary adrenal axis to cope with surgical stress; the safety limit of hydrocortisone is 75 mg/24 h for three days[1].

Acute cholecystitis should be managed by urgent cholecystectomy without delay. In patients who are unfit for surgery, imaging-guided percutaneous cholecystostomy may be an alternative choice[3].

Acute appendicitis should be managed by urgent appendectomy without any delay[3,13,14].

Laparoscopic cholecystectomy or laparoscopic appendectomy are not contraindicated and must be the first-line procedure[3,14].

Patients with uncomplicated cases of acute diverticulitis require conservative treatment with broad-spectrum antibiotics[3]. However, patients with complicated acute diverticulitis require urgent segmental colectomy without delay. In unstable severely ill patients, damage control surgery involving laparoscopic peritoneal lavage and drainage is preferred[23].

Surgical intervention is urgently needed for gastrointestinal tract perforation and bowel obstruction[3].

The use of minimally invasive surgery, including laparoscopic[24] and robotic surgery[25], has been documented to play an important role in the management of patients with acute abdomen, including transplantation patients. The additional advantage in the latter case is that there is no need for perioperative immunosuppressant regulation, as it is anticipated that the patients who undergo minimally invasive surgery have a shorter time to oral feeding postoperatively after these procedures.

In addition to intense monitoring and immunosuppression adjustment, the postoperative care of these patients includes multimodal pain management, *i.e.*, nonsteroidal anti-inflammatory drugs, paracetamol, COX2 inhibitors such as celecoxib, and possibly even antiepileptic gabapentinoids, thus decreasing the use of opioids[7].

The motivation of writing this article is to raise the general surgeon's awareness of the peculiarities and specific altered manifestation features of acute abdomen in the immunosuppressed patient with the caused diagnostic difficulties and the problems that arise during therapeutic management. It should be emphasized particularly, the choice of a multidisciplinary management plan and the performance of operative manipulations with great caution and gentleness.

CONCLUSION

Early accurate diagnosis and management of acute abdomen patients after transplantation is crucial. Preoperative computed tomography is necessary for precise assessment and decision-making. The therapeutic plan usually includes open or minimally invasive emergency surgery, but conservative treatment is indicated in some limited cases. Future work and perspectives, besides the improvement in immunosuppressant drugs, must be concentrated on evidence-based protocols including novel high resolution imaging modalities for precise diagnosis, more application of minimally invasive surgery, and damage control surgery in patients with severe sepsis or hypovolemic conditions.

FOOTNOTES

Author contributions: Pavlidis TE designed research, contributed new analytic tools, analyzed data, review and approved the paper; Galanis IN analyzed data, review and approved the paper; Pavlidis ET performed research, analyzed data, review and wrote the article; Tsoulfas G contributed new analytic tools, analyzed data, review and approved the paper; Katsanos G performed research, analyzed

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REVIEW

Expanding the liver donor pool worldwide with hepatitis C infected livers, is it the time?

Mai Hashem, Mohammed A Medhat, Doaa Abdeltawab, Nahed A Makhlouf

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Abstract

Liver transplantation (LT) provides a life-saving option for cirrhotic patients with complications and hepatocellular carcinoma. Despite the increasing number of liver transplants performed each year, the number of LT candidates on the waitlist remains unchanged due to an imbalance between donor organ supply and the demand which increases the waitlist time and mortality. Living donor liver transplant had a great role in increasing the donor pool and shortened waitlist time for LT candidates. Nevertheless, further strategies can be implemented to increase the pool of potential donors in deceased donor LT, such as reducing the rate of organ discards. Utilizing hepatitis C virus (HCV) seropositive liver grafts is one of the expanded donor organ criteria. A yearly increase of hundreds of transplants is anticipated as a result of maximizing the utilization of HCV-positive organs for HCV-negative recipients. Direct-acting antiviral therapy's efficacy has revolutionized the treatment of HCV infection and the use of HCV-seropositive donors in transplantation. The American Society of Transplantation advises against performing transplants from HCV-infected liver donors (D+) into HCV-negative recipient (R-) unless under Institutional Review Board-approved study rules and with full informed consent of the knowledge gaps associated with such transplants. Proper selection of patients to be transplanted with HCV-infected grafts and confirming their access to direct-acting antivirals if needed is important. National and international consensuses are needed to regulate this process to ensure the maximum benefit and the least adverse events.

Key Words: Donor pool; Hepatitis C-viremic organs; Non-viremic organs; Direct acting antivirals; Hepatitis C virus treated; Liver transplantation.

Core Tip: There is an imbalance between donor organ supply in liver transplantation and the demand. Unfulfilled demands in organ transplant communities prompt new approaches to increasing donor pools. Direct acting antiviral (DAA) regimens have proved higher efficacy in treating hepatitis C virus (HCV). Available data shows that HCV non-viremic donor organs can be used in HCV-negative or positive liver transplant candidates safely. Furthermore, using liver grafts from HCV-viremic donors in liver transplant candidates, even if they were HCV negative, is showing favorable outcomes. Preoperative informed consent and easy access to DAAs with the engagement of clinical pharmacists are indispensable to ensuring these good outcomes.

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INTRODUCTION

Liver transplantation (LT) provides a life-saving option for cirrhotic patients with complications and hepatocellular carcinoma[1]. There were 10.6 million cases of decompensated cirrhosis globally in 2017, with a mortality rate of 2.4% of total mortality[2]. The increasing cirrhosis and its sequelae globally mean increasing demand for LT. The volume of LT is increasing, with 34694 liver transplants performed globally in 2021 and 23% from living donors[3]. There will be changing trends in liver transplant indications in the future. Non-alcoholic steatohepatitis-related cirrhosis will be the leading indication for LT in Europe, the United States, and the Middle East[4]. The declining trend of hepatitis C virus (HCV) prevalence, with the resurgence of alcoholism, has resulted in alcoholic liver disease becoming the first indication for LT in the United States, passing HCV[5]. Nowadays, non-alcoholic fatty liver disease is the second most common indication for LT in the United States and is expected to be the first in the future. These changes in LT indications will project new and unique challenges to the liver transplant community[6].

The demand for LT exceeds the supply of available organs, leading to a death rate of approximately 20% among patients on the waiting list[7]. Thus, reducing mortality and improving overall outcomes could be achieved by any means of increasing the organ pool to provide patients with faster access to transplants. One potential strategy for increasing the number of patients served by organ banks is using organs from HCV-infected donors in HCV-uninfected recipients[8]. This review will discuss the advantages, disadvantages, and reported outcomes of using HCV-infected organs in LT.

FACTS ON DONOR SHORTAGE AND UNMET NEEDS FOR DIFFERENT STRATEGIES TO EXPAND DONOR POOLS

Despite the increasing number of liver transplants performed each year, the number of LT candidates on the waitlist remains unchanged. This is due to an imbalance between donor organ supply and demand, which increases the waitlist time and mortality[9]. In 2020, 470 liver transplant candidates died while waiting for a suitable donor[10]. Unfulfilled demands in organ transplant communities prompt new approaches to increasing donor pools[11]. Of these, using high-risk organs, such as organs donated after cardiac death, from advanced donor age, and grafts with minimal hepatic steatosis[12,13].

Living donor liver transplant (LDLT) greatly increased the donor pool and shortened waitlist time for LT candidates [14]. Therefore, expanding LDLT is a goal in North America and Europe, where deceased donor LT (DDLT) represents a major LT practice. Nevertheless, further strategies can be implemented to increase the pool of potential donors in DDLT, such as reducing the rate of organ discards[1].

RATIONALE FOR USING HCV-POSITIVE ORGANS IN LIVER TRANSPLANT

Using less-than-ideal organs, provided the risk/benefit ratio is still beneficial compared to the patient's chances of staying on the transplant list without an organ, is one strategy to improve the supply of organs. Expanded criteria donors have been used for many years, pushing the bounds of what is considered appropriate to enhance organ access for recipients and reduce organ discarding. Donors with chronic diseases, such as hepatitis viruses, or acute illnesses, such as bacterial infections, can be deemed appropriate donors if a successful treatment to prevent or treat the recipient's infection is available[15].

Utilizing HCV seropositive liver grafts is one of the expanded donor organ criteria[16]. A yearly increase of 300-500 transplants is anticipated as a result of maximizing the utilization of HCV-positive organs for HCV-negative recipients (R-)[17]. Figure 1 illustrates the impact of adopting HCV-infected liver grafts in transplantation.

There were some concerns regarding the utilization of HCV-infected liver donors (D+) into (R-). These concerns were related to the risk of HCV transmission, the outcomes, and complications to the graft and patients, including accelerated graft hepatitis, acute rejection, premature graft failure, or the risk of fibrosis progression post-transplantation up to death. Also, the previous standard of care for HCV management, including pegylated interferon and ribavirin, restricted the acceptance of using D+ into R-, fearing undesirable side effects post-transplant triggering treatment discontinuation[18,19].

A revolutionary event was raised in the management of chronic HCV with the emergence of direct acting antivirals (DAA) in 2011, with a cure rate of nearly > 95% and high efficacy and tolerability for patients[20]. The efficacy of direct-acting antiviral therapy has dramatically altered the treatment of HCV infection and the use of HCV-seropositive donors in transplantation. Patients who developed viremia following transplantation from an HCV-seropositive donor have been successfully treated for HCV post-transplantation at multiple institutions[21,22].

Data obtained for a national survey from 57 of the largest LT centers of the United States, mainly from hepatologists (82.5%), to learn more about their practices for donors, recipients, and HCV positive (HCV+) candidates before and after DAAs, revealed that 21 centers (38.9%) were willing to consider using HCV+ donors for HCV negative (HCV-) candidates after DAAs, in contrast to 3 centers (5.6%) that reported it before DAAs. Six centers had at least 1 HCV+ to HCV- LT, for a total of 12 LTs, during the pre-survey phase. This number increased to 26 centers through the post-survey period, for a total of 129 HCV+ to HCV- LTs[23].

There are currently no restrictions under the Organ Procurement and Transplantation Network (OPTN) that limit the transplantation of infected donors to recipients who are either HCV+ or HCV-. In the next ten years, this is expected to be the primary source of accessible HCV-infected livers due to the rise in drug overdose mortality[8].

Liver allografts from donors who are HCV-RNA positive - as determined by the extremely sensitive HCV NAT testing - have been transplanted into HCV-negative recipients at a significantly higher rate than before. Since the introduction of DAA medication, the frequency of transplanting HCV viremic donor organs into recipients who do not have HCV infection has grown by more than 30 times[24].

Donors with detectable levels of HCV antibodies are considered to be HCV+. The window period, or the interval between infection and diagnosis using a particular testing approach, may enhance the possibility of HCV transmission in a donor with high-risk behavioral features[25]. For these high-risk donors, it is recommended to use a nucleic acid testing (NAT) assay that finds HCV viral RNA in the donor's blood. The duration between HCV infection and detection was shortened from 70 days to 3–5 days by using NAT tests[8].

The American Society of Transplantation (AST) has redefined the term "HCV-positive donor" in light of the introduction of NAT[8]. A donor with HCV who tests negative for NAT (non-viremic) suggests that the infection has either resolved on its own or has been effectively treated. Active infection and a high risk of disease transmission are indicated by an HCV-seropositive and NAT-positive donor (viremic) (D NAT+)[26]. Traditionally, all donors were serologically tested for HCV infection in accordance with the OPTN guideline recommendations. It was modified in 2014 to incorporate NAT testing for HCV infection in addition to serological testing[27,28].

THE RISK OF HCV TRANSMISSION AFTER LIVER TRANSPLANTATION

The risk of HCV transmission to recipients is highest for D NAT+, whereas the risk of transmission is likely negligible for allografts that test negative for HCV NAT[16]. HCV non-viremic donor (D NAT-) is considered safe for transplantation into R- in the absence of other risk factors such as increased risk donors (IRDs). Despite the safety of using HCV non-viremic graft into R-, the risk of HCV transmission still exists, with IRDs reaching up to 16%[29]. IRDs are defined according to the United States Public Health Service guidelines as donors who are recently exposed to HCV infection, and HCV RNA may not yet be detectable[8,30].

According to the data mentioned earlier, the utilization of IRD grafts is considered the highest risk for unexpected HCV transmission during the eclipse period. Therefore, in the absence of additional risk factors, donors who are HCV antibody positive (HCV Ab+) but NAT- are not thought to be at an elevated risk of HCV transmission. This is supported by studies reporting no HCV transmission by organ transplantation from (HCV Ab+/D NAT-)[31-33]. Consequently, post-transplant recipient testing is mandated by OPTN policies exclusively in cases where the transplant center expresses concern over the possibility of disease transmission[8]. Liver transplant recipients who receive HCV NAT+ donor livers are invariably infected with HCV[15,33-36].

USE OF HCV NON-VIREMIC LIVER DONORS INTO HCV-NEGATIVE RECIPIENTS

There have been controversies regarding the risk of HCV transmission from (HCV Ab+/D NAT-) into R-. Some reported no evidence of infection, while others reported a risk of transmission up to 16%.

Aqel *et al*[32] reported that up until a median of 6 months (range 3-18 months) post-LT follow-up, 14 recipients of HCV non-viremic grafts had undetectable HCV RNA. In another study by Crismale *et al*[33], none of the patients who received livers from (HCV Ab+/D NAT−) developed HCV viremia post-transplant.

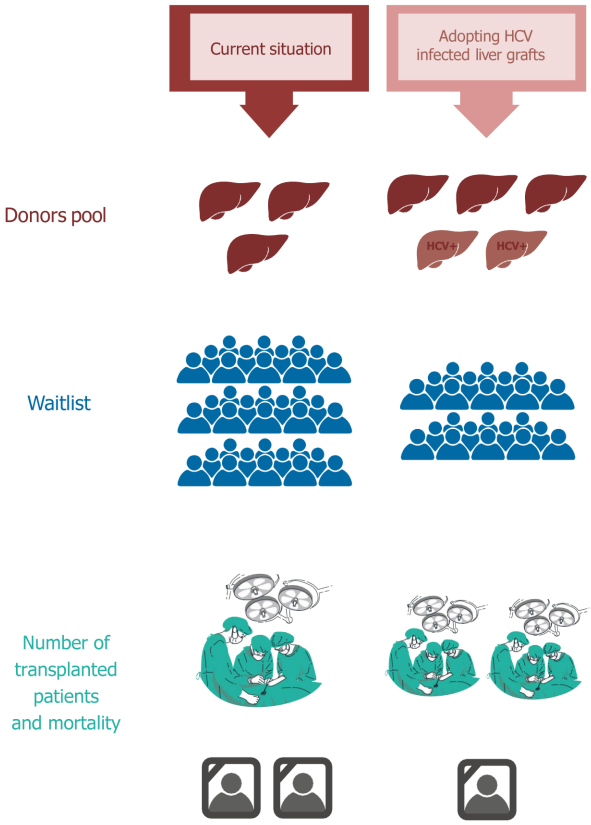

Figure 1 Impact of adopting hepatitis C virus-infected liver grafts in transplantation. HCV+: Hepatitis C virus infected liver.

A 16% risk of HCV transmission was documented by Bari *et al*[29] following LT from (HCV Ab+/D NAT−) to R-. Donors who transmitted HCV were all IRDs who died from drug overdose.

HCV viremia was experienced by 10% of the 21 R- who received LT from (HCV Ab+/D NAT-) in a study by Sobotka *et al*[37], with a high rate of reaching SVR in patients who develop HCV post-transplant. Prior research has documented a comparable incidence of HCV viremia, approximating 10%[29,34,38].

The existing literature supports various possible mechanisms of HCV transmission in these circumstances. One reasonable cause for HCV transmission in HCV Ab+ donors could be false negative NAT tests[38]. Sensitivity estimates for HCV NAT testing range from 96% to 99%, and their negative predictive value exceeds 99%[39-41].

Some donors may have been within the eclipse period for NAT detection. The report of Suryaprasad *et al*[42] on organ transplantation from seronegative, NAT-negative, high-risk donors resulting in HCV transmission to non-HCV recipients provides supporting literature for eclipse period infection. Sources of the HCV genome were isolated from stored donor splenocyte or lymphatic tissue samples despite the fact that none of the six recipients who developed HCV had received a liver transplant.

Transient low-level viremia, which occurs during the early phase of acute HCV infection when the innate and cellular immune systems are attempting to eliminate the virus and is below the limit of detection for current assays, is an additional potential mechanism by which HCV is transmitted[43,44].

Occult hepatitis C infection (OCI) in the donated tissue could cause HCV to be transmitted. The clinical significance of OCI remains uncertain, as spontaneous relapse of viremia appears to be exceptionally rare, even in immunocompromised patients post-solid organ transplant (estimated 1% to 2% after successful treatment with interferon-based regimens)[45]. Estimates of OCI prevalence vary widely, ranging from 0% to 95%, depending on the study population and methodology [46,47].

USE OF HCV-VIREMIC LIVER DONORS INTO HCV-NEGATIVE RECIPIENTS

Introducing HCV D NAT+ into HCV-transplant programs represents an innovative approach that holds promise for expanding the donor pool, enhancing transplanted organ quality, and reducing transplant list waiting times. The results of the clinical trials undertaken thus far have been encouraging[48].

Ten non-viremic recipients who underwent liver transplantation with HCV-infected livers were described by Kwong *et al*[49]. They all acquired hepatitis C infection and achieved sustained virologic response at 12 wk post-treatment (SVR-12) when treated with DAA-based regimens.

In a retrospective study by Ting *et al*[50], the 20 R- of HCV D NAT+ all acquired active HCV infection post-LT. Twelve of them reached SVR12, while the remaining were in different stages of treatment when the study was published.

In a study that included 14 R-, 9 of them underwent LT from HCV D NAT+, and viremia developed in all 9 recipients post-transplantation. The recipients received a 12-wk course of oral DAAs within 5 d after transplantation, all achieving SVR. In this study, it was reported that immediate use of DAAs post-transplantation in NAT-positive recipients is safe and effective; in addition, they did not record any cases with HCV-related complications[51].

Another study conducted at a single center examined the application of HCV-viremic allografts in non-viremic recipients; of these, 6 underwent LT (4 patients received a liver transplant, and 2 patients received a liver-kidney transplant). HCV infection was universally transmitted to the recipients. Three patients reached SVR12, 1 patient finished DAA therapy, and 2 were still receiving treatment when the study was published[52].

In another retrospective study, 61 R- that received LT from HCV D NAT+ (study group) were compared to 231 R- that received a liver from NAT- donors (control group). It was reported that 83.3% of the study group developed viremia by detecting HCV RNA within the first week and 98.3% by the end of the second week post-LT. The study concluded that using HCV D NAT+ in R- followed by DAA treatment provides good outcomes comparable to the control group[53].

In a prospective multicenter study that Aqel *et al*[32] had conducted, the study enrolled 34 donors (20 HCV-viremic, 14 non-viremic) used for graft donation to R-. The 20 recipients from HCV D NAT+ were confirmed to be infected with HCV by detection of HCV RNA within 3 d post-transplant, and they all achieved SVR12 following DAA therapy.

In a prospective multicenter study where 24 patients received organs from HCV-viremic donors (13 liver transplants and 11 kidney transplants), all 13 liver recipients had detectable HCV RNA in their serum on day 3 following transplant, and all achieved SVR12[15].

Table 1 shows the estimated risk of HCV transmission and SVR rate in HCV negative LT recipients of HCV viremic and non-viremic donors, as reported in the literature.

OBSTACLES FACED IN CASE OF USING HCV-POSITIVE DONOR ORGANS

The ethical dilemma surrounding HCV D+/R- LT pertains to the balance between the potential risks of intentionally infecting the patient with HCV and subjecting them to the consequences of HCV infection, such as fibrosing cholestatic hepatitis (FCH), heightened rates of graft rejection, DAA side effects or ineffective treatment leading to chronic HCV infection and the advantages, which could include mitigating patient mortality and waitlist abandonment rates caused by extended waiting periods, especially in a time when donor grafts are scarce[54-58].

Conversely, some experts contend that the utilization of infected donors is not a novel concept in transplantation, as evidenced by the routine use of organs from donors exposed to other infections (*e.g.*, cytomegalovirus) with adequate measures in place to control infections; therefore, HCV should not be regarded differently[59].

One of the most significant impediments to using organs from HCV D NAT+ is the expensive cost of DAAs, as well as the possibility that the recipient will not be able to get HCV treatment after transplantation. The Food and Drug Administration has not yet approved the use of DAAs for the prevention or treatment of donor-derived HCV, and it is unknown if insurance companies will pay for these drugs[35].

Certain insurance companies have the right to refuse payment for various reasons. For example, they can insist on documentation of a chronic infection for a minimum of six months, excluding treatment in an acute situation[60].

Furthermore, there is a considerable variation in perspective recipients' willingness to accept an HCV+ donor. The potential use of HCV+ organs in recipients who are HCV- also presents some ethical issues and is still debatable, especially when considered as a purposeful spread of an infectious disease to accomplish a desired result[61,62].

ETHICAL CONSIDERATIONS AND INFORMED CONSENT

The AST advises against performing HCV D+/R- transplants unless under Institutional Review Board (IRB)-approved study rules and with full informed consent of the knowledge gaps associated with such transplants[8]. A number of recent single-center studies demonstrate how quickly transplant doctors in the United States have adopted this practice [49,52,63]. However, significant questions remain about the most effective way to use antiviral medication in this situation[15].

The following factors should be taken into account while planning and carrying out HCV D+/R- transplants[64]: (1) Transplant centers should design and maintain a plan for educating and obtaining informed consent from HCV-negative transplant candidates who are considering receiving an organ from an HCV-viremic donor[64]. Standardization and use of specialized informed consent will be required to provide patients with unbiased, comprehensive information so they may make independent decisions about their care[65]; (2) Centers performing transplants from HCV-viremic donors should have a diagnostic and treatment regimen in place for HCV-negative transplant candidates[64]; And (3) Transplant centers should make sure that obstacles pertaining to payment and reimbursement will not cause a delay in the HCV diagnosis or treatment of recipients who receive organs from HCV-viremic donors[64].

An expert multidisciplinary team is required to transmit the labs and begin the approval process of getting DAA while the patient is hospitalized following transplantation to speed the start of treatment, including a committed pharmacy team to expeditiously provide data for cost assistance, prior authorizations, and appeals[35].

Table 1 The estimated risk of hepatitis C virus transmission and sustained virologic response rate in hepatitis C virus negative liver transplantation recipients of hepatitis C virus viremic and non-viremic donors

Ref.	Study design	Study group	Post LT viremia *n*/*N* (%)	SVR12	Time from transplant to start of DAA (d)
Luckett *et al* [38], 2019	Prospective	55 HCV non-viremic candidates received HCV Ab+/NAT- LT, including 6 SLKT	5/53 (9)	4/5 SVR12	NA
Kwong *et al* [49], 2019	Single-center, retrospective	10 HCV non-viremic candidates received HCV NAT+ LT	10/10 (100)	10/10 SVR12	Median 43 (IQR 20–59)
Ting *et al*[50], 2019	Single-center, retrospective	6 seronegative candidates received HCV NAT+ LT, including 2 SLKT	6/6 (100)	3/6 SVR12	Median 37 (range 9-74)
				1/6 completed DAA	
				2/6 ongoing DDA	
Bethea *et al*[51], 2020	Single-center, prospective	14 HCV negative recipients, including 4 SLKT:			
		9 received HCV NAT+ LT	9/9 (100)	9 SVR12	Range 0-29
		5 received HCV Ab+/NAT- LT	1/5 (20)	NA	
Kapila *et al*[52], 2020	Single-center, retrospective	26 HCV negative recipients:			
		20 received HCV NAT+ LT	20/20 (100)	11/20 SVR12	Median 51 (range 19-121)
				3/20 completed DAA	
				5/20 ongoing DAA	
				1/20 pending insurance approval	
		6 received HCV Ab+/NAT- LT	2/5 (40)	1/5 SVR12	
				1/5 ongoing DAA	
Anwar *et al* [34], 2020	Single-center, prospective, matched cohort trial	32 NAT- recipients received HCV NAT+ LT, including 7 SLKT	31/31 (100)	19/30 SVR12	Median 47 (IQR 18-140)
				6/30 ETR	
				5/30 ongoing DAA	
				1/30 is yet to start treatment	
Crismale *et al* [33], 2020	Single-center prospective observational	19 HCV negative recipients, including 4 SLKT:			
		13 received HCV NAT+ LT	13/13 (100)	12/13 SVR12	Median 42 (IQR 35-118)
		6 received HCV Ab+/NAT- LT	0/6 (0)		
Aqel *et al*[32], 2021	Multicenter, prospective study	34 HCV negative recipients, including 6 SLKT:			Median 27.5
		20 received HCV NAT+ LT	20/20 (100)	20/20 SVR12	
		14 received HCV Ab+/NAT- LT	0/14 (0)		
Sobotka *et al* [37], 2021	Single-center, retrospective	42 HCV-seronegative recipients:			
		21 received HCV NAT+ LT	20/21 (95)	15/15 (patients with data) SVR12	Mean 38
		21 received HCV Ab+/NAT- LT, including 1 SLKT	2/21 (9.5)	2/2 SVR12	
Bohorquez *et al* [53], 2021	Single-center, retrospective, case-control study	61 HCV negative recipients, including 3 SLKT, received HCV NAT+ LT	60/61 (98.3)	51/56 SVR12	Median 66.9 (IQR, 36-68.5)
				5/56 ongoing DDA when study published	
Hudson *et al* [36], 2021	Single-center, retrospective	18 HCV negative recipients, including received HCV NAT+ LT	18/18 (100)	18/18 SVR12	mean ± SD, 48 ± 23

Terrault *et al* [15], 2021	Multicenter (6 US centers), prospective study	13 HCV non-viremic candidates received HCV NAT+ LT	13/13 (100)	13/13 SVR12	Median 7 (IQR 6-12)
Nair *et al*[104], 2021	Retrospective cohort	23 HCV negative recipients received an HCV Ab+/NAT+ LT	23/23 (100)	23/23 SVR12	Median 118 (IQR 46-129)
Bova *et al*[35], 2022	Single-center, retrospective	29 HCV-negative recipients received HCV-viremic or HCV-seropositive LT, including 4 SLKT	29/29 (100)	NA	Median 29 (range 0-84)

Ab+: Antibody positive; DDA: Direct acting antiviral; HCV: Hepatitis C virus; IQR: Interquartile range; LT: Liver transplantation; NA: Not applicable; NAT-: Non-viremic; NAT+: Viremic; SLKT: Simultaneous liver kidney transplant; SVR12: Sustained virologic response at 12 wk post-treatment.

According to an expert consensus report from the 2019 Controversies in Transplantation workshop, the best treatment should be proactive, and all HCV-naive patients should have insurance coverage for DAAs following transplantation. Most experts agree that treatment should be preemptive. However, in real life, this is not feasible because most insurance plans require HCV testing in the recipient to approve medicine[66].

Next, it must be determined whether the recipient has viremia for treatment to be warranted. Another element is the HCV genotype, which may have a significant role in determining the particular antiviral treatment used in each case. Hence, early genotype assessment and therapy matching may be necessary for treatment considerations; however, the advent of pangenotypic antiviral regimens may eliminate this requirement. Pharmacological interactions and renal function are two other issues to be taken into account, along with the planning of DAA therapy[60].

Given that HCV D+/R- LT is already taking place, guaranteeing its fairness and justice for patients in need of LT is critical. It is imperative for LT providers to guarantee that the provision of HCV D+/R- LT does not pose a disadvantage to patients or communities that might have outdated or misguided information regarding HCV pathology and therapy following LT. According to a recent study on patient surveys, African Americans had a lower acceptance rate of HCV+ kidney transplants than White people. While it is uncertain if this perspective also applies to liver grafts, more research is required to ascertain whether attitudes toward HCV D+/R- LT differ[65].

Additionally, transplant centers that do not practice HCV D+/R- LT should notify their patients that other transplant centers might be performing HCV D+/R- LT in order to promote equality in liver graft allocation[65].

ASSESSMENT OF DONOR GRAFTS PRIOR TO TRANSPLANTATION

An optimal evaluation of the HCV-viremic liver allograft would consist of three tissue samples: Two 16-gauge needle cores, each measuring 2 cm, taken from the right and left lobes, and a wedge biopsy measuring 1 cm subcapsular from the right lobe[67]. Experts advise transporting biopsies from donor hospitals back to the recipient hospital with the donor's liver for examination by a skilled liver pathologist.

The recommendations from a consensus meeting report in 2019 regarding the obtainment of liver biopsy from HCV+ donors were: (1) Younger HCV viremic donors (less than 35 years old) probably have less fibrosis and do not need a liver biopsy prior to donation; (2) To rule out donors with advanced (F3 or F4) fibrosis, older donors (≥ 35 years old) with a chronic infection may have a liver biopsy; and (3) Donor liver biopsy results of F2 or lower are suitable for transplant[66].

The influence of donor steatosis on the outcomes of liver transplants differs across studies due to the fact that the majority of transplant surgeons decline these organs, and there is presently no data regarding the use of HCV-positive fatty grafts[68].

RECIPIENT SELECTION AND PRIORITIZATION

Who is the appropriate R- for LT from D+? Who should be prioritized? These significant questions require further research because the solutions are not entirely obvious. Based on the HCV-infected donor pool, the total supply and demand for organs, the Model for End-Stage Liver Disease (MELD) score, and the blood type, this could differ in each location[69].

In general, this strategy may be applicable to certain recipient situations[69]: (1) Individuals suffering from acute liver failure, for whom the timing of LT is crucial; (2) Patients with hepatocellular cancer in whom there is the possibility of waitlist dropout; And (3) Patients who have substantial complications from portal hypertension despite having a low MELD score, where their MELD score does not accurately reflect the severity of their condition. How long a patient stays on the waitlist depends on the number of offered grafts and their MELD score, or exception MELD score, while on the list [66].

The MELD score has demonstrated efficacy in predicting mortality among cirrhotic patients[70]. However, it has long been known that, even within a single MELD score, clinical manifestations of liver disease can vary greatly, and patients with the same MELD scores can have widely different mortality risks. Access to the larger pool of donors, made possible by HCV viremic liver allografts, may help many currently underprivileged populations, such as women, people of short stature, people with low frailty index scores, and people with sarcopenia[71-73].

While some patients and providers are willing to offer or accept HCV-positive organs, others are not. A study examined 50 individuals awaiting organ transplants. Just 30 of them were aware that HCV could be cured, and only 23 were open to receiving an infected organ. Furthermore, there were also expressions of concern regarding the curability of HCV, insurance coverage, and failed allografts[74].

HCV-infected organs should not be offered to individuals who are expected to experience a complicated posttransplant course. The following would be recipients of concern: Individuals who undergo complex transplant procedures such as liver re-transplantations, encounter early allograft dysfunction, are recipients of donations from donors who have passed away of circulatory death, are afflicted with posttransplant seizure disorders that necessitate multiple anti-epileptic medications (which are contraindicated with all DAAs) or have cardiopulmonary diseases that demand prolonged posttransplant intubation or arrhythmias that require amiodarone (contraindicated with sofosbuvir) and require high-dose proton-pump inhibitors (most DAAs)[66].

DIRECT ACTING ANTIVIRAL DRUGS

Strategies to start DAA

Strategies for liver recipients may differ from those for non-liver recipients. Preventing HCV infection in recipients can be achieved through prophylactic, preemptive, or delayed treatment. Prophylactic treatment aims to prevent the occurrence of post-transplant viremia, while preemptive treatment involves initiating therapy shortly after transplantation, even before any clinical symptoms manifest. On the other hand, delayed treatment is typically administered several weeks to months after transplantation, when clinical disease may already be evident[15].

The advantages and disadvantages of prophylactic and preemptive versus delayed methods are subjects of intense discussion in the transplant field[15].

Multiple studies suggested that administering preemptive treatment to individuals receiving HCV viremic grafts, starting at the time of transplantation and continuing for a specified period after liver transplantation, may provide the most favorable outcome in terms of achieving viral clearance and preventing early hepatic and extrahepatic complications associated with HCV[32,66,75].

A comparative analysis was conducted on the time of initiation of DAA treatment. DAA therapy was given prior to transplantation, at the time of transplantation, and during disease recurrence. Based on the premise of a 96% likelihood of attaining sustained SVR, DAA medication retained its status as the most economically efficient option when administered prior to transplantation in individuals with decompensated cirrhosis and possessing a MELD score below 20. Nevertheless, in the case of a MELD score over 20 or for patients diagnosed with HCV, administering medication upon recurrence has demonstrated superior efficacy in comparison to treatment administered pre-transplantation or at the time of transplantation[76].

When to begin DAA therapy varies among guidelines. Early therapy with pangenotypic DAA regimens should start during the first month following LT, with initiation preferred within the first week if patients are clinically stable, according to the American Association for the Study of Liver Diseases (AASLD)[16]. According to AST guidelines, until larger multicenter trials are available, peri-operative DAA introduction should be part of an IRB-approved study protocol [8].

Considerations with DAA regimens

The post-LT recipient's newly acquired genotype will determine the type and length of DAA therapy. Additional variables that have been found to impact the choice of DAA include the patient's capacity to swallow, renal function, and medication interactions[77].

Pharmacodynamics and pharmacokinetics regarding administering DAA medications *via* nasogastric tube while crushed are poorly documented. Crushing (GLE/PIB) tablets decreased glecaprevir exposures by 27%-61% and increased pibrentasvir exposures by 21%-83% in a phase 1, single-dose study involving 25 healthy adults[78]. These findings may or may not have clinical significance. Additionally, a case report describes a patient who exhibited a sustained virologic response subsequent to using a percutaneous gastrostomy tube for administration of ledipasvir/sofosbuvir[79].

Data demonstrating the safety of sofosbuvir/velpatasvir in individuals with any degree of renal impairment led three studies to acknowledge that kidney function would no longer be a determining factor in DAA selection[15,51,53].

Avoiding protease inhibitors is recommended in the presence of liver dysfunction, such as increased bilirubin levels. Certain medications shouldn't be taken with specific DAA agents or are contraindicated, such as but not restricted to high-dose antacid treatment (such as taking a proton pump inhibitor twice a day), amiodarone (contraindicated with regimens including sofosbuvir), and certain statins, such as atorvastatin[77].

After receiving a liver transplant from an HCV-positive donor, the best time to start taking DAAs is yet unknown. In a recent systematic review including 16 studies and 2 case reports, the mean or median duration to DAA commencement after transplant varied from 1.7 d to 118 d among the included studies. Although studies differed in the time required to initiate DAA, this factor did not seem to have an impact on the rate at which SVR was achieved[11].

HCV-negative recipients of HCV-viremic liver allografts seem to respond very well to treatment with a pangenotypic DAA for 12 wk, in compliance with treatment recommendations[11]. However, the duration of DAA therapy may be prolonged at the discretion of the transplant team and sometimes due to insurance preference[49].

DAA and immunosuppressive regimen

A significant worry about the potential interaction between DAA and immunosuppressive regimens, particularly for

protease inhibitors containing regimens, remains present. Nevertheless, recent small clinical trials have provided evidence for their safety in kidney and LT without necessitating any adjustments to baseline immunosuppressive regimens' dosage[80-82].

Drug interactions between DAA agents and calcineurin inhibitors are complicated and hard to predict without standardized drug interaction studies. The metabolism of grazoprevir and elbasvir shows that when cyclosporine is added, the area under the curve for grazoprevir will rise 15 times, and the area under the curve for elbasvir will rise two times. Hence, it is advisable to refrain from utilizing this particular combo. When tacrolimus is co-administered with grazoprevir, its level is expected to rise by 40% to 50%. Although no dosage modifications are expected, tacrolimus levels should be monitored. As for regimens containing sofosbuvir, there have been no reports of clinically significant drug-drug interactions[77].

Protocols for DAA treatment following LT and the optimal management of immunosuppression to prevent drug interactions with DAA therapy are additional issues that should be investigated. Risk-benefit analysis will have to be performed on an individual basis for each patient until more data are presented[65].

POST-TRANSPLANT FOLLOW UP

Post-transplant documentation of the chosen HCV treatment regimen and duration, any barriers to initiating HCV therapy, exposure to immunosuppressive agents, HCV RNA viral kinetics, liver chemistry profile, and renal function, modifications to immunosuppression, and any potential complications, such as rejection, HCV-related hepatitis, acute kidney injury, graft failure, and mortality is recommended during the post-transplant follow-up[49].

Considering the similar characteristics exhibited by all presently accessible pangenotypic DAA agents and their notable efficacy in managing donor-derived HCV infection subsequent to liver transplantation, payor choice appears to be the main factor in DAA selection[11].

These examples show that insurance formulary rather than the most recent recommendations from the AASLD and the Infectious Diseases Society of America govern the choice of DAA regimen for HCV therapy[77]. In a study, two patients were given ledipasvir/sofosbuvir + ribavirin because it was covered by their insurance[32]. In another one, a patient received sofosbuvir/daclatasvir plus ribavirin for HCV treatment after his insurance denied glecaprevir/pibrentasvir[49].

Monitoring for HCV viremia and the efficacy of DAA treatment varied among various studies of a recent systematic review. A significant proportion of research investigations evaluated donor-derived viremia through the assessment of the recipient's HCV viral load by post-operative day 7. Following transplantation, the majority of the authors reported continuous surveillance in non-viremic recipients, with weekly monitoring for the first month and then monthly monitoring for the next two months. The HCV genotype was ascertained, and DAA therapy was instituted following confirmation of HCV viremia[11].

While the results of R- utilizing D NAT+ organs are promising, there are several concerns and unknowns. It is still unclear how long HCV surveillance is required after LT. Although late conversion is uncommon, it is possible, as one patient in the Anwar *et al*[34] report became viremic on day 84 and another patient in a study by Bohorquez *et al*[53] remained HCV-free for 10 months after LT before becoming viremic. These results indicate that persistent aviremic patients require long-term HCV surveillance.

OUTCOMES OF LT FROM HCV-INFECTED DONORS

Even though the aim of expanding the use of organs from D+ is to overcome the organ shortage, the absence of favorable short-term and long-term outcomes will rule out this process. Short-term outcomes include the length of in-hospital stay, inpatient mortality, and inpatient acute rejection, while long-term outcomes include graft failure and mortality rates. In general, using D+ may allow earlier transplantation for patients with a lower MELD score and decrease the rate of worsening complications, hospitalization, and death (dropout from the waiting list). Furthermore, studies showed that D+ are usually young with lesser comorbidities and lower BMI, meaning that their grafts are healthier. These criteria of recipients and donors are associated with better outcomes[24,83]. Additionally, a 2019 cost-effectiveness analysis found that accepting either an HCV+ or HCV-free liver is cost-effective in patients with a MELD score of 22, and even at lower MELD scores if the patient's quality of life is worse than taking solely HCV-free livers[84]. Another study illustrated that receiving any liver, regardless of HCV status, in contrast to accepting only an HCV negative liver, demonstrated a survival benefit if the recipient's MELD was ≥ 20 and an even more significant benefit with MELD scores > 28[85].

A large retrospective study compared the outcomes of liver transplantation using organs from HCV+ and HCV- donors between 1995 and 2013. Patients who had liver transplants from HCV+ donors had better short-term outcomes in the initial analysis and similar outcomes when the year of the transplant was taken into account. The long-term outcomes were comparable in both groups. The mortality rates at 1 and 2 years after transplantation were slightly better in patients who received their transplants from HCV donors. However, this was once again entirely explained by the bias in the year of the transplant. Moreover, the 10-year mortality and graft failure rates were similar in both groups[86]. It is noteworthy that these good results were obtained before the DAAs.

Another study evaluated these outcomes in liver transplant HCV positive and negative recipients who received organs from HCV+ and HCV- donors before and after the era of DAAs. The 3-year survival of patients who received HCV Ab+ livers was significantly lower than that of patients who received HCV Ab- livers prior to the DAA era. However, this difference vanished after the DAA era, with identical 3-year survival rates in both groups. Additionally, donor's viremia

did not impact the survival rates in the study groups[24]. Another study reported that patients and graft survival rates were excellent in liver transplant recipients from HCV viremic and non-viremic donors[32].

Acute rejection of the graft is a post-transplant complication classified into acute cellular rejection (ACR) and antibody-mediated rejection. A liver biopsy from the graft is mandatory to differentiate between the two types and assess the rejection's severity[87]. About 10%-30% of liver transplant recipients experience ACR in general[88-91]. However, this percentage increases to 24%-80% among recipients of HCV seropositive grafts[92,93], which may be due to the interaction between DAAs and immunosuppression leading to decreased levels of immunosuppressive drugs[94]. In a small case series that included 10 liver HCV non-viremic transplant recipients from HCV D NAT+, 3 recipients developed acute rejection[49]. Notably, those recipients had an increased risk of acute rejection, and liver biopsies of the allograft did not reveal any signs of HCV infection[49,93]. ACR was also seen in 15% of liver transplant recipients from D+ in another larger study that included 34 patients who received livers from HCV D NAT+ and HCV D NAT-[32]. Greater evidence on whether rejection risk is actually elevated for recipients of HCV D NAT+ in the contemporary era - either from HCV therapy or HCV itself - may be more evident from larger prospective trials and randomized controlled trials with longer follow-up periods[49,65].

A multicenter prospective study showed that 13 HCV-negative liver transplant and 11 kidney transplant recipients who received allografts from HCV-viremic donors developed serious complications. These adverse events included AMR, biliary sclerosis, cardiomyopathy, and graft-versus-host disease[15]. Biliary complications were also noted to be more frequent in recipients of anti-HCV-positive grafts compared with the control group in a European multicenter study. However, this difference was not statistically significant[95]. Acute HCV-related glomerulonephritis and focal proliferative glomerulonephritis were rarely reported as complications of using HCV-infected liver grafts[32,96]. Patient and graft survival in R- of HCV-positive donors was evaluated in a comprehensive systematic review that included 15 studies. There was no difference in graft or patient survival in 6 of these studies, which were drawn from national LT registries from multicenter European databases and the United States. Sample sizes varied from 38 to 1930 patients. Overall, graft survival was independently predicted by the recipient's HCV serostatus rather than the donor graft[13,54].

Fibrosing cholestatic hepatitis is a rapidly progressive cholestatic hepatic inflammation associated with hepatocyte ballooning and advanced fibrosis, leading to significant hepatic impairment and potential mortality[97]. It has been documented in the past that FCH has a sub-fulminant course of hepatitis and fatal outcomes[98,99]. The fear of FCH evolution was one of the major obstacles hindering the expansion of using organs from D+ in HCV-infected recipients. Before the era of DAAs, some data showed that FCH in HCV-infected recipients after transplantation could respond well to interferon-α therapy. However, the duration of therapy for those patients was not precise, and they also required stoppage of azathioprine, which may affect graft survival in the long run[24]. The availability of DAA therapy for FCH following transplantation has been proven to be an effective and well-tolerated treatment option with high SVR rates[99, 100]. The early initiation of DAA regimens, even before grafts function, can treat FCH and prevent it[100].

CURRENT LT PRACTICE AND INSIGHT INTO THE FUTURE

To the best of our knowledge, HCV-infected donors were predominantly used in DDLT, with only 2 cases reported in LDLT. One of them was from an HCV-positive donor into an HCV-negative recipient, where LT was done after the end of DAA therapy. No DAAs were administered to the recipient perioperatively, and follow-ups revealed no HCV viremia [101]. The other was from an HCV-viremic donor who received DAA therapy before donating to an HCV-viremic recipient who received DAA therapy within 2 months post-transplantation with good 2-year graft survival of the recipient[102]. There were no remarkable incidents throughout the donors' recovery.

Thus, using HCV-infected organs would probably face many obstacles in countries that adopt LDLT programs, like Egypt. Egypt had the world's highest prevalence rate of HCV infection and succeeded in founding a successful program for HCV management through an amazing experience after treating more than 4 million patients and screening about 57 million[103]. In this context, the liver transplant community in Egypt will face some potential donors who are anti-HCV positive but are non-viremic (previously treated) and could be the primary source to expand the donor pool. Using organs other than the liver from HCV-infected living donors can be accepted with great precautions. However, using liver grafts from HCV infected living donors may be associated with significant risks as regards the donor's morbidity and mortality. Prospective trials and national and international consensuses are needed to determine whether using HCV-infected donors in LDLT is safe or not.

CONCLUSION

Based on all that was mentioned, it is clear that the benefits of using grafts from D+ in R-outweigh the risks. The outcomes of using organs from HCV seropositive donors were good even before the era of DAAs. The availability of DAAs allowed for more secure usage of organs from HCV-infected organs, even if they were viremic. Liver graft biopsies excluding hepatic fibrosis > grade 2 appear to be a good predictor of the graft's well-being before its adoption for transplantation. Ensuring the appropriate selection of patients undergoing HCV-infected graft transplantation and confirming their access to DAAs if needed may also increase this practice's benefits. National and international consensuses are needed to regulate this process to ensure the maximum benefit and the least adverse events.

FOOTNOTES

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REVIEW

Whole-eye transplantation: Current challenges and future perspectives

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Abstract

Whole-eye transplantation emerges as a frontier in ophthalmology, promising a transformative approach to irreversible blindness. Despite advancements, formidable challenges persist. Preservation of donor eye viability post-enucleation necessitates meticulous surgical techniques to optimize retinal integrity and ganglion cell survival. Overcoming the inhibitory milieu of the central nervous system for successful optic nerve regeneration remains elusive, prompting the exploration of neurotrophic support and immunomodulatory interventions. Immunological tolerance, paramount for graft acceptance, confronts the distinctive immunogenicity of ocular tissues, driving research into targeted immunosuppression strategies. Ethical and legal considerations underscore the necessity for

stringent standards and ethical frameworks. Interdisciplinary collaboration and ongoing research endeavors are imperative to navigate these complexities. Biomaterials, stem cell therapies, and precision immunomodulation represent promising avenues in this pursuit. Ultimately, the aim of this review is to critically assess the current landscape of whole-eye transplantation, elucidating the challenges and advancements while delineating future directions for research and clinical practice. Through concerted efforts, whole-eye transplantation stands to revolutionize ophthalmic care, offering hope for restored vision and enhanced quality of life for those afflicted with blindness.

Key Words: Eye; Transplantation; Optic nerve; Nerve regeneration; Immunological tolerance

Core Tip: Whole-eye transplantation remains a theoretical endeavor. Innovative technologies like bioengineered eyes holding promise for future breakthroughs. The foremost challenge is to restore the functional connectivity between the optic nerve and the retina. The challenge of reconnecting the optic neural axis is explained by its peculiar anatomical features where the cell bodies of the sensory neurons are located within the retina itself. Regeneration of axonal populations within the optic nerve from the occipital cortex towards the retina is physiologically not feasible. Research in cell and animal models may provide new frontiers to overcome these functional hurdles, with hopes that eye-sight can be restored with eye transplantation.

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INTRODUCTION

Nowadays, 43 million people are blind, with cataract, diabetic retinopathy, and glaucoma as leading causes[1]. Whole-eye transplantation holds profound significance due to its potential to revolutionize the treatment of blindness and severe visual impairments[2]. By offering the possibility of restoring sight in cases where current medical and surgical interventions fall short, this approach could drastically improve the quality of life, independence, and social integration for individuals living with vision loss[3]. The significance of whole-eye transplantation extends beyond the individuals directly impacted by these conditions, touching broader societal and economic factors. Successful whole-eye transplantation could reduce the healthcare and social support costs associated with blindness and visual impairment, contributing to greater overall productivity, and reducing the economic burden on families and communities.

The quest for whole-eye transplantation is a long-standing endeavor, marked by initial fascination and complex challenges[4]. Early experiments in the late 19th and early 20th centuries explored the feasibility of such transplants in animals, focusing on the technical and biological hurdles involved. A major obstacle identified by mid-20th-century research was the optic nerve's inability to regenerate, crucial for restoring vision in transplanted eyes[5]. This challenge, coupled with the difficulty of preventing immune rejection, steered scientific efforts towards more achievable goals like component transplantation and regenerative medicine. Corneal transplants became successful, routine procedures, while advances in stem cell therapy, gene therapy, and tissue engineering offered new hope for vision restoration without full eye transplants[6,7].

In parallel, significant advancements have been made in the development of eye prostheses and assistive technologies [8,9]. Modern ocular prosthetics not only offer aesthetic improvements but also incorporate advanced materials and designs that enhance wearer comfort and integration with the ocular socket. Beyond traditional prosthetics, cutting-edge research into electronic visual prostheses, often referred to as "bionic eyes", aims to restore sight through the direct stimulation of visual pathways in the brain or the remaining parts of the visual system[10]. These devices, which can include retinal implants and cortical visual prostheses, translate external visual information captured by cameras into electrical signals that the brain can interpret, offering a form of sight to those with certain types of blindness[11,12].

As of today, whole-eye transplantation remains a partially theoretical endeavor, with research in regenerative medicine and innovative technologies like bioengineered devices, such as retinal prosthesis and artificial cornea, holding promise for future breakthroughs[13,14]. Although the first whole-eye transplantation in human was recently performed, no functional restoration of vision has been achieved, highlighting that aesthetic improvement alone is not sufficient[4]. The foremost challenge is to restore the functional connectivity between the optic nerve and the retina. The challenge of reconnecting the optic neural axis is explained by its peculiar anatomical features where the cell bodies of the sensory neurons (ganglion cell) are located within the retina itself. Thus, regeneration of axonal populations within the optic nerve from the occipital cortex towards the retina is physiologically not feasible. Making the re-establishment of vision connections to the brain is of the highest importance for eyesight restoration. Sight is primarily a brain function rather than a purely ocular one[15,16].

On the other hand, immune rejection poses another major problem, as the body's defense mechanisms often attack the transplanted tissue, considering it foreign. Overcoming these obstacles requires breakthroughs in regenerative medicine, immunology, and surgical techniques, including promoting nerve regeneration and developing effective strategies to manage or prevent immune responses against the transplanted eye[17-22].

In this review, we assess the current state of art on whole-eye transplantation, addressing both the advancements and the future challenges, encompassing innovations in immune acceptance and neural regeneration for visual function restoration following eye transplant.

ADVANCES AND INSIGHTS

Surgical techniques and interdisciplinary insights from animal models in whole-eye transplantation

Whole-eye transplantation, a pioneering endeavor in medical science, frequently intersects with the intricacies of face transplantation, particularly regarding surgical techniques, tissue integration challenges, and the nuances of immunosuppression[23]. This confluence is particularly apparent in the comprehensive approach both fields demand, encompassing not just the transplantation of the primary organ but also the intricate reconnection of nerves, blood vessels, and surrounding tissues to reinstate function and achieve aesthetic congruence[3,24-26].

In the realm of surgical advancements, the insights garnered from face transplantation have significantly informed whole-eye transplantation efforts, especially in mastering the microsurgical techniques essential for successful tissue integration. The expertise in microvascular anastomosis, cultivated through vascularized composite allograft (VCA) transplantation, proves invaluable for whole-eye transplantation by ensuring the establishment of a functional blood supply essential for the transplanted eye's viability[27]. Furthermore, the shared challenges of immunosuppression and managing tissue rejection highlight the interdisciplinary synergy between these fields. This collaborative framework enriches the understanding and development of strategies to mitigate rejection and optimize post-transplant recovery[28-30]. The exploration of whole-eye transplantation has ventured into animal models, providing a tangible basis for assessing its feasibility and delineating the procedural complexities[31,32] (Figure 1). Notably, research has concentrated on rodents and swine, selected for their anatomical and physiological similarities in eye structure and immune response, offering a closer approximation to human applications[26,31].These animal studies have been instrumental in refining surgical techniques, such as precise optic nerve alignment and reconnection strategies, and advancing our comprehension of vascularization necessities for the transplanted eye.

These endeavors in animal models have underscored the procedural feasibility of whole-eye transplantation, albeit with the caveat that restoring vision remains a formidable challenge yet to be surmounted[33]. It has been achieved in some animals (cold-blooded vertebrates), but not in mammals[34-38]. The learnings from these models are invaluable, serving as a foundation for future innovations and the eventual translation of whole-eye transplantation into a viable clinical procedure for humans[39-41]. In 2023, Laspro *et al*[42] highlighted the feasibility of WET, noting its safety with no recorded complications for recipients as per existing literature. They emphasized its potential for functional restoration, supported by evidence of positive retinal survival in live models. However, the capability for optic nerve regeneration still requires clarification. The surgical expertise necessary to attain our objectives has been attained; attention must now be directed towards advancing other areas.

Through this meticulous research, the goal of restoring sight to those with severe visual impairments moves closer to reality, demonstrating the power of interdisciplinary collaboration in pushing the boundaries of medical science.

Immunological background

The eye is unique as it consists of immunologically privileged and avascular structures[20]. The intricate journey towards achieving successful whole-eye transplantation is significantly influenced by the immunological landscape unique to the eye, a topic extensively explored in the literature[17,18,20,22]. This body of work sheds light on the nuanced challenges and considerations inherent in transplanting an organ as complex and immunologically distinct as the eye.

Recognizing the eye as an immune-privileged site elucidates both the advantages and complications these characteristic poses for transplantation[17-19,21]. The privilege, which under normal circumstances safeguards the eye from inflammatory damage, becomes a double-edged sword in the context of transplantation, necessitating innovative approaches to manage the immune response. The term “immune privilege” was first coined in the first half of the 18th century, when Medawar and colleagues recognized the extended survival of skin allografts placed in the anterior chamber of the eye[19,43]. Years later, Streilein and Niederkorn[44,45] demonstrated that immune privilege was in fact the result of an actively maintained and “deviant” suppressive immune response to ocular antigens, a phenomenon that was later referred to as anterior chamber-associated immune deviation. This process was mediated by antigen presenting cells (APCs), CD4+ T cells, and particularly antigen-specific regulatory T cells (Tregs) which orchestrate immune changes in the setting of autoimmune diseases and graft-rejection[46-48] (Figure 2). As a consequence of this knowledge, corneal transplantation has become one of the most successfully performed solid organ transplantation, with a more than 90% rate of success in low-risk condition, while in high-risk setting it lowers to less than 50%[49,50]. Interestingly, the impressive success rate often witnessed in low-risk corneal grafts, unlike with other solid organ transplants, can be attained without relying on HLA matching or extensive systemic immune suppression[51,52]. Following transplantation, inflammation in the eye triggers the upregulation of proinflammatory cytokines like IL-1, IL-6, and TNF-α, as well as chemokines such as MIP-1α, MIP-1β, MIP-2, and RANTES[53]. This inflammatory environment also leads to increased expression of adhesion molecules like ICAM-1 and VLA-1[54,55]. Consequently, both resident and infiltrating host APCs exhibit elevated levels of MHC class II and costimulatory molecules like CD80 (B7-1), CD86 (B7-2), and CD40[56]. This

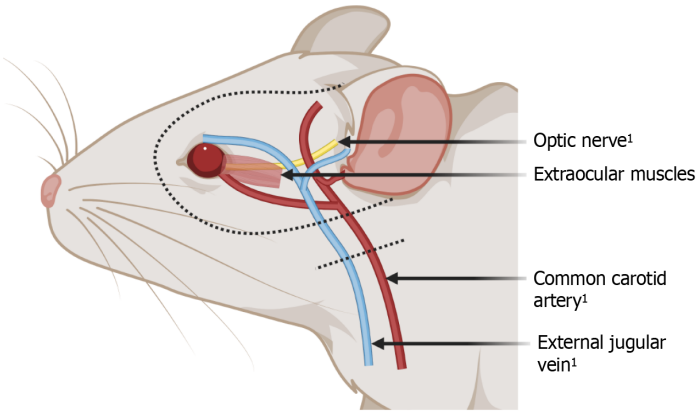

Figure 1 Anatomical illustration of a rodent model for whole-eye transplantation. [1]Anastamosis with the recipient. Created with BioRender.com (Supplementary material).

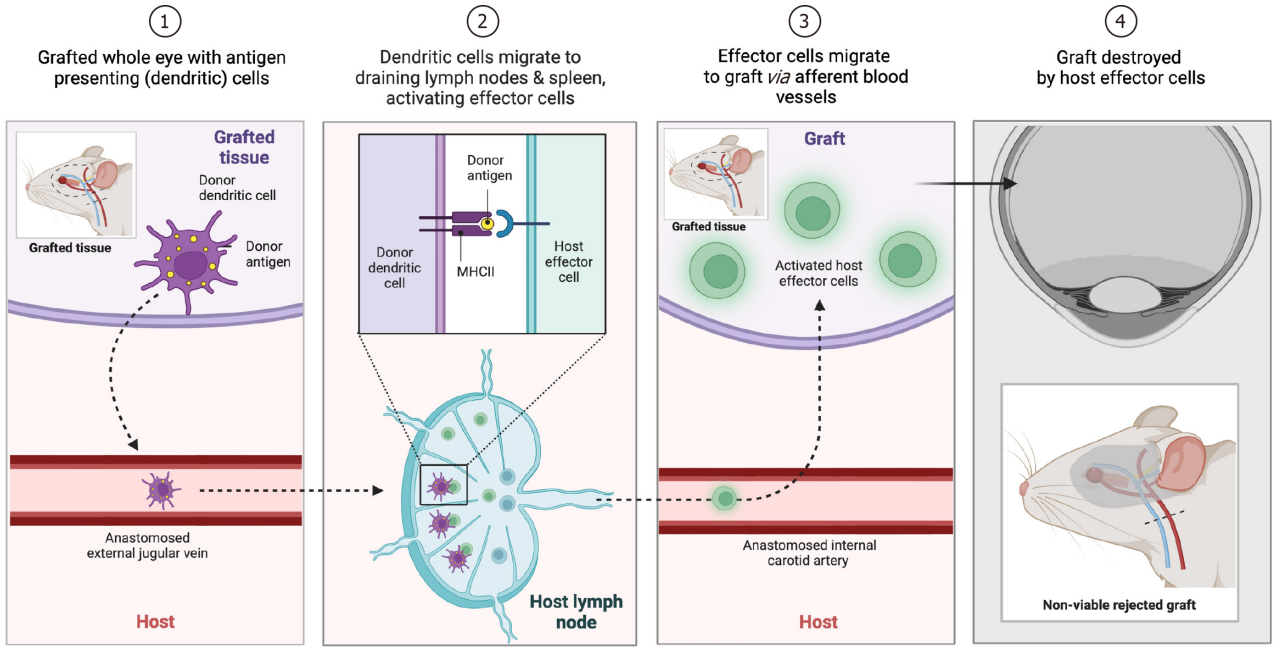

Figure 2 Schematic figure of different phases of the rejection process, mediated by antigen-presenting cells and activated effector cells, following whole-eye transplantation in a representative rodent model. Created with BioRender.com (Supplementary material).

enhances the ability of donor corneal APCs, typically incapable of T cell stimulation, to prime naïve T cells into Th1 effectors, which play a crucial role in acute graft rejection[57]. When considering the retina, studies regarding the retinal pigmented epithelium transplantation demonstrated that, besides the cellular and molecular pathways mentioned before, there is a strong activation of pro-inflammatory phenotype of microglial cells which lead to an increase of TNFα, IL-1β, IL-6, nitric oxide, and ROS signaling and, ultimately, rejection and neuronal damage[58]. The critical balance between avoiding graft rejection and preserving the eye's immune privilege underscores the complexity of immunological considerations in whole-eye transplantation. This balance involves a deep understanding of the eye's specific immune responses and developing strategies that can foster graft acceptance while mitigating adverse reactions.

Addressing the challenges of graft rejection and the maintenance of immune privilege involves a multifaceted strategy, incorporating advances in immunosuppressive therapies and the exploration of tolerance-inducing techniques. The demand for localized immunosuppression, as opposed to systemic treatments, makes this field a promising area of investigation, potentially offering a more focused approach that minimizes broader immunosuppressive side effects.

Moreover, compatibility between donor and recipient, the exploration of novel immunomodulatory agents, and the potential role of regenerative medicine and stem cell therapies in promoting graft tolerance. In this realm, mesenchymal stem cells represent a beacon of hope given their both regenerative and immunoregulatory capacities secreting numerous substances that can promote immune-regulated environment in the setting of eye transplantation[59]. These considerations are pivotal in devising comprehensive strategies that tackle the immunological barriers to whole-eye transplantation.

Whole-eye transplantation is commonly performed in hybrid animal models with face transplant. The comprehensive immunosuppressive regimens developed for face transplant recipients, aimed at preventing the body's rejection of transplanted tissues, are of significant relevance to whole-eye transplantation. Understanding how to balance these regimens to minimize side effects while ensuring the survival of the transplanted tissue is a shared challenge that benefits from interdisciplinary research and clinical experience in both areas.

Optic nerve regeneration

The eye is the only 'peripheral' organ that is directly connected to the brain *via* the optic nerve. Unlike the nerves of the peripheral nervous system (PNS), the optic nerve do not spontaneously regenerate[60]. This lack of regeneration has been attributed primarily to differences in the molecular and cytokine environments between the two systems[61-63]. In the peripheral system, factors that stimulate regeneration are present, whereas, in the central system, inhibitory factors predominate[64]. Additionally, the reduced clearance of cellular debris in the central nervous system (CNS) further hampers regeneration efforts[64,65].

One of the distinguished features of the visual neural axis compared to the neural axis in the somatosensory system is the location of the cell bodies of the corresponding sensory neurons. While in the PNS, the sensory neurons are located in the dorsal root ganglia (DRG), which receive afferent information from distal targets like cutaneous mechanoreceptors *via* afferent axons. When the axonal continuity of the peripheral nerve is disrupted distally to its cell bodies in DRGs, the afferent axons regenerate anterogradely towards their targets in the periphery[66]. The anatomy of the eye and the visual neural axis differs from the peripheral somatosensory axis in that the sensory cell bodies, retinal ganglion cells (RGCs), are migrated topographically more distally and are located within the retina in direct proximity to the photoreceptors. Thus, continuity disruption of the optic nerve proximally from the retina is analogous to preganglionic brachial plexus injury in the upper extremity, where the axons fail to regenerate as the sensory neurons and signal pattern generation are not lost[67]. This underlines the major limitation in optic nerve regeneration, which does not allow for retrograde axonal growth.

In this context, Aguayo *et al*'s[68] work stands out, demonstrating that CNS nerves may grow long distances when placed in the appropriate environment, such as within a peripheral nerve. This finding opened new avenues for optic nerve regeneration research, particularly relevant for RGCs[68]. RGC axons, which course through the optic nerve, are the sole carriers of visual information to the brain. Following injury, these axons fail to regrow, and RGC cell bodies typically die, resulting in permanent vision loss. To preserve RGCs and stimulate their axons' regeneration, researchers must overcome four major hurdles: Increasing RGC survival, navigating the inhibitory environment of the optic nerve, enhancing the intrinsic axon growth potential of RGCs, and optimizing the reestablishment of RGC connections to their targets in the brain[69,70]. The death of RGCs in post-optic nerve injury can be traced back to the disruption of axonal connections to their targets, eliminating the target-derived neurotrophic support[71]. These signals, which are retrogradely transported to the cell body, are crucial for neuronal survival. Thus, strategies to promote optic nerve regeneration must simultaneously address the post-injury death of RGCs, the inhibitory glial environment, changes in RGCs' intrinsic axon growth potential, and the guidance of regenerating axons to their correct targets in the brain[33].

Efforts in CNS regeneration research have provided valuable insights that could be applied to optic nerve injuries. By leveraging a multi-faceted approach that includes enhancing neurotrophic support, modifying the inhibitory environment, and boosting the intrinsic growth capacity of RGCs, the field moves closer to viable strategies for optic nerve regeneration[72,73]. These strategies range from molecular and cellular therapies, such as the application of neurotrophic factors and stem cell transplantation, to innovative technologies like optogenetics and nanotechnology-based delivery systems[74-76]. Stem cells hold immense promise in the field of ophthalmology for optic nerve regeneration[77]. These versatile cells possess the capability to differentiate into various cell types, including those crucial for repairing damaged optic nerves. By harnessing the regenerative potential of stem cells, researchers aim to restore vision in conditions such as glaucoma and optic nerve injuries[78,79]. Exosomes and extracellular vesicles (EVs) play pivotal roles in stem cell-based therapies for optic nerve regeneration[80]. These tiny membrane-bound vesicles secreted by stem cells contain a cargo of bioactive molecules, including proteins, nucleic acids, and growth factors[79]. Exosomes and EVs act as messengers, facilitating intercellular communication and transferring regenerative signals to target cells within the optic nerve[81]. Through their ability to modulate cellular processes and promote tissue repair, exosomes and EVs enhance the therapeutic efficacy of stem cell treatments for optic nerve regeneration. This synergy between stem cells and their secreted vesicles offers new avenues for developing innovative regenerative therapies to restore vision and improve the quality of life for individuals with optic nerve disorders. Each approach aims not only to stimulate axon growth but also to ensure the precise navigation and integration of these axons into their brain targets, a critical step for restoring vision. As some of these approaches progress into human clinical trials for optic nerve and spinal cord injuries, the convergence of new technologies and strategies brings us closer to offering tangible hope for those affected by optic nerve diseases. The complexity of the optic nerve's environment and the need for precise axonal guidance underscore the challenges ahead. However, the ongoing advances in understanding and manipulating this environment suggest that overcoming the barriers to optic nerve regeneration may soon be within reach. By continuing to explore and integrate these diverse strategies, the goal of restoring sight through whole-eye transplantation and optic nerve regeneration becomes increasingly attainable, marking a potential paradigm shift in the treatment of blindness and visual impairment.

LIMITS TO SUCCESS

Whole-eye transplantation represents a pioneering frontier in the field of regenerative medicine and ophthalmology,

holding the promise of restoring vision to those with irreversible blindness. However, this ambitious endeavor faces several formidable challenges, including maintaining: (1) Donor eye viability; (2) achieving regeneration of the neuronal networks, ensuring; (3) immunological tolerance, and navigating; and (4) ethical and legal considerations. This chapter delves into the current state of research in these critical areas, underlining both the progress and the obstacles that lie ahead.

Donor eye viability

Maintaining the viability of the donor eye post-enucleation stands as a paramount challenge in whole-eye transplantation, underpinned by three critical parameters: The recovery of visual function post-transplant, the resilience of the outer retina to ischemia, and the survival of RGCs[33,82,83]. The journey toward understanding and optimizing these factors reveals a complex interplay of biological and technical considerations.

The quest for visual function recovery post-transplant has yielded intriguing insights, particularly from studies on cold-blooded vertebrates[34-38]. These creatures demonstrate a capacity for visual function recovery that, while offering a glimmer of hope, also underscores a significant barrier due to the vastly different regenerative abilities between these species and humans. This disparity poses a formidable challenge, emphasizing the need for innovative approaches to bridge the gap in regenerative potential.

The outer retina's function, highly sensitive to ischemia, varies notably in the crucial hours following enucleation, typically ranging from 4 to 9 hours. The application of electroretinography has proven instrumental in assessing the functionality of this layer. Immediate reperfusion, ideally within a 10-min window of ischemia, has been shown to preserve its function for an extended period, suggesting that the timing and method of reperfusion are critical to maintaining the retina's viability[33,82].

Furthermore, the survival of RGCs, pivotal for the transmission of visual information from the eye to the brain, hinges on minimizing ischemic time and optimizing the point of optic nerve transection. Intracranial sections, with transections made more than 8 mm away, have shown better outcomes, potentially enhanced by the application of neurotrophic factors. This highlights the intricate balance between surgical technique and biological intervention necessary to support RGC survival[84,85].

Notably, the understanding of RGC survival has evolved over time. For instance, Scalia *et al*'s[86] study in 1985 provided a quantitative analysis of RGC survival following optic nerve injury and regeneration, revealing that even with a full recovery of vision, only 29% of RGCs remained after 50 wk[84,86-89]. While other researchers have reported higher survival rates, these findings collectively underscore that less than 100% RGC survival might still suffice for visual recovery. This perspective, primarily derived from studies in cold-blooded vertebrates, holds promise for the enhanced ability to maintain RGC survival in mammalian systems, including humans.

Taken together, these parameters outline a landscape of challenges and opportunities in whole-eye transplantation. Each factor, from visual function recovery and outer retina resilience to RGC survival, contributes to the intricate puzzle of maintaining donor eye viability, underscoring the need for continued research and innovation in this pioneering field.

Restoration of the neural pathways

The quest for successful whole-eye transplantation is a journey through uncharted territories in medical science, particularly due to the complexity of optic nerve regeneration and its integration into the CNS. The optic nerve, comprising axons of RGCs, forms the critical link between the eye and the brain, making its regeneration essential for the restoration of vision (Figure 3). However, a fundamental hurdle in this endeavor is the mammalian CNS's inherent inability to regenerate damaged axons, a trait that starkly contrasts with the regenerative capabilities observed in many other vertebrates[40,68]. This limitation means that any damage to the RGCs results in irreversible vision loss. Despite these challenges, the rapid accumulation of knowledge regarding axonal destruction and regeneration signals a beacon of hope, edging us closer to the possibility of developing effective regenerative therapies for CNS injuries.

The regeneration of the optic nerve stands as a formidable barrier to the success of whole-eye transplantation. Achieving this feat requires not only the regeneration of damaged axons but also their successful integration and functional connection with the recipient's brain. This dual challenge implicates both regenerative and connective hurdles within the intricate environment of the CNS.

Several factors, both intrinsic and extrinsic, contribute to the optic nerve's limited regenerative capacity. Firstly, the CNS environment itself is not conducive to optic nerve regeneration, in stark contrast to the PNS, where regeneration is more readily facilitated[90,91]. Studies utilizing peripheral nerve grafts have shown promising results in enabling RGC axon regeneration through the transected rodent optic nerve, highlighting the CNS's inhibitory nature towards regeneration. Moreover, the myelin proteins within the CNS, which are crucial for insulating axons and facilitating the rapid conduction of electrical signals, play a paradoxical role in optic nerve regeneration. While myelin is beneficial for signal transmission, the myelin produced by oligodendrocytes in the CNS has an inhibitory effect on axon regeneration, a phenomenon not observed with Schwann cells in the PNS[92]. This inhibitory effect underscores the stark differences in regenerative capacities between the CNS and PNS.

In addition to the environmental and myelin-related challenges, the response to injury, including inflammation and immune reactions, significantly impacts the regenerative potential of RGCs. The cellular and molecular processes initiated by optic pathway transection can create barriers to regeneration. Immunomodulatory therapies may offer a pathway to mitigate these effects, as the astrocytes, which support synaptic development and plasticity, can form physical and molecular barriers post-injury that impede axonal regrowth.

Intrinsic factors within the RGCs themselves also play a crucial role in their regenerative capacity. As RGCs mature, they undergo significant changes in their molecular programming, including the down-regulation of growth-promoting molecules such as phosphorylated mammalian target of rapamycin (phosphor-mTOR). This down-regulation signi-

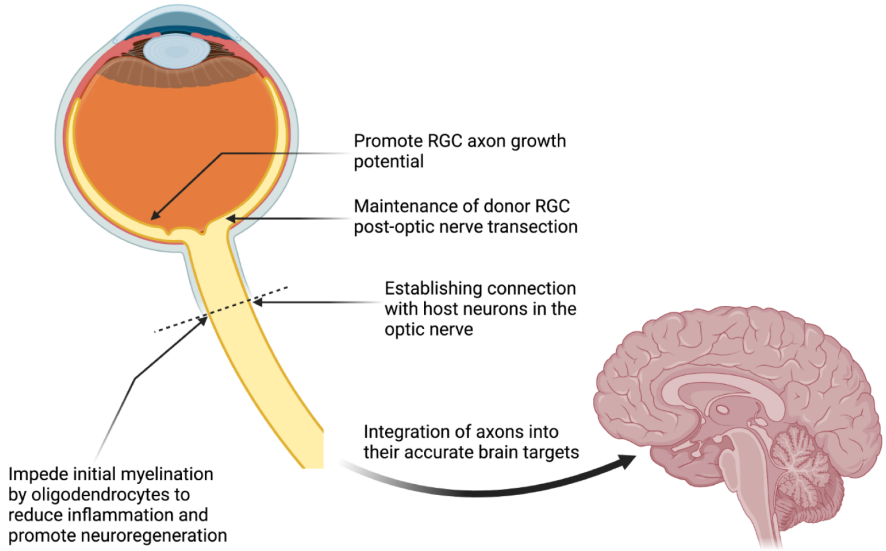

Figure 3 Challenges in neural pathway regeneration for restoring visual function following whole-eye transplantation. RGC: Retinal ganglion cell. Created with BioRender.com (Supplementary material).

ficantly hampers the axons' ability to regenerate after injury. However, research has demonstrated that targeting these intrinsic factors, such as by deleting an mTOR inhibitor like phosphatase and tensin homolog (PTEN), can markedly enhance the axonal regeneration capacity of RGCs following injury[93-95].

The challenges of optic nerve regeneration extend beyond the optic nerve itself, encompassing the need for precise reconnection of regenerated axons with the appropriate targets in the brain. Achieving such precise reintegration is crucial for restoring complex visual functions. Studies have shown some success in enhancing RGC axon regeneration into critical brain structures involved in visual processing, offering a glimpse into the potential for functional recovery. Nevertheless, the meticulous reconnection of optic nerve fibers to their designated targets in the brain, coupled with the immunological considerations inherent in transplanting an entire eye, including the optic nerve, presents significant challenges that must be addressed to ensure the long-term success and viability of whole-eye transplantation[95].

In addressing these multifaceted challenges, the exploration of biomaterials and engineered scaffolds represents a promising avenue for research. These materials can be designed to release growth factors and present cues that encourage axonal extension towards their targets, potentially overcoming some of the intrinsic and extrinsic barriers to optic nerve regeneration. Despite the advancements in understanding and experimental approaches to facilitate optic nerve regeneration, translating these findings into successful clinical applications remains an arduous task[93,94]. The journey toward whole-eye transplantation is fraught with obstacles, yet the pursuit of overcoming these barriers continues to drive forward the frontiers of ophthalmology and regenerative medicine.

Immunological tolerance

In the domain of immunological tolerance, the adaptation of protocols from those employed in face transplantation is indeed pertinent. However, it's essential to delineate specific therapies utilized for eye transplantation[96]. Current immunosuppressive regimens for face and eye transplantation typically involve agents such as tacrolimus, mycophenolate mofetil, cyclosporine, and corticosteroids[97,98]. Nevertheless, previous studies indicate that every patient who underwent face transplantation and was followed up postoperatively for one year encountered at least one episode of immune rejection[99]. A significant effort has been directed towards minimizing immunosuppressive regimens by employing lower dosages and reducing the number of medications; however, this has been associated with an increased risk of allograft rejection. Novel immunomodulatory agents, such as anti-T-cell targeting molecules[100], interleukin-2 receptor antibodies[101], and monoclonal antibodies like alemtuzumab and rituximab[102,103], have demonstrated promising outcomes in this context. The heterogeneity of ocular tissue renders eye transplantation highly immunogenic, despite its immune-privileged characteristic, and challenging to manage without robust immune suppression, which inevitably carries its own set of side effects[102,104,105]. One advantage that researchers should consider in future endeavors is the accessibility of the eye, which allows for localized therapy to be tested. Localized therapy can potentially minimize the side effects associated with immunosuppressants while simultaneously enhancing the efficacy of concomitant systemic therapy[106]. This approach capitalizes on the unique anatomical features of the eye, allowing for targeted delivery of medications to the site of action while reducing systemic exposure and associated adverse effects. By exploring localized therapies, researchers can strive to optimize the balance between effective immunosuppression and minimizing systemic side effects, ultimately improving outcomes for patients undergoing eye transplantation. The pursuit of functional eye transplants prompts a reassessment of whether a standalone eye transplantation approach might be preferable, prompting a reevaluation of immunosuppression protocols to optimize outcomes. Ensuring immunological tolerance while minimizing the risk of rejection and adverse effects is a delicate balance that requires further research.

Ethical and legal considerations

Ethical and legal considerations form an integral part of the dialogue on whole-eye transplantation. The prospect of restoring sight through such transplants raises profound ethical questions, from the allocation of donor eyes to the psychological impact on recipients and donors' families. Furthermore, legal frameworks must evolve to address the nuances of whole-eye transplantation, ensuring that these procedures are conducted with the highest ethical standards[4, 107].

CHALLENGES AND FUTURE PERSPECTIVES

In the realm of eye transplantation, navigating future challenges is pivotal for advancing the field. Among these challenges, the neural component stands out as a central focus demanding thorough investigation. Currently, it acts as a tyrant, dictating the success and viability of transplantation endeavors. Therefore, minimizing neural damage during the isolation of the donor eye and reducing ischemic times, ideally below 20 min, emerge as paramount objectives. Achieving these goals necessitates a meticulously organized and finely tuned surgical technique. Efforts to mitigate neural damage and minimize ischemic times are multifaceted. Emphasizing the importance of preserving retinal cell viability, techniques leveraging cold preservation and refining surgical methodologies are imperative. By meticulously optimizing surgical procedures, researchers aim to curtail ischemic durations, safeguarding the integrity of retinal cells crucial for visual function.

Furthermore, promoting optic nerve regeneration constitutes another critical frontier. Stem cell therapies emerge as promising avenues in this endeavor, holding potential for stimulating nerve regrowth and facilitating functional recovery. These innovative approaches underscore the importance of interdisciplinary collaborations and continued exploration of regenerative medicine strategies.

In navigating these challenges, finding a delicate balance in immunosuppressive regimens poses another significant hurdle. The ideal regimen should strike a nuanced equilibrium, minimizing adverse effects while preventing rejection of the transplanted eye. This necessitates a nuanced understanding of immune responses and the development of tailored immunosuppressive protocols.

Future directions in eye transplantation necessitate a comprehensive approach, addressing not only the surgical intricacies but also the complex interplay between neural regeneration and immune responses. By leveraging advancements in surgical techniques, regenerative therapies, and immunomodulation strategies, researchers endeavor to overcome these challenges and pave the way for improved outcomes and enhanced quality of life for individuals undergoing eye transplantation.

CONCLUSION

Whole-eye transplantation stands on the cusp of revolutionizing the treatment of blindness. However, the path forward is fraught with challenges that span the biological, technical, and ethical domains. Maintaining donor eye viability, mastering optic nerve regeneration, achieving immunological tolerance, and navigating the ethical landscape are hurdles that the scientific community must overcome. The journey towards whole-eye transplantation is a testament to the resilience and innovation inherent in the quest to restore sight, promising a future where vision restoration is within reach. In summary, the current state of the art is one of cautious optimism, marked by innovative research directions that address both biological and technical challenges. Continuous advances in molecular biology, regenerative medicine, and surgical techniques fuel the hope for overcoming the current limitations, potentially paving the way for successful whole-eye transplantation in the future.

FOOTNOTES

Author contributions: Scarabosio A and Surico PL contributed equally as co-first authors; Scarabosio A, Surico PL, Salati C, Parodi PC, Leopoldo S and Zeppieri M wrote the outline; Scarabosio A, Surico PL did the research and writing of the manuscript; Salati C, Parodi PC, Spadea L, Tereshenko V, Singh RB, Caputo G, Winograd J Zeppieri M assisted in the writing of the paper; Scarabosio A, Surico PL, Zeppieri M were responsible for the conception and design of the study and Zeppieri M completed the English and scientific editing; Scarabosio A, Surico PL, Tereshenko V, Singh RB, Salati C, Caputo G, Parodi PC, Spadea S, Gagliano, Winograd J and Zeppieri M assisted in the editing and making critical revisions of the manuscript; all authors provided the final approval of the article.

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MINIREVIEWS

Sarcopenic obesity in patients awaiting liver transplant: Unique challenges for nutritional recommendations

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Abstract

Sarcopenic obesity increases the risk of mortality in patients with liver disease awaiting liver transplantation and in the post-transplant period. Nutrition recommendations for individuals with sarcopenia differ from recommendations for patients with obesity or sarcopenic obesity. While these nutrition guidelines have been established in non-cirrhotic patients, established guidelines for liver transplant candidates with sarcopenic obesity are lacking. In this paper, we review existing literature on sarcopenic obesity in patients with chronic liver disease and address opportunities to improve nutritional counseling in patients awaiting liver transplantation.

Key Words: Nutrition; Sarcopenia; Sarcopenic obesity; Liver transplant; Cirrhosis; Chronic liver disease; Body composition; Myostatin

Core Tip: Sarcopenic obesity is common among patients with chronic liver disease and is associated with increased mortality both pre- and post-liver transplantation. Although nutrition guidelines exist for non-cirrhotic patients with sarcopenic obesity, there is limited data on nutrition recommendations for those with liver disease. Here, we discuss sarcopenic obesity in liver transplant candidates and review nutrition recommendations for this specific population.

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INTRODUCTION

Malnutrition and sarcopenia are common in patients with chronic liver disease (CLD) and are critical predictors of outcomes for those pursuing liver transplant (LT)[1]. The American Association for the Study of Liver Disease defines malnutrition as deficiency in caloric or nutrient intake and defines sarcopenia as the loss of muscle mass[1]. Importantly, malnutrition and sarcopenia can occur independently of weight or body mass index (BMI). In fact, 20% to 35% of patients with cirrhosis experience both substantial muscle wasting and accumulation of body fat, and up to 35% of patients with cirrhosis who are obese have low muscle mass[2-4]. Despite this burden, there is a paucity of literature on nutrition in patients with cirrhosis who have concurrent sarcopenia and obesity. This gap in the literature prevents comprehensive nutritional support for our patients with the phenotype of both sarcopenia and obesity. In this review, we discuss the definitions, pathophysiology, and clinical implications of sarcopenic obesity in LT candidates and review nutrition recommendations aimed toward weight management with concurrent preservation of muscle mass in the pre-transplant setting.

DEFINING SARCOPENIA, OBESITY, AND SARCOPENIC OBESITY

Sarcopenia is a progressive and generalized disorder of skeletal muscle that is defined by low muscle mass with or without loss of muscle strength[1]. Most studies conducted in patients with cirrhosis define sarcopenia by muscle mass metrics detected on routine imaging studies alone[1]. Professional guidelines recommend the use of Skeletal Muscle Mass Index (SMI) as assessed by computed tomography at the time of routine health assessments[1,5].

Obesity is a chronic disease clinically characterized by excess fat accumulation and elevated body weight (BW) relative to height. Historically, obesity is defined by BMI ≥ 30 kg/m^2[6]. Several well-recognized limitations exist for BMI as an index for health. Limitations include the inability to characterize body composition or to account for additional factors that influence muscle *vs* fat mass such as ethnicity, sex, and age[7]. These limitations are particularly important in patients with liver disease who experience additional dynamic shifts in volume status in the setting of ascites and anasarca[8]. Alternative definitions for obesity are either based on the percentage of body fat or the abdominal fat distribution. Specifically, central obesity is defined as either elevated waist circumference or high visceral fat content on imaging[3].

Sarcopenic obesity is characterized the presence of concurrent low muscle mass and excess visceral fat[3]. However, a universal definition of this term is lacking, and the metrics used to define sarcopenic obesity vary across studies. Key radiographic indicators of sarcopenic obesity include visceral adipose tissue and subcutaneous adipose tissue (SAT)[8]. The prevalence of sarcopenia is higher than that of sarcopenic obesity in patients with cirrhosis[9]. This can be explained by the positive correlation between SMI and BMI[10]. Routine use of BMI in the definition of sarcopenic obesity is not reco-mmended as BMI has been shown to correlate poorly with visceral fat indices in both the pre- and post-transplant setting[11].

PATHOPHYSIOLOGY OF SARCOPENIC OBESITY

Obesity and sarcopenia are closely connected at a biochemical level. Pre-disposition to sarcopenic obesity is largely tied to changes in body composition throughout aging, such as skeletal muscle mass loss and adipose tissue dysfunction and associated chronic, low-grade inflammation[12]. Sarcopenic obesity ultimately develops from maladaptive interactions between adipose tissue and skeletal muscle that occur in states of metabolic derangement (*e.g.*, liver disease), as these organ systems cross-talk with one another to reach a new state of homeostasis[13,14].

Patients with obesity often have excessive adipose tissue, characterized by adipocyte hyperplasia and hypertrophy. Excessive adipose tissue leads to diminished capacity to store lipids and result in ectopic accumulation of free fatty acids (FFAs) within skeletal muscle[15]. Oversupply of FFAs drives an adaptive increase in mitochondrial β-oxidation and production of active lipid metabolite. In the absence of increased energy demand, this leads to excess production of reactive oxygen species and oxidative stress, and results in adipocyte dysfunction[16]. This cascade impairs the endocrine function of adipose tissue, which produces hormones crucial to maintaining skeletal muscle health.

Leptin and adiponectin have been recognized as the chief adipokines mediating the reciprocal control of fat and skeletal muscle[17]. While leptin has long been implicated in the pathogenesis of insulin resistance in obesity, new studies have indicated that minimal threshold levels of adipose-derived leptin are necessary to achieve normal skeletal muscle mass and contraction[18]. It has been suggested that leptin resistance and the consequent downregulation of leptin receptors contribute to muscle atrophy and persistent visceral fat[19,20]. Conversely, adiponectin promotes muscle regeneration and suppression of proteolysis[21]; with obese patients demonstrating both lower adiponectin levels and a significant decrease in muscle strength[22]. Additionally, irisin has been identified as an exercise-induced myokine that contributes to the browning of white fat and acts as a regulator of adipocyte differentiation. Decreased irisin level contributes to skeletal muscle adiposity, while upregulation may lead to decreased myostatin gene expression and delay muscle catabolism[23,24]. Myostatin, a member of the transforming growth factor-β superfamily, is also considered a key regulator for maintaining muscle mass. An overexpression of this protein leads to muscle atrophy, whereas knockout studies have reported muscle overgrowth[23]. At the same time, although myostatin is predominantly secreted by skeletal muscle, animal models have shown that this myokine is also implicated in the regulation of brown fat. Specifically, deletion of myostatin has shown to activate both brown and beige adipocytes, while also protecting from adipocyte hypertrophy and hepatic steatosis[25,26]. Furthermore, myostatin overexpression has been associated with states of sarcopenic obesity both in middle-aged and older adults[27]. These hormonal pathways demonstrate the complex interactions between adipose tissue and skeletal muscle, and how alterations in this inter-organ crosstalk can contribute to development and progression of sarcopenic obesity.

PATHOPHYSIOLOGY OF SARCOPENIC OBESITY IN CHRONIC LIVER DISEASE

The liver, which acts as a hub to metabolically connect various tissues, is implicated in the critical physiological pathways that drive the skeletal muscle loss and adipocyte dysfunction of sarcopenic obesity (Figure 1). The liver is responsible for the synthesis of insulin-like growth factor-1 (IGF-1) which plays a key role in the regulation of both anabolic and catabolic pathways in skeletal muscle, adipose, and hepatic tissues[28]. In the context of sarcopenic obesity, IGF-1 acts as the gatekeeper of myostatin by controlling its expression and secretion, and therefore promotes conditions that favor adipocyte hyperplasia[29]. As part of this biochemical pathway, leptin plays a major role in stimulating hepatic production of pro-inflammatory cytokines like tumor necrosis factor alpha and interleukin-6. This state favors the recruitment of Kupfer cells and CD8+ lymphocytes that exert a critical role in both the pathogenesis and progression of metabolic dysfunction–associated steatotic liver disease (MASLD)[30]. Importantly, MASLD, which is becoming the most common indication for LT in the United States[31]. Interestingly, research has shown that not only sarcopenic obesity is associated with a significantly increased prevalence of metabolic associated fatty liver disease (MAFLD) and liver fibrosis, but that the major biomarkers of sarcopenic obesity, such as adiponectin, leptin, and IGF-1, can also be utilized for diagnosis and stratification of MAFLD[32-34]. Furthermore, the implications of sarcopenic obesity can have vast ramifications in the realm of decompensated liver disease[35,36]. In fact, as the catabolic state of sarcopenia worsens, muscle break down and the consequent increase in ammonia production may critically affect the progression of liver disease and facilitate the onset of hepatic encephalopathy[37].

IMPLICATIONS OF SARCOPENIC OBESITY SURROUNDING LIVER TRANSPLANT

The assessment of nutrition and strength are routinely performed in the evaluation for liver transplantation[38]. Poor nutritional status and reduced functional capacity are increasingly common reasons that patients are declined for LT candidacy or are removed from the LT waitlist. These decisions occur in light of robust showing that frailty and sarcopenia are associated with hepatic decompensation, increased healthcare use, worse quality of life, adverse post-transplant outcomes (*e.g.*, small for size syndrome) and increased mortality in patients with cirrhosis[1,39,40]. Additionally, obesity has been associated with increased LT waitlist mortality and increased incidence of post-transplant surgical complications such as wound infections, wound dehiscence, and biliary complications[41].

Importantly, there is emerging data to suggest that sarcopenic obesity is associated with worse outcomes than sarcopenia or obesity alone. A 2016 study of 161 patients with cirrhosis found an increased risk of death in patients with elevated visceral fat area (VFA) and low muscle mass, compared to low muscle mass or high VFA alone[42]. This has been supported in larger cohorts as well, including a study of 277 patients where sarcopenia and myosteatosis were associated with a 1.5 times greater mortality risk compared to patients without muscular abnormalities[9]. In pre-liver transplant patients specifically, a study prospectively assessed sarcopenic obesity in deceased-donor LT candidates and found that sarcopenic obesity was associated with significantly increased waitlist mortality[8]. The impact of sarcopenic obesity has also been seen in post-transplant outcomes, where rates of post-transplant mortality are higher in patients with sarcopenic visceral obesity compared to patients with sarcopenia or visceral obesity alone[2]. In addition to deceased donor LT, post-transplant survival rates were lower for patients with sarcopenic obesity who underwent living donor liver transplantation (LDLT) compared to non-sarcopenic and non-obese patients[43].

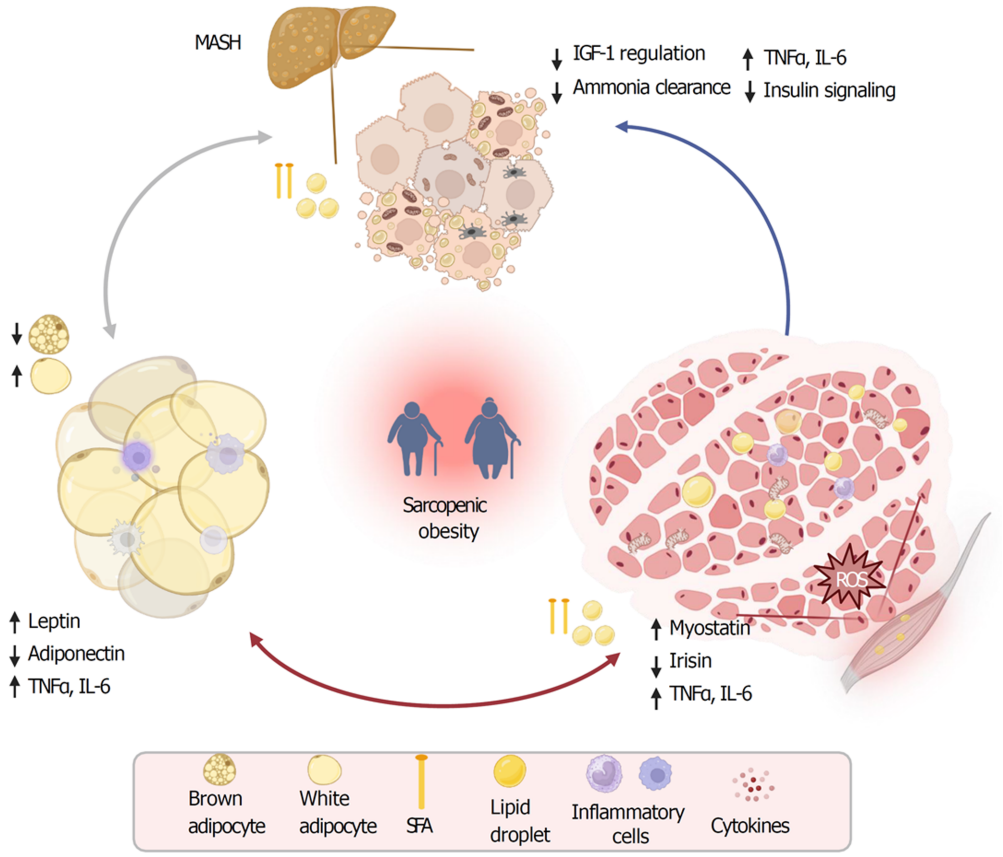

Figure 1 A Pathophysiology of sarcopenic obesity. Obesity and sarcopenia share biological alterations such as insulin resistance, increased pro-inflammatory cytokines, oxidative stress and age-associated hormonal changes. Adipocyte hypertrophy induces a state of systemic inflammation characterized by decreased adiponectin and elevated levels of leptin, tumor necrosis factor, and interleukin 6 (red arrow). Also, obesity and aging contribute to changes in skeletal muscle homeostasis, leading to increased expression of myostatin and reduced irisin, which ultimately favors muscle wasting (red arrow). Concomitantly, excess delivery of fatty acids to the liver leads to fat deposition into the hepatocytes which results in hepatic insulin resistance as well as decreased insulin-like growth factor production. These processes contribute to a vicious cycle leading to adipose tissue expansion, muscle loss and hepatic dysfunction (gray and blue arrows). TNF-α: Tumor necrosis factor; IL-6: Interleukin 6; IGF-1: Insulin-like growth factor; GH: Growth hormone; SFA: Saturated fatty acid; ROS: Reactive oxygen species; MASH: Metabolic dysfunction-associated steatohepatitis. Adapted from "Cycle Diagram", by BioRender.com (2023). Retrieved from https://app.biorender.com/biorender-templates with permission for re-publication.

GENERAL NUTRITION RECOMMENDATIONS FOR PATIENTS WITH LIVER DISEASE

For patients listed for liver transplantation, it is essential that timely nutritional assessments occur with frequent reassessments until transplant. Nutritional assessments should occur routinely using a validated tool such as the Subjective Global Assessment or Royal Free Hospital-nutritional prioritizing tool (RFH-NPT)[44]. The RFH-NPT was developed to assess nutritional status in patients with CLD and includes BMI, unplanned weight loss, dietary intake, and severity of disease in its assessment[45]. All nutritional assessments should include a physical exam that focuses on evaluating subcutaneous fat loss, muscle wasting, and fluid retention[44,46,47]. It is important to note that nutrition alone is insufficient to improve functional status in patients with CLD, malnutrition, and frailty[1]. Recent studies on prehabilitation in patients preparing for liver transplantation have shown that interventions such as increased daily step count, and introduction of strength exercises is safe, feasible, and can improve aerobic and functional capacity[48,49].

Specific nutritional recommendations for patients with CLD include shortening fasting periods by adopting a high protein breakfast and late evening snack[1]. Historically, concerns have existed that high protein intake could contribute to the development of hepatic encephalopathy. This has since been disproven, and optimal protein intake in patients with CLD should not be lower than the recommended 1.2-1.5 g/kg (BW)/d[44]. Research has shown that among patients with CLD, total energy expenditure varies between 28-38 kcal/kg (BW)/d. As a result, current studies have recommended an energy intake between 25-40 kcals/kg (BW)/d for patients depending on clinical and nutritional status[1,44,46].

For patients with sarcopenia, it is critical to optimize nutritional intake in the pre-transplant period to mitigate the loss of muscle tissue. The nutrition plan should optimize protein intake, with most studies supporting a goal of 25-30 g of high-quality protein from a diverse range of sources per meal to maximally stimulate muscle protein synthesis[1,44,46]. In some selected studies, additional supplements such as testosterone, growth hormone, and L-carnitine has shown to be helpful in improving muscle mass and suppressing muscle loss[1,5,46]. Exercise can also serve as an additional tool to improve muscle mass and function in patients with sarcopenia. Current guidelines recommend 20 to 30 min of a combination of aerobic and resistance training three times a week[1,46].

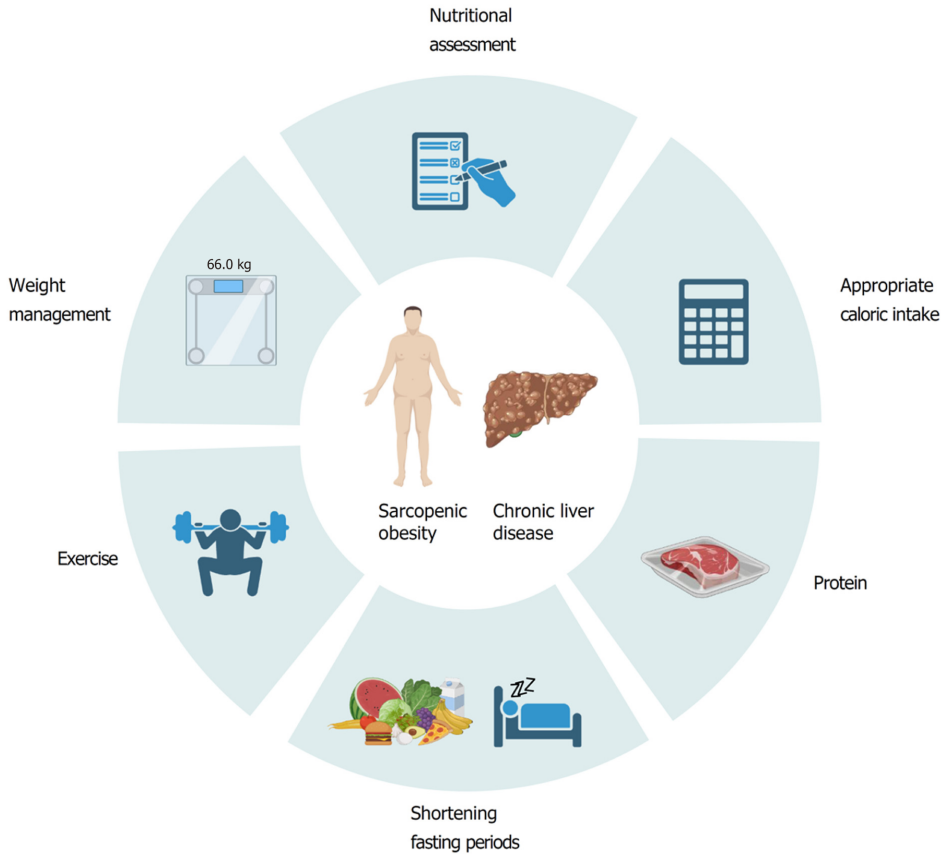

Figure 2 A summary of nutrition and lifestyle recommendations for concurrent chronic liver disease and sarcopenic obesity. Lifestyle recommendations for patients with chronic liver disease and sarcopenic obesity include thorough nutritional assessments and re-assessments, weight management, and exercise. Nutritional recommendations include maintaining an appropriate caloric, shortening fasting periods, and obtaining and adequate amount of protein through diet. Adapted from "Cycle Diagram", by BioRender.com (2023). Retrieved from https://app.biorender.com/biorender-templates with permission for re-publication.

Despite current recommendations to avoid using BMI as the sole measure of obesity, some guidelines still recommend that all patients awaiting LT with a BMI greater than 35 implement lifestyle changes to achieve a BMI target below 30[41]. However, while it is generally agreed upon that although weight loss may be beneficial, very low-calorie diets should be avoided in this population[1,5,44,46,50]. Currently, limited data exists on energy use among patients with cirrhosis across a spectrum of BMIs. When making calorie intake recommendations, resting energy expenditure should be assessed using indirect calorimetry, or can be estimated using the Harris Benedict or Mifflin St Jeor equation[44]. There are also tools available to provide personalized daily caloric targets using BMI stratification based on ideal body weight corrected for fluid retention[5].

To facilitate achievement of nutritional goals, care should also be taken to improve diet palatability in patients following a sodium restriction, as unfavorable flavors can cause a reduction in calorie intake[1]. For patients who cannot tolerate an oral diet or oral supplementation, enteral nutrition is recommended, and nasogastric tubes can be placed in patients with non-bleeding esophageal varices. Parenteral nutrition should be considered if enteral nutrition is not feasible. Due to the risk of platelet dysfunction and ascites, percutaneous endoscopic gastrostomy insertion is contraindicated in patients with CLD[44].

NUTRITION RECOMMENDATIONS FOR SARCOPENIC OBESITY

Few studies exist that have investigated the effects of nutritional interventions on sarcopenic obesity in both the general population and in patients with CLD. It is understood that a nutrition strategy for sarcopenic obesity must target optimal nutrient intake to preserve muscle, while simultaneously preventing excess fat mass[44] (Figure 2). There are conflicting opinions on whether calorie deficit is effective for achieving fat reduction while preserving muscle mass. One study done in older adults supports an energy deficit of 200-700 kcal/d[51]. However, a very low-calorie diet increases the risk of skeletal muscle loss and worsening micronutrient status[4,44]. Although there are limited long-term studies evaluating the optimal protein intake for patients with sarcopenic obesity, it is generally accepted that these patients may have higher protein needs. One study recommends a minimal protein intake of at least 1-1.2 g/kg[4]. Additionally, many studies have shown that resistance exercise is an effective strategy, in addition to nutrition, to preserve muscle mass in patients with sarcopenic obesity[4,52].

Patients with CLD and concurrent sarcopenic obesity frequently have multiple providers involved in their care and may subsequently receive conflicting advice regarding specific nutritional needs. While some studies argue against weight loss in patients with decompensated cirrhosis and sarcopenic obesity given the role of adequate protein[1], others guidelines propose that nutritional management specific to cirrhotic patients with sarcopenic obesity be no different than general nutritional management of cirrhosis[53]. However, it is agreed upon that excessive energy restriction in very low-calorie diets should be avoided in this patient population due to the poor tolerance of fasting and risk of worsening sarcopenia. As a result, it is recommended to achieve specific caloric goals using BMI-stratified target caloric intake guidelines[3]. If caloric restriction must occur, such as for cases in metabolic dysfunction-associated steatohepatitis, protein intake should not drop below 1.2-1.5 g/kg/d[1]. Although recommendations for structured exercise exists for patients with CLD, limited data exists on recommendations for this specific population with concurrent sarcopenic obesity[48]. Current literature supports 150 min per week of moderate intensity resistance exercise for improving body composition and physical function, but this an area where future study is needed[3,54].

CONCLUSION

It is widely known that nutrition status substantially contributes to outcomes in patients with CLD. Sarcopenic obesity among patients with CLD is common, and this phenotype is associated with increased mortality in patients pursuing LT. Although extensive literature focuses on nutritional recommendations for patients with CLD and concurrent sarcopenia or obesity, we identified a lack of data specifically supporting nutritional recommendations for patients with sarcopenic obesity and concurrent CLD. More primary literature is needed on optimal nutrition recommendations for patients with liver disease and coexisting sarcopenic obesity.

FOOTNOTES

Author contributions: Herscovici DM formulated the scope of this review and led writing; Cooper KM, Colletta A contributed to writing sections of the manuscript; Rightmyer M, Shingina A and Feld LD provided expert review of this subject matter; Herscovici DM, Cooper KM, Colletta A, Rightmyer M, Shingina A and Feld LD contributed to editing, revising, and finalizing the manuscript; Feld LD supervised the project; All authors have read and approved the final manuscript.

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MINIREVIEWS

Controversies regarding transplantation of mesenchymal stem cells

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Abstract

Mesenchymal stem cells (MSCs) have tantalized regenerative medicine with their therapeutic potential, yet a cloud of controversies looms over their clinical transplantation. This comprehensive review navigates the intricate landscape of MSC controversies, drawing upon 15 years of clinical experience and research. We delve into the fundamental properties of MSCs, exploring their unique immunomodulatory capabilities and surface markers. The heart of our inquiry lies in the controversial applications of MSC transplantation, including the perennial debate between autologous and allogeneic sources, concerns about efficacy, and lingering safety apprehensions. Moreover, we unravel the enigmatic mechanisms surrounding MSC transplantation, such as homing, integration, and the delicate balance between differentiation and paracrine effects. We also assess the current status of clinical trials and the ever-evolving regulatory landscape. As we peer into the future, we examine emerging trends, envisioning personalized medicine and innovative delivery methods. Our review provides a balanced and informed perspective on the controversies, offering readers a clear understanding of the complexities, challenges, and potential solutions in MSC transplantation.

Key Words: Mesenchymal stem cells; Transplantation controversies; Regenerative medicine; Autoimmune diseases; Chronic inflammatory illnesses; Tumor growth; Metastasis; Therapeutic potential; Clinical use of mesenchymal stem cell

Core Tip: Controversies surrounding mesenchymal stem cell (MSC) transplantation demand nuanced evaluation. Autologous *vs* allogeneic choices, long-term efficacy, and safety remain hot topics. Understanding the mechanisms of homing, integration, and paracrine signaling is vital for predictable outcomes. Standardization, regulatory clarity, and cost considerations require urgent attention. Combining MSCs with other therapies offers a promising horizon. Ethical, legal, and publication quality concerns persist. Rigorous research, informed patient selection and personalized strategies are paramount. In this dynamic field, our review underscores the need for clarity, transparency, and evidence-based practice to harness the transformative potential of MSCs effectively.

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INTRODUCTION

Mesenchymal stem cells (MSCs), once hailed as regenerative medicine's promising panacea, have ushered in a new era of therapeutic possibilities. With their multipotent nature and immunomodulatory capabilities, MSCs have attracted widespread attention for their potential to treat various diseases and injuries. However, amid the optimism, a series of controversies has emerged, casting a critical spotlight on the clinical translation of MSC transplantation[1].

First and foremost, the fundamental properties of MSCs are based on their unique characteristics and therapeutic potential. Many surface markers define MSCs and intricate to their immunomodulatory properties. This groundwork sets the stage for a critical analysis of their applications, focusing on autologous *vs* allogeneic transplantation, efficacy concerns, and safety considerations[2].

One of the central controversies we address revolves around the comparison between using a patient's MSCs and those from an allogeneic source[3]. While autologous MSCs may seem the logical choice, they raise questions concerning cell quality and availability. Conversely, allogeneic sources offer scalability and accessibility but pose potential immunogenicity risks. Balancing these considerations is pivotal to the field's progression.

Furthermore, we examine the efficacy and long-term outcomes associated with MSC transplantation, emphasizing the need for rigorous clinical evidence. The clinical community grapples with variances in therapeutic outcomes, raising uncertainties about the consistency and durability of MSC-based therapies. Safety concerns, including the potential for tumorigenesis and adverse effects, are also addressed, highlighting the imperative to navigate these issues in the clinic[4].

We delve into the intricate processes of homing, integration, and paracrine signaling to unravel the mechanisms and uncertainties surrounding MSC transplantation. Understanding these mechanisms is crucial for optimizing therapeutic outcomes and addressing unresolved questions. We also scrutinize the balance between MSC differentiation and immunomodulation, a central dilemma in harnessing their therapeutic potential[5].

In summary, the controversies surrounding MSC transplantation underscore the need for a nuanced understanding of their properties, applications, and limitations. By navigating these controversies with precision and objectivity, we aspire to contribute to the informed dialogue that shapes the future of MSC-based regenerative medicine. As we look toward the future, we discuss emerging trends and research directions, including the potential for personalized medicine, innovative delivery methods, and integrating MSC therapies with other treatment modalities.

This review extends its purview to the clinical domain, analyzing ongoing clinical trials and the regulatory landscape. Promising trials offer glimpses of hope, while regulatory challenges underscore the need for standardized guidelines and oversight. We focus on a comprehensive and up-to-date overview of the controversies and debates surrounding the transplantation of MSCs; exploring MSC characteristics, analysing controversial applications, mechanisms and uncertainty, assessing clinical trials and regulatory landscape, and exploring future directions. We tried to offer a balanced and informed perspective on the controversies surrounding MSC transplantation, providing readers with a clear understanding of the complexities, challenges, and potential solutions in this rapidly evolving field. By addressing these objectives, this review paper aims to contribute to the ongoing dialogue and decision-making processes regarding the transplantation of MSCs within the scientific and clinical communities.

SEARCH STRATEGY

A systematic literature search was conducted for this comprehensive review to identify relevant studies and publications. The following databases were used: PubMed/Medline, Scopus, Web of Science, Embase, and Google Scholar. The search strategy employed a combination of Medical Subject Headings terms and free-text keywords. The following template was used to construct search queries: ("Mesenchymal Stem Cells" OR "MSCs") AND ("Transplantation" OR "Transplant" OR "Transplantation Techniques" OR "Cell Transplantation") AND ("Controversies" OR "Debate" OR "Challenges" OR "Issues" OR "Uncertainties" OR "Controversial Applications").

The search queries were adapted to the specific syntax and features of each database to ensure a comprehensive retrieval of relevant articles. Filters were applied to include articles published within the last 15 years to align with the clinical experience and recent developments addressed in this review. The initial search yielded a substantial number of articles, and duplicates were removed to ensure the accuracy of the search results. Titles and abstracts of the remaining articles were screened for relevance to the scope of the review, and full texts of potentially relevant articles were retrieved and assessed for inclusion in the review. This systematic search strategy ensured the comprehensive coverage of controversies regarding the transplantation of MSCs in clinical practice.

CHARACTERISTICS OF MSC AND THEIR APPLICATION IN CLINICAL PRACTICE

MSCs represent a fascinating class of multipotent cells that have garnered significant attention in regenerative medicine and tissue engineering[6]. These remarkable cells can differentiate into various cell types, including osteoblasts, chondrocytes, and adipocytes, making them a potent tool for tissue repair and regeneration. MSCs can be sourced from diverse tissues within the body, with the most commonly utilized sources being bone marrow, adipose tissue, and umbilical cord tissue[7].

Characterization of MSCs is essential, and a set of surface markers and functional properties typically defines them. Commonly expressed surface markers include CD73, CD90, and CD105 while lacking hematopoietic markers like CD45 and CD34[8].

However, MSCs exhibit considerable heterogeneity, varying depending on their tissue of origin and donor-specific factors. Beyond their differentiative capacity, MSCs possess a remarkable immunomodulatory profile, a feature that has led to their investigation as potential immune modulators in various disease contexts. MSCs can suppress the activity of immune cells, such as T cells, B cells, and dendritic cells (DCs), by secretion of anti-inflammatory cytokines like interleukin-10 (IL-10) and transforming growth factor-beta (TGF-β). Furthermore, their capacity to regulate the immune response has made MSCs appealing candidates for treating inflammatory and autoimmune disorders[9,10].

Additionally, MSCs secrete a wide array of bioactive molecules, known as paracrine factors, that contribute to their therapeutic potential. These factors encompass growth factors, chemokines, and extracellular vesicles, which collectively orchestrate tissue repair processes, stimulate angiogenesis, and modulate inflammation[11].

MSCs have gained prominence for their remarkable immunomodulatory properties, making them valuable candidates for various therapeutic applications. These cells exert their immunomodulatory effects through a multifaceted array of mechanisms that help regulate immune responses[12-15].

Here, we delve into some of the most common immunological mechanisms employed by MSCs, with references[15-25] to support their significance in Table 1.

Suppression of T-cell proliferation

MSCs are adept at inhibiting the proliferation and activation of T lymphocytes, a vital component of the adaptive immune response. This effect is mediated by releasing soluble factors such as indoleamine 2,3-dioxygenase and prostaglandin E2, which create an immunosuppressive microenvironment[15,16].

Induction of regulatory T cells: MSCs promote the generation and expansion of regulatory T cells, or regulatory T cells (Tregs), which play a crucial role in immune tolerance and suppressing excessive immune reactions. This induction of Tregs is partly attributed to interactions between programmed death-ligand 1 on MSCs and programmed cell death protein 1 on T cells[17-19].

Modulation of DCs: MSCs influence the maturation and function of DCs, pivotal antigen-presenting cells in the immune system. They inhibit the expression of co-stimulatory molecules on DCs and reduce their ability to activate T cells, thereby tempering immune responses[20].

Reduction of inflammatory cytokines

MSCs secrete anti-inflammatory cytokines like IL-10, TGF-β, and hepatocyte growth factor, while simultaneously dampening the production of pro-inflammatory cytokines, including tumor necrosis factor-alpha and interferon-gamma [21,22].

Promotion of macrophage polarization

MSCs can skew macrophages towards an anti-inflammatory, tissue-healing M2 phenotype, fostering a regenerative environment and mitigating tissue damage[23].

Immune cell anergy

MSCs can induce a state of anergy in T cells, rendering them functionally inactive and refractory to activation signals. This effect is conducive to immune tolerance and reduced autoimmune responses[24].

Exosome-mediated communication

MSCs release immunomodulatory exosomes that carry bioactive molecules, including microRNAs and proteins, capable of regulating immune cell behavior and suppressing inflammation[25].

Table 1 The most common immunological mechanisms employed by mesenchymal stem cells

Properties	Mechanisms	Ref.
Suppression of T-cell proliferation	MSCs are adept at inhibiting the proliferation and activation of T lymphocytes, a vital component of the adaptive immune response. This effect is mediated by releasing soluble factors such as IDO and PGE2, which create an immunosuppressive microenvironment	[15,16]
Induction of Tregs	MSCs promote the generation and expansion of regulatory T cells, or Tregs, which play a crucial role in immune tolerance and suppressing excessive immune reactions. This induction of Tregs is partly attributed to interactions between PD-L1 on MSCs and PD-1 on T cells	[17-19]
Modulation of DCs	MSCs influence the maturation and function of DCs, pivotal antigen-presenting cells in the immune system. They inhibit the expression of co-stimulatory molecules on DCs and reduce their ability to activate T cells, thereby tempering immune responses	[20]
Reduction of inflammatory cytokines	MSCs secrete anti-inflammatory cytokines like IL-10, TGF-β, and HGF, while simultaneously dampening the production of pro-inflammatory cytokines, including IFN-γ	[21,22]
Promotion of macrophage polarization	MSCs can skew macrophages towards an anti-inflammatory, tissue-healing M2 phenotype, fostering a regenerative environment and mitigating tissue damage	[23]
Immune cell anergy	MSCs can induce a state of anergy in T cells, rendering them functionally inactive and refractory to activation signals. This effect is conducive to immune tolerance and reduced autoimmune responses	[24]
Exosome-mediated communication	MSCs release immunomodulatory exosomes that carry bioactive molecules, including microRNAs and proteins, capable of regulating immune cell behavior and suppressing inflammation	[25]

Tregs: Regulatory T cells; IDO: Indoleamine 2,3-dioxygenase; PGE2: Prostaglandin E2; PD-L1: Programmed death-ligand 1; PD-1: Programmed cell death protein 1; DCs: Dendritic cells; MSCs: Mesenchymal stem cells; IL-10: Interleukin-10; TGF-β: Transforming growth factor-beta; HGF: Hepatocyte growth factor; IFN-γ: Interferon-gamma.

These immunological mechanisms collectively contribute to the immunomodulatory potential of MSCs, rendering them pivotal in managing autoimmune disorders, inflammatory diseases, and conditions marked by aberrant immune responses. As research advances, a deeper understanding of these mechanisms holds promise for enhancing the therapeutic applications of MSCs in clinical settings.

This extensive repertoire of immunomodulatory and trophic effects highlights MSCs as promising agents in regenerative medicine, with ongoing research exploring their applications in diverse clinical scenarios, ranging from musculoskeletal disorders and cardiovascular diseases to neurological conditions and graft-versus-host disease (GVHD). Despite the controversies and challenges surrounding their clinical use, MSCs remain at the forefront of therapeutic innovation, continuously revealing new facets of their biology and therapeutic potential that hold immense promise for the future of personalized medicine and regenerative therapies[26,27].

MSCs have garnered immense interest in regenerative medicine due to their remarkable clinical potential. These versatile cells hold promise in various therapeutic applications, offering new avenues for treating multiple diseases and injuries. Here, we explore the clinical potential of MSCs in 400 words, with references supporting their diverse applications (Table 2)[28-37].

Musculoskeletal disorders

MSCs have shown great promise in treating musculoskeletal conditions, including osteoarthritis, rheumatoid arthritis, and bone fractures. Their ability to differentiate into bone and cartilage cells and their anti-inflammatory properties make them valuable for tissue repair and regeneration[28].

Cardiovascular diseases

MSCs exhibit cardio-protective effects and can enhance cardiac repair following myocardial infarction. Clinical trials have explored their potential for improving heart function, reducing scar formation, and stimulating angiogenesis[29].

Neurological disorders

MSCs hold potential for treating neurodegenerative conditions such as Parkinson's disease, Alzheimer's disease, and spinal cord injuries. They promote neuroprotection, neural differentiation, and the secretion of neurotrophic factors, fostering neural tissue repair[30].

Autoimmune disorders

In autoimmune diseases like multiple sclerosis and systemic lupus erythematosus, MSCs' immunomodulatory properties help suppress aberrant immune responses and reduce disease severity. They promote tolerance and reduce inflammation [31,32].

GVHD

MSCs have demonstrated effectiveness in managing GVHD, a potentially fatal complication of hematopoietic stem cell transplantation. They modulate immune reactions, aiding in GVHD prevention and treatment[33].

Table 2 The clinical potential of mesenchymal stem cells

Application	Effects	Ref.
Musculoskeletal disorders	MSCs have shown great promise in treating musculoskeletal conditions, including osteoarthritis, rheumatoid arthritis, and bone fractures. Their ability to differentiate into bone and cartilage cells and their anti-inflammatory properties make them valuable for tissue repair and regeneration	[28]
Cardiovascular diseases	MSCs exhibit cardio-protective effects and can enhance cardiac repair following myocardial infarction. Clinical trials have explored their potential for improving heart function, reducing scar formation, and stimulating angiogenesis	[29]
Neurological disorders	MSCs hold potential for treating neurodegenerative conditions such as Parkinson's disease, Alzheimer's disease, and spinal cord injuries. They promote neuroprotection, neural differentiation, and the secretion of neurotrophic factors, fostering neural tissue repair	[30]
Autoimmune disorders	In autoimmune diseases like multiple sclerosis and systemic lupus erythematosus, MSCs' immunomodulatory properties help suppress aberrant immune responses and reduce disease severity. They promote tolerance and reduce inflammation	[31, 32]
GVHD	MSCs have demonstrated effectiveness in managing GVHD, a potentially fatal complication of hematopoietic stem cell transplantation. They modulate immune reactions, aiding in GVHD prevention and treatment	[33]
IBD	MSCs are under investigation for their role in managing Crohn's disease and ulcerative colitis. They promote mucosal healing, reduce inflammation, and regulate the immune system within the gut	[34]
Diabetes	MSCs hold the potential for treating type 1 diabetes by promoting pancreatic beta-cell regeneration and modulating the autoimmune response that leads to beta-cell destruction	[35]
Wound healing and dermatological conditions	MSCs facilitate wound healing by enhancing tissue regeneration and reducing scar formation. They are explored for treating skin conditions like chronic ulcers and epidermolysis bullosa	[36]
Lung disorders	In conditions like COPD and idiopathic pulmonary fibrosis, MSCs can mitigate inflammation, promote lung tissue repair, and enhance pulmonary function	[37]

COPD: Chronic obstructive pulmonary disease; GVHD: Graft-versus-host disease; IBD: Inflammatory bowel disease; MSCs: Mesenchymal stem cells.

Inflammatory bowel disease

MSCs are under investigation for their role in managing Crohn's disease and ulcerative colitis. They promote mucosal healing, reduce inflammation, and regulate the immune system within the gut[34].

Diabetes

MSCs hold the potential for treating type 1 diabetes by promoting pancreatic beta-cell regeneration and modulating the autoimmune response that leads to beta-cell destruction[35].

Wound healing and dermatological conditions

MSCs facilitate wound healing by enhancing tissue regeneration and reducing scar formation. They are explored for treating skin conditions like chronic ulcers and epidermolysis bullosa[36].

Lung disorders

In conditions like chronic obstructive pulmonary disease and idiopathic pulmonary fibrosis, MSCs can mitigate inflammation, promote lung tissue repair, and enhance pulmonary function[37].

Ongoing clinical trials are investigating the use of MSCs in various conditions, including solid organ transplantation, kidney diseases, and hematological disorders. Personalized medicine approaches, combinatorial therapies, and innovative delivery methods are also being explored to optimize MSC-based treatments[38-41].

While MSC-based therapies hold significant promise, challenges remain, including standardization of protocols, safety concerns, and regulatory frameworks. Nonetheless, their clinical potential continues to expand, offering hope for improved outcomes and novel treatments across a spectrum of medical conditions.

Controversies regarding the use of MSCs in clinical practice: General aspects

Some controversies regarding MSC use in regenerative medicine are related to their immunomodulatory properties, sources, safety and efficacy concerns, *etc*. In Figure 1, we present some of the MSC sources and the potential of MSC to be used in regenerative medicine.

Autologous *vs* allogeneic msc transplantation: The choice between using a patient's MSCs (autologous) or MSCs from a donor (allogeneic) raises debates. Autologous MSCs may reduce the risk of immune rejection but can be limited in quantity and may have reduced quality, while allogeneic MSCs offer scalability but carry potential immunogenicity risks. Allogeneic MSCs can provide several advantages such as donor selection, various sources, low immunogenicity, and off-the-shelf availability; however, autologous MSCs require a few weeks for isolation, in-vitro expansion and release, and patient-derived autologous MSCs may underlie systemic diseases[3].

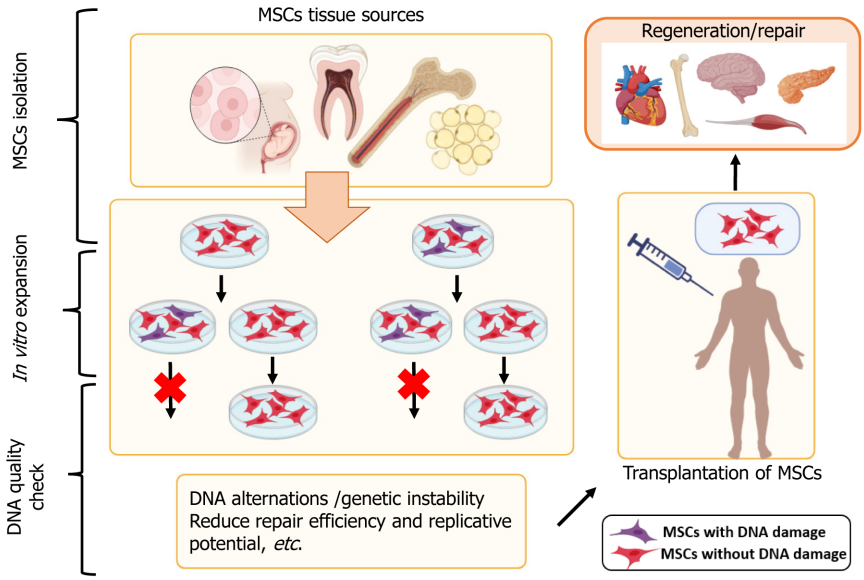

Figure 1 Transplantation of mesenchymal stem cells: Sources, use and challenges regarding safety and efficacy, including genetic instability. MSCs: Mesenchymal stem cells.

Efficacy and long-term outcomes: Variability in therapeutic outcomes and long-term durability of MSC-based therapies is a contention. Robust clinical evidence is needed to establish the efficacy and assess the longevity of these treatments. A systematic review and meta-analysis by Xie *et al*[42] on human MSC therapy's clinical efficacy and safety for degenerative disc diseases revealed that MSC could significantly improve patients' clinical outcomes. However, the optimal dosage, frequency, time, route of administration, and suitable stages of the diseases should be elucidated.

Safety concerns: Safety concerns include the potential for tumorigenicity, immunogenic reactions, and adverse effects. Ensuring the safety of MSC transplantation is essential for its widespread clinical adoption.

Wang *et al*[43] discussed the safety of MSC therapy over the past 15 years in their meta-analysis. A total of 62 randomized clinical trials with 3546 patients treated with intravenous or local implantation against placebo or no treatment were included. The participants were diagnosed with about 20 different types of illnesses. In conclusion, when compared to alternative placebo modalities, MSC delivery proved safe in a variety of demographics, where the most common side effects were transient fever, administration site adverse effects, constipation, fatigue and insomnia.

Homing and integration mechanisms

The mechanisms by which MSCs home to target tissues and integrate into host environments are not fully understood. This raises questions about the predictability and control of MSC behavior *in vivo*. Ullah *et al*[44] reviewed the molecular mechanisms underlying MSC homing based on a multistep model involving: (1) Initial tethering by selectins; (2) activation by cytokines; (3) arrest by integrins; (4) diapedesis or transmigration using matrix remodelers; and (5) extravascular migration toward chemokine gradients. Unfortunately, MSC homing is inefficient, with only a small percentage of cells reaching the target tissue following systemic administration. This attrition represents a significant bottleneck in realizing the full therapeutic potential of MSC-based therapies. Therefore, a variety of strategies have been employed in the hopes of improving this process.

Paracrine effects vs differentiation

The balance between the paracrine signaling effects of MSCs and their potential to differentiate into specific cell types is a critical dilemma. Deciphering the optimal mode of action for various clinical applications remains a challenge[45,46].

Standardization of protocols

The lack of standardized protocols for MSC isolation, expansion, and characterization hampers comparability across studies and poses challenges for regulatory approval and clinical translation.

Throughout the past few decades, adult bone marrow has been the usual source of MSCs; however, this process is highly invasive, and the quality and quantity of isolated cells are significantly influenced by patient age, medication, and related comorbidities. As a result, there is a debate on the convenience of allogeneic over autologous treatments despite potential drawbacks like host rejection. This move to the allogeneic setting necessitates high MSC production to ensure the availability of sufficient cell numbers for transplantation. Searching for alternative tissue sources of highly proliferative MSC cultures with low levels of senescence occurrence is one of the biggest obstacles currently facing the scaling up of therapeutic use.

García-Muñoz and Vives[47] revealed the primary techniques for isolating MSCs from bone marrow, adipose tissue, and Wharton's jelly of the umbilical cord here; and compared their attributes from a bioprocess perspective, addressing both quality and regulatory considerations.

Regulatory oversight

The regulatory landscape for MSC therapies varies between countries and regions. Establishing consistent and clear regulatory guidelines is essential for safe and effective clinical implementation.

Notwithstanding the differences in the field, MSC shareholders are united by a single objective: To employ MSCs as a therapeutic modality to enhance the quality of life for individuals afflicted with a disease whose current standard of care is inadequate or ineffective. Currently, no MSC therapy approved by the Food and Drug Administration is available for purchase in the United States. However, several MSC products have received regulatory approval in other nations[48].

Commercialization and cost

The commercialization of MSC therapies has led to concerns about affordability, accessibility, and equitable distribution, potentially limiting access to these treatments for some patients.

A systematic review protocol by Pettitt *et al*[49] outlined the factors affecting the commercialization of cell-based therapeutics and the assessment of these factors. The translation of cellular-based therapeutics from "bench to bedside" remains challenging, and the number of industry products available for widespread clinical use is still relatively low, despite a notable increase in basic science activity within the cell therapy arena, a growing portfolio of cell therapy trials, and promising investment.

Patient selection and stratification

Identifying the most suitable patient populations for MSC-based therapies and developing personalized treatment approaches is a complex issue with significant implications for clinical practice[50].

It was shown that patient selection and stratification are crucial for better outcomes in MSC-based therapies. Soto-Gordoa *et al*[51] showed that a thorough, patient-centered, integrated care intervention was linked to a lower risk of hospital admission among patients who were prioritized to receive it but not among patients who were not, according to a before-and-after study utilizing propensity score matching.

Combination therapies

Integrating MSC transplantation with other therapeutic modalities, such as drugs or gene therapies, poses challenges in timing, dosing, and potential interactions, raising questions about optimal combination strategies[52,53].

Ethical and legal concerns

Ethical dilemmas include the use of fetal-derived MSCs and concerns about informed consent, especially in cases where unproven treatments are offered to vulnerable patient populations.

Volarevic *et al*[54] and other investigators highlighted the ethical challenges surrounding the research of human embryonic stem cells (hESCs), highlighting that the destruction of a human embryo is a significant factor that may have hindered the development of hESC-based clinical therapies. This problem has been resolved with the previous development of induced pluripotent stem cells (iPSCs), but there are still issues with current perspectives regarding the clinical translation of iPSCs. One major ethical issue is the unlimited differentiation potential of iPSCs, which can be used in human reproductive cloning, posing a risk of resulting in genetically altered human embryos and human-animal chimeras. On the other hand, there are significant safety issues with undesired differentiation and malignant transformation[54-56].

Reporting bias and publication quality

Variability in the quality of published studies and potential reporting bias in clinical trials can make it challenging to assess the true efficacy and safety of MSC-based interventions.

These controversies underline the complexity and ongoing debates surrounding the clinical application of MSCs, highlighting the need for rigorous research, standardized practices, and transparent regulatory frameworks to address these challenges[43,57,58].

Controversies regarding the use of MSCs in clinical practice: Oncogenic potential

The predominant applications of MSCs are in autoimmune, musculoskeletal, and vascular diseases, regenerative medicine, wounds, injuries, *etc.* These applications for different clinical conditions require continuous monitoring for their safety. The most important question for risk assessment is related to the genetic stability of MSCs, which can alter during *in vitro* manipulations[59,60]. There are over 1000 clinical trials on their safety and effectiveness, but the results of their use as immunomodulatory agents have yet to provide a clear answer. In most trials, only a few patients show sufficient or poor therapeutic response; therefore, it can still be said that they are unstable and controversial for clinical practice.

Genome stability is an essential characteristic of any species to preserve and accurately transmit genetic material from generation to generation. This is associated with correct replication, repair of replication errors or damaged DNA, and proper cell cycle progression. Genomic instability, in turn, is associated with a high rate of mutation occurrence because of direct and indirect mutagens, external factors, and epigenetic changes in the genome. Various methods can be used to analyze genetic instability-karyotyping[61], fluorescence in situ hybridization, array-wide comparative genomic hybrid-

ization, microsatellite analysis, *in vitro* micronucleus assay, spectral karyotyping, RNA sequencing, and others[62-66]. Each gives a very informative analysis and shows if there are genetic alternations.

Genome evaluation is most important for MSC stability, and all DNA alterations, even smaller ones, should be assessed. MSCs senesce with vast cultivation *in vitro*, so they lose their proliferation and differentiation potential[67]. Such culture expansion can generate genetic and epigenetic instability, including different chromosomal changes, which pose a risk to MSC therapy[59].

Much research has shown that MSCs get changes in both autosomes and sex chromosomes[64,68-72] and other anomalies[73-75], while other studies have reported unchanged chromosomes in MSC cultures of different tissues, such as humanfetal dermis[76], adipose[77], human adult mesenchymal stromal cells[78-82]. Depending on various factors such as culture times, conditions, and sources, these changes can occur in early or late passages with varying frequency [73].

In 2011, a study described a 4% incidence of aneuploidy in large numbers of MSC preparations[62]. A few years later, Kim *et al*[83] observed cytogenetic changes in different MSC preparations. They estimated the genetic stability of MSCs on 68 preparations with varying origins of tissue and found variable aneuploidy clonal proportions of 1%-20% with overwhelming X, 16, 17, and 18 chromosomes. In 2017, a study revealed that MSCs show genomic instability during *ex vivo* expansion, with the most remarkable change associated with single nucleotide variations that appear at later passages[66]. They performed whole genome sequencing of two peripheral blood-derived MSC lines and described that 90% and 70% of all such variations were observed at passage 9 (for MSC1) and passage 7/9 (for MSC2), respectively.

Roselli *et al*[64] also assessed the genomic stability of MSCs of chorionic villus by different methods. They found abnormal clones after passage 10, which showed no growth advantage, no signs of transformation, and stable microsatellites. This suggests that if the cells in MSC culture become senescent, the mismatch repair system is efficient, and it is doubtful to form tumors in patients[64,84]. A study reported alternations in the gene expression from passage [59]. This suggests using cells up to passage four and analyzing cells from higher culture passages.

Different DNA alternations are still subject to elucidation because the genomic instability (chromosomal changes) is characteristic of cancer, transformation and/or aging[73,84-86]. Through these changes, the tumorigenicity and impaired biological activity of MSCs can be predicted.

MSCs are potent tools in regenerative medicine because of their potential to self-renew, multipotency, and trophic and immunosuppressive properties[87]. The various genetic alternations/aberrations reported in MCS cultures should be analyzed in detail because the gaps in our understanding of MSC applications have to become more precise. Therefore, monitoring the genetic profiles during culture passages is vital because possible modifications and genetic changes can potentially affect the therapeutic efficiency of cell therapy.

Future directions: Exploring emerging trends and research directions in MSC therapy

MSC therapy has entered a dynamic phase of exploration and innovation. As researchers and clinicians gain a deeper understanding of MSCs' capabilities and limitations, new frontiers emerge. In this section, we delve into three promising areas that represent the future directions of MSC therapy: Personalized medicine, advanced delivery methods, and combining therapies. These evolving trends hold significant potential to enhance the effectiveness and applicability of MSC-based treatments across various medical conditions.

Personalized medicine: Tailoring MSC therapies to individual patients

Personalized medicine, a paradigm that tailors medical treatment to the specific characteristics of each patient, is becoming increasingly relevant in the field of MSC therapy. The unique genetic makeup, medical history, and disease profile of each necessitate a more precise and patient-centered approach to treatment. Personalized medicine can be applied to MSC therapy in several ways (Table 3).

Patient-specific MSCs: One of the critical strategies in personalized medicine involves using patient-derived MSCs. These autologous MSCs are obtained from the patient's own tissues, such as bone marrow or adipose tissue. Using a patient's cells minimizes the risk of immune rejection, and treatment can be tailored to the individual's needs.

Genomic and molecular profiling: Advances in genomics and molecular profiling techniques enable the identification of specific markers or genetic characteristics that influence a patient's response to MSC therapy. This information can guide treatment decisions, allowing for the selection of the most appropriate MSC source and optimization of the therapeutic regimen.

Disease-specific approaches: Tailoring MSC therapies to the unique features of a particular disease is another aspect of personalized medicine. For example, MSCs can be engineered in cancer therapy to deliver anti-tumor agents or enhance immune responses, depending on the patient's cancer type and stage.

Dosage and timing optimization: Personalized medicine also extends to optimizing the dosage and timing of MSC treatments. Factors such as the severity of the condition, the patient's age, and comorbidities can all influence the treatment protocol, ensuring the best possible outcomes.

Microencapsulation and biomaterials: Microencapsulation involves encapsulating MSCs within biocompatible materials or hydrogels. This protective environment shields MSCs from immune responses while providing a sustained release of therapeutic factors. This approach is encouraging for conditions like diabetes, where encapsulated MSCs can help regulate blood sugar levels.

Table 3 Future directions in mesenchymal stem cell treatments

Aspect		MSC treatment
Personalized medicine	Patient-specific MSCs	One of the critical strategies in personalized medicine involves using patient-derived MSCs. These autologous MSCs are obtained from the patient's own tissues, such as bone marrow or adipose tissue. Using a patient's cells minimizes the risk of immune rejection, and treatment can be tailored to the individual's needs
	Genomic and molecular profiling	Advances in genomics and molecular profiling techniques enable the identification of specific markers or genetic characteristics that influence a patient's response to MSC therapy. This information can guide treatment decisions, allowing for the selection of the most appropriate MSC source and optimization of the therapeutic regimen
	Disease-specific approaches	Tailoring MSC therapies to the unique features of a particular disease is another aspect of personalized medicine. For example, MSCs can be engineered in cancer therapy to deliver anti-tumor agents or enhance immune responses, depending on the patient's cancer type and stage
	Dosage and timing optimization	Personalized medicine also extends to optimizing the dosage and timing of MSC treatments. Factors such as the severity of the condition, the patient's age, and comorbidities can all influence the treatment protocol, ensuring the best possible outcomes
Advanced delivery methods	Microencapsulation and biomaterials	Microencapsulation involves encapsulating MSCs within biocompatible materials or hydrogels. This protective environment shields MSCs from immune responses while providing a sustained release of therapeutic factors. This approach is encouraging for conditions like diabetes, where encapsulated MSCs can help regulate blood sugar levels
	Intravenous infusion techniques	Intravenous delivery of MSCs is a common method, but refinements in infusion techniques are being explored to maximize cell retention and tissue homing. Pre-conditioning or priming MSCs before infusion can enhance their migratory properties and tissue-specific targeting
	Nanoparticle-based carriers	Nanoparticles can serve as carriers for MSCs, protecting them during transit and improving their ability to reach target sites. These carriers can be loaded with therapeutic or imaging agents for tracking and treatment monitoring
	Direct injection and endoscopic delivery	For localized conditions, such as osteoarthritis or IBD, direct injection of MSCs into the affected area or endoscopic delivery methods are being refined to target tissues and minimize invasiveness precisely
	Exosome-mediated delivery	MSC-derived exosomes, tiny vesicles containing bioactive molecules, offer a cell-free approach to therapy. Exosomes can be isolated and administered to mediate therapeutic effects, making them a promising alternative to whole-cell therapy
Combining therapy	Immunomodulatory Combinations	Combining MSC therapy with immunomodulatory agents or immune checkpoint inhibitors can potentiate the immunosuppressive effects of MSCs, particularly in the context of autoimmune diseases or organ transplantation
	Gene editing and engineering	Genetic modification of MSCs allows for the precise manipulation of their properties. Engineered MSCs can be equipped with therapeutic genes or targeted for specific functions, such as enhancing tissue regeneration or tumor suppression
	Drug delivery systems	MSCs can serve as drug delivery vehicles, transporting therapeutic compounds directly to diseased tissues. This approach is particularly relevant in cancer therapy, where MSCs can deliver anti-cancer drugs to tumor sites
	Stem cell combinations	Combining different types of stem cells, such as iPSCs or neural stem cells, with MSCs can offer multi-pronged approaches to conditions like spinal cord injuries or neurodegenerative diseases
	Adjunct therapies	MSC transplantation can complement traditional treatments, such as surgery or radiation therapy. For example, MSCs can be used alongside surgical procedures in bone repair to accelerate healing and improve outcomes

MSC: Mesenchymal stem cell; IBD: Inflammatory bowel disease; iPSCs: Induced pluripotent stem cells.

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Applying personalized medicine principles to MSC therapy holds great promise for improving treatment efficacy while minimizing potential side effects. However, it also presents cost, logistics, and regulatory challenges. As research in this area continues, we expect to see more tailored and effective MSC-based therapies for various diseases.

Advanced delivery methods: Innovations in MSC administration

Effective delivery of MSCs to target tissues or organs is critical to successful therapy. Advanced delivery methods aim to enhance MSC administration's precision, efficiency, and safety. Several innovative approaches are being explored: Advanced delivery methods improve the therapeutic potential of MSCs and expand the range of conditions that can be effectively treated. These innovations address challenges related to MSC homing, survival, and engraftment, enhancing the clinical feasibility of MSC-based therapies.

Combining therapies: Synergizing MSC transplantation with other modalities

The future of MSC therapy lies in harnessing the synergistic potential of combinatorial approaches. By integrating MSC transplantation with other therapeutic modalities, researchers aim to enhance treatment outcomes and address complex medical conditions more comprehensively. Several strategies are being explored: These combinatorial approaches hold immense potential for addressing complex and multifaceted diseases that may not respond optimally to single-modality treatments. However, they also present safety, regulatory approval, and treatment optimization challenges.

Challenges and considerations

While these emerging trends and research directions in MSC therapy offer great promise, they also raise important considerations and challenges.

Safety and regulation: Ensuring the safety of personalized, genetically modified, or engineered MSCs is paramount. Regulatory frameworks need to adapt to accommodate these innovations while safeguarding patient well-being.

Standardization: As MSC therapies become increasingly personalized and complex, standardized protocols and quality control measures are more critical to ensure consistency and reproducibility.

Cost and accessibility: Some advanced delivery methods and combinatorial approaches may be cost-prohibitive or less accessible to specific patient populations. Balancing innovation with affordability is a significant challenge.

Ethical considerations: The genetic engineering of MSCs and their use in certain applications, such as cancer therapy, raise ethical questions that must be addressed in research and clinical practice.

Long-term safety and efficacy: Ensuring the long-term safety and efficacy of personalized, genetically modified, or engineered MSC therapies requires ongoing monitoring and research.

In conclusion, the future of MSC therapy is characterized by personalized medicine, advanced delivery methods, and the synergy of multiple treatment modalities. These emerging trends hold immense potential to revolutionize regenerative medicine and offer new hope to patients with various medical conditions. However, addressing the associated challenges and ethical considerations is essential to unlock the full therapeutic potential of MSCs safely and effectively.

CONCLUSION

MSC therapy has journeyed far from its early beginnings as an intriguing scientific discovery to a dynamic and rapidly evolving field of regenerative medicine. The discussion of emerging trends and research directions in this paper underscores the transformative potential of MSCs, paving the way for a new era in healthcare. As we conclude this exploration, several vital insights emerge.

First and foremost, personalized medicine is poised to reshape the landscape of MSC therapy. Tailoring treatments to individual patients enhances efficacy and minimizes the risks associated with immune reactions. Patient-specific MSCs, genomic profiling, and disease-specific approaches usher in a new era of precision medicine, offering hope to those facing previously insurmountable medical challenges.

Secondly, advanced delivery methods are revolutionizing how MSCs reach their intended targets. From microencapsulation to nanoparticle carriers, these innovations address longstanding challenges related to cell homing, engraftment, and survival. Such advancements expand the therapeutic reach of MSCs, making treatment more accessible and practical.

Lastly, the future of MSC therapy lies in the power of synergy—combining MSC transplantation with other treatment modalities to tackle complex diseases comprehensively. Immunomodulatory combinations, gene editing, drug delivery systems, and stem cell co-therapies promise to unlock new possibilities for conditions once considered intractable.

However, amidst the promise and potential of MSC therapy, it is essential to acknowledge the challenges. Safety and regulatory concerns, standardization of protocols, cost considerations, and ethical dilemmas require diligent attention. The responsible and ethical advancement of MSC-based treatments necessitates collaboration among scientists, clinicians, policymakers, and regulatory bodies to ensure these therapies reach their full potential while safeguarding patient well-being.

In closing, the future of MSC therapy is marked by a confluence of innovation and responsibility. As researchers and clinicians continue to push the boundaries of what is possible, the transformative potential of MSCs remains boundless. With personalized medicine, advanced delivery methods, and the integration of complementary therapies, we stand at the threshold of a new era in regenerative medicine—where MSCs offer hope and healing to individuals facing diverse medical conditions. By carefully navigating the evolving landscape of MSC therapy, we can transform these possibilities into realities, improving lives and shaping the future of healthcare.

FOOTNOTES

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ORIGINAL ARTICLE

Retrospective Cohort Study

Impact of COVID-19 on liver transplant recipients: A nationwide cohort study evaluating hospitalization, transplant rejection, and inpatient mortality

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Abstract

BACKGROUND

The coronavirus disease 2019 (COVID-19) pandemic has posed a major public health concern worldwide. Patients with comorbid conditions are at risk of adverse outcomes following COVID-19. Solid organ transplant recipients with concurrent immunosuppression and comorbidities are more susceptible to a severe COVID-19 infection. It could lead to higher rates of inpatient complications and mortality in this patient population. However, studies on COVID-19 outcomes in liver transplant (LT) recipients have yielded inconsistent findings.

AIM

To evaluate the impact of the COVID-19 pandemic on hospital-related outcomes among LT recipients in the United States.

METHODS

We conducted a retrospective cohort study using the 2019–2020 National Inpatient Sample database. Patients with primary LT hospitalizations and a secondary COVID-19 diagnosis were identified using the International Classification of Diseases, Tenth Revision coding system. The primary outcomes included trends in LT hospitalizations before and during the COVID-19 pandemic. Secondary outcomes included comparative trends in inpatient mortality and transplant rejection in LT recipients.

RESULTS

A total of 15720 hospitalized LT recipients were included. Approximately 0.8% of patients had a secondary diagnosis of COVID-19 infection. In both cohorts, the median admission age was 57 years. The linear trends for LT hospitalizations did not differ significantly before and during the pandemic ($P = 0.84$). The frequency of in-hospital mortality for LT recipients increased from 1.7% to 4.4% between January 2019 and December 2020. Compared to the pre-pandemic period, a higher association was noted between LT recipients and in-hospital mortality during the pandemic, with an odds ratio (OR) of 1.69 [95% confidence interval (CI): 1.55-1.84), $P < 0.001$]. The frequency of transplant rejections among hospitalized LT recipients increased from 0.2% to 3.6% between January 2019 and December 2020. LT hospitalizations during the COVID-19 pandemic had a higher association with transplant rejection than before the pandemic [OR: 1.53 (95%CI: 1.26-1.85), $P < 0.001$].

CONCLUSION

The hospitalization rates for LT recipients were comparable before and during the pandemic. Inpatient mortality and transplant rejection rates for hospitalized LT recipients were increased during the COVID-19 pandemic.

Key Words: Liver transplant recipients; Solid organ transplantation; COVID-19; Hospitalization; Transplant rejection; Mortality

Core Tip: Patients with solid organ transplants may be at higher risk of severe coronavirus disease 2019 (COVID-19). However, there is a dearth of large-scale population-based data. Using a multicenter database, this retrospective cohort study evaluates the impact of the COVID-19 pandemic on hospital-related outcomes for liver transplant (LT) recipients in the United States. Our findings show that the LT hospitalization rates were similar before and during the pandemic. LT recipients had increased rates of inpatient mortality and transplant rejection during the COVID-19 pandemic. It underscores the importance of tailored clinical management to improve outcomes and reduce morbidity and mortality for hospitalized LT recipients.

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INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic has posed a significant morbidity and mortality burden worldwide. The World Health Organization reported over 772 million confirmed cases and 6.9 million deaths as of December 2023 [1]. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can potentially lead to serious infection even in relatively lower-risk individuals[2]. However, certain demographic characteristics and underlying medical conditions may particularly increase the probability of a life-threatening disease. These risk factors include advanced age, male gender, underlying comorbidities, and immunosuppression[3-5]. Solid organ transplant (SOT) recipients receive lifelong immunosuppressive drugs, which significantly lower the risk of organ rejection[6,7]. These patients are at a higher risk of severe COVID-19 infection and mortality due to their comorbidity status and concomitant immunosuppression[8-11]. However, population-based research on COVID-19 outcomes in SOT recipients revealed conflicting results[12-14].

LT recipients have experienced improved outcomes due to recent advancements in the field of transplantation medicine[15]. Prior studies have shown that COVID-19 infection may cause acute liver injury that has been linked to increased mortality[16-19]. Moreover, patients with chronic liver disease and cirrhosis also have higher rates of healthcare utilization, morbidity, and mortality from COVID-19[20-22]. However, existing clinical evidence has not consistently shown worse clinical outcomes in LT recipients[23]. A meta-analysis of 17 studies demonstrated congruence for unfavorable clinical outcomes among LT and non-LT COVID-19 patients[24]. A meta-analysis of 12 studies also revealed similar mortality in transplant and non-transplant individuals with COVID-19[25]. A nationwide prospective study from Spain showed that LT recipients had a lower mortality rate compared to the matched general population[26]. An Italian prospective double-center study also demonstrated that the risk of hospitalization or mortality did not differ significantly between LT recipients and the general population[27]. Contrarily, a retrospective study revealed that LT recipients with COVID-19 had higher odds of mortality and complications, such as sepsis and acute kidney injury[28]. A nationwide retrospective study also revealed a 5-fold higher risk of mortality in LT recipients with COVID-19 compared to those without COVID-19[29]. Therefore, available data reveals inconsistent findings on the COVID-19 outcomes in LT recipients. These inconclusive results could be attributed to the design of the published studies (case series) and the significant heterogeneity in nationwide cohort and international research studies. The majority of these studies had a number of limitations, including low power and a lack of robustness because of their small sample sizes. Therefore, clinical evidence from large-scale population-based studies has been warranted.

Our aim is to investigate the influence of the COVID-19 pandemic on hospitalized LT recipients by studying substantial epidemiological trends. To our knowledge, this is the first retrospective cohort study from the United States analyzing the impact of COVID-19 on LT recipients by comparing the rates of hospitalization, transplant rejection, and inpatient mortality before and during the pandemic using a multicenter database. It broadens the applicability of our results by offering greater generalizability. Our findings could potentially assist clinicians in providing improved care decisions and prognostic guidance for LT recipients with COVID-19.

MATERIALS AND METHODS

Design and data source

This retrospective cohort study utilized the National Inpatient Sample (NIS) database from 2019 to 2020[30]. It is part of the Healthcare Cost and Utilization Project, which is sponsored by the Agency for Healthcare Research and Quality[30]. The NIS represents one of the biggest inpatient databases in the United States[30]. It is based on hospital billing data from 46 states, which account for 97% of the nation's population. The design of this database allows for computing national estimates with a 20% stratified sample of hospitals and sampling weights. Detailed information on design and sampling methods is available at https://www.hcup-us.ahrq.gov. NIS 2020 utilized the International Classification of Diseases, Tenth Revision (ICD-10) coding system to store and report data.

Study population

Patients with primary LT hospitalizations were identified using ICD-10 codes. The hospitalizations with a secondary diagnosis of COVID-19 were identified using the "U07.1" ICD-10 code, which was introduced in March 2020[31]. However, the first diagnosis of COVID-19 in the United States was made in January 2020. Therefore, we included the entire year 2020 for the COVID-19 pandemic for adequate comparison[32]. Exclusion criteria included participants under the age of 18, transfers, elective cases, and those with a history of quadriplegia, malignant tumors, lymphomas, or end-stage renal disease needing dialysis. These were considered high-risk conditions because they could potentially confound the current analysis. This study report was prepared and revised according to the Strengthening the Reporting of Observational Studies in Epidemiology recommendations[33].

Outcome measures

The primary outcome was the LT hospitalization trend prior to (January 2019–December 2020) and during (January 2020–December 2020) the COVID-19 pandemic. Secondary outcomes included comparative trends of mortality and transplant rejection in hospitalized LT recipients.

Statistical analysis

Statistical analysis was performed using the Statistical Software for Data Science (StataCorp LLC, College Station, TX,

United States), version 16.1. The Kruskal-Wallis test was performed on continuous data, and the results were presented with an interquartile range (IQR). The χ^2 test was applied to categorical variables, and results were reported as frequency (%). The non-parametric trend analysis utilizing the "nptrend" command was used to report linear trends over time. Logistic regression outcomes were reported as odds ratios (OR) with 95% confidence intervals (CI).

Ethical considerations

The NIS is a third-party, de-identified hospital-level database. The privacy of patients, physicians, and hospitals is protected by the design of the NIS. Patient consent was waived as the hospitalization data were anonymized. The current study did not require approval from the institutional review board (IRB). According to the Healthcare Cost and Utilization Project Data Use Agreement, any individual table cell counts of ≤ 10 have been masked to ensure privacy and compliance. In such instances, data are designated as < 10.

RESULTS

A total of 15720 hospitalized LT recipients were included. There were 49.7% and 50.3% of LT hospitalizations in 2019 and 2020, respectively. Approximately 0.8% of hospitalized LT recipients had a secondary diagnosis of COVID-19 infection. In both cohorts, the median admission age was 57 years. There was no gender disparity for LT hospitalization before or during the COVID-19 pandemic (P = 0.9). The median (IQR) hospital stay was comparable in both cohorts [12.0 (7.0, 23.0) *vs* 12.0 (8.0, 24.0) d, P = 0.2]. The median charges were higher for LT hospitalizations during the COVID-19 pandemic $473252 (IQR $334552, $744322) than the pre-pandemic time $428177 (IQR $307282, $689844) ($P$ < 0.001). The inpatient mortality rate (3.2% *vs* 2.7%, P = 0.079) and LT rejection rate (2.3% *vs* 1.5%, P < 0.001) were higher during the pandemic compared to before the pandemic (Table 1).

The rate of LT hospitalizations increased from 22.9/100000 NIS hospitalizations in January 2019 to 24.7/100000 in December 2019 (P = 0.18). In 2020, the rate of LT hospitalizations increased from 24.2/100000 NIS hospitalizations in January to 28.6/100000 in December (P = 0.001) (Figure 1). The linear trends for LT hospitalizations did not differ significantly before and during the pandemic (P = 0.84).

The frequency of in-hospital mortality for LT recipients increased from 1.7% to 4.4% between January 2019 and December 2020 (P = 0.78) (Table 2). In 2020, the frequency of in-hospital mortality for LT recipients was 1.6% and 4.4% in January and December (P = 0.55), respectively (Figure 2). The linear trends for inpatient mortality showed a significant difference between before and during the pandemic (P = 0.011). Compared to the pre-pandemic period, a higher association was noted between LT recipients and in-hospital mortality during the pandemic [OR: 1.69 (95%CI: 1.55-1.84), P < 0.001].

The frequency of LT rejection in 2019 was 0.2% and 0.1% in January and December (P < 0.001), respectively. In 2020, the frequency of transplant rejection among hospitalized LT recipients increased from 0.8% to 3.6% between January and December (P = 0.23) (Figure 3). The linear trends for transplant rejection showed a significant difference between before and during the pandemic (P = 0.021). There was a higher association of transplant rejection for LT hospitalizations in 2020 compared to 2019 [OR: 1.53 (95%CI: 1.26-1.85), P < 0.001].

DISCUSSION

This nationwide cohort study shows that COVID-19 pandemic did not significantly increase the risk of hospitalization among LT recipients. However, inpatient mortality and transplant rejection rates increased during the early phase of the pandemic in the United States. Therefore, this high-risk patient population requires effective prognostication and tailored treatment strategies.

The hospitalization rates for LT recipients were similar before and during the COVID-19 pandemic in our study. A number of studies showed that the early phase of the pandemic had higher LT hospitalization rates due to safety precautions[34-36]. However, previous research also argued that at-home management of COVID-19 in LT recipients could be feasible[27]. Effective preventive strategies such as close monitoring of clinical status, telemedicine services with long hours, and mobile health facilities are important in this regard[27]. Moreover, a case-control study from the United States revealed no difference in hospitalization risk and clinical outcomes of COVID-19 in LT and non-LT patients[37]. Our data also suggest that the hospitalization rates of LT recipients were not affected by the COVID-19 pandemic. Recently, a cohort study of 14464 LT recipients demonstrated that the use of tacrolimus may also decrease the risk of COVID-19 hospitalization compared to steroids and mycophenolic acid[38]. In our LT cohorts, it is possible that a number of patients were on tacrolimus, potentially decreasing the need for hospitalization. It is also notable that LT activity was suspended after the onset of the pandemic, with a temporary shift toward teleconsultations[39,40]. These changes could also contribute to decreased overall hospitalization in LT recipients. In our data, the median length of hospital stay was also similar in both cohorts. Our results are in line with research that shows COVID-19 has no influence on the length of hospital stays for LT patients[37]. Interestingly, hospitalization expenditures increased during the pandemic in comparison to the pre-pandemic era (473252.0$ *vs* 428177.0$). As the length of hospital stay was comparable in both cohorts, the hospital course and treatment choice could have impacted inpatient costs for LT recipients during the pandemic.

Table 1 Baseline characteristics of liver transplant hospitalizations, *n* (%)

Factor	2019	2020	*P* value
Total liver transplant hospitalizations	7810 (49.7)	7910 (50.3)	
Liver transplant rejections	120 (1.5)	180 (2.3)	< 0.001
Elixhauser comorbidity index score			< 0.001
≤ 2	325 (4.2)	235 (3.0)	
≥ 3	7490 (95.8)	7680 (97.0)	
Age in years at admission, median (IQR)	57.0 (49.0, 64.0)	57.0 (48.0, 64.0)	0.75
Gender			0.90
Male	4885 (62.51)	4940 (62.41)	
Female	2930 (37.49)	2975 (37.59)	
Median household income national quartile for patient ZIP code			< 0.001
1st (0-25th)	1770 (23.2)	1935 (24.8)	
2nd (26th-50th)	1850 (24.2)	2070 (26.6)	
3rd (51st-75th)	2115 (27.7)	1830 (23.5)	
4th (76th-100th)	1905 (24.9)	1955 (25.1)	
Primary payer			0.39
Medicare	2405 (32.2)	2345 (31.0)	
Medicaid	1205 (16.1)	1260 (16.7)	
Private and other	3943 (50.5)	3991 (50.5)	
Inpatient mortality	210 (2.7)	250 (3.2)	0.079
Length of stay (d), median (IQR)	12.0 (7.0, 23.0)	12.0 (8.0, 24.0)	0.2
Total charges (USD), median (IQR)	428177.0 (307282.0, 689844.0)	473252.0 (334552.0, 744322.0)	< 0.001

IQR: Interquartile range.

Our study showed increased inpatient mortality for LT recipients during the COVID-19 pandemic ($P < 0.001$). The available data on the mortality of LT recipients following COVID-19 showed considerable heterogeneity. A study from Italy involving 111 long-term (> 10 years) post-LT recipients revealed 3 deaths after severe SARS-CoV-2 infection[41]. Among the 40 recent (< 2 years) posttransplant patients, 3 patients contracted COVID-19 and experienced an uneventful course of disease[41]. An European study involving 57 post-LT patients with COVID-19 revealed overall and in-hospital fatality rates of 12% and 17%, respectively[42]. Contrary to our findings, a multicenter cohort study with 151 adult LT recipients revealed that the mortality rate for non-LT patients was higher than the LT recipients with COVID-19 infection (27% *vs* 19%, $P = 0.046$)[43]. Notably, LT recipients had higher rates of mechanical ventilation and intensive care unit (ICU) admission[43]. In the same study, propensity score-matched analysis showed that patients with COVID-19 did not have a statistically higher risk of mortality with LT history[43]. However, in a French registry-based nationwide study, hospitalized LT recipients had a 30-d mortality rate of 28.1%[44]. These findings suggest that there is still a significant degree of heterogeneity in the mortality burden. Therefore, further research is required to evaluate the long-term effects of the COVID-19 pandemic on LT recipients.

A narrative review discussed that transplantation status may not be predictive of COVID-19 outcomes in LT recipients [45]. Similarly, a recent comprehensive review considered medical comorbidities unrelated to LT as possibly influencing clinical outcomes[46]. Our findings showed that the LT cohort hospitalized during the COVID-19 pandemic had an Elixhauser Comorbidity Index (ECI) score ≥ 3 higher than the cohort hospitalized before the pandemic (97.0% *vs* 95.8%). It could have added to the mortality burden in our cohort during the pandemic. Advanced age is also a risk factor for poor clinical outcomes in transplant recipients infected with SARS-CoV-2[46]. However, the age of both cohorts was comparable in our analysis. Participants in our study had not received the COVID-19 vaccination. It might have also contributed to the higher mortality rate during the early phase of the pandemic. The vaccines against SARS-CoV-2 in LT recipients have been strongly recommended[47,48]. However, the efficacy of several vaccines can be hampered by suboptimal immune responses, vaccine hesitancy, lower vaccination rates, and adverse events in this high-risk population[49-51]. Therefore, clinical outcomes may be improved by effective prevention and treatment of COVID-19 in LT recipients.

There is a dearth of population-based data on transplant rejection among LT recipients during the COVID-19 pandemic. Our results revealed that LT hospitalizations during the pandemic had a higher association with transplant rejection than before the pandemic ($P < 0.001$). Transplant rejection rates increased from 1.5% in 2019 to 2.3% in 2020. A

Table 2 Linear trends of baseline characteristics of liver transplant hospitalizations included in the present study

	Jan	Feb	March	April	May	June	July	Aug	Sep	Oct	Nov	Dec	*P* value
Total liver transplant hospitalizations, *n* (%)													
2019	600 (7.7)	635 (8.1)	690 (8.8)	625 (8.0)	615 (7.9)	675 (8.6)	670 (8.6)	710 (9.1)	685 (8.8)	705 (9.0)	600 (7.7)	635 (8.1)	0.98
2020	635 (8.0)	655 (8.3)	560 (7.1)	595 (7.5)	700 (8.9)	710 (9.0)	670 (8.5)	695 (8.8)	690 (8.7)	650 (8.2)	665 (8.4)	685 (8.7)	0.73
Liver transplant rejections, *n* (%)													
2019	< 10	35 (5.5)	30 (4.3)	25 (4.0)	25 (4.1)	< 10	15 (2.2)	15 (2.1)	< 10	15 (2.1)	< 10	< 10	< 0.001
2020	< 10	35 (5.3)	15 (2.7)	15 (2.5)	15 (2.1)	< 10	25 (3.7)	< 10	< 10	15 (2.3)	< 10	25 (3.6)	0.23
Elixhauser comorbidity index score, *n* (%)													
2019													< 0.001
≤ 2	30 (5)	35 (5.5)	30 (4.3)	20 (3.2)	30 (4.9)	45 (6.7)	15 (2.2)	25 (3.5)	20 (2.9)	15 (2.1)	30 (5.2)	30 (4.8)	
≥ 3	570 (95.0)	600 (94.5)	660 (95.7)	605 (96.8)	585 (95.1)	630 (93.3)	655 (97.8)	685 (96.5)	665 (97.1)	690 (97.9)	545 (94.8)	595 (95.2)	
2020													< 0.001
≤ 2	35 (5.5)	20 (3.1)	20 (3.6)	15 (2.5)	30 (4.3)	25 (3.5)	0 (0.0)	20 (2.9)	< 10	30 (4.6)	15 (2.3)	< 10	
≥ 3	600 (94.5)	635 (96.9)	540 (96.4)	580 (97.5)	670 (95.7)	685 (96.5)	665 (99.3)	675 (97.1)	680 (98.6)	620 (95.4)	650 (97.7)	675 (98.5)	
Age in years at admission, median (IQR)													
2019	58.5 (52.0, 65.0)	57.0 (49.0, 63.0)	57.0 (46.0, 62.0)	57.0 (50.0, 64.0)	57.0 (49.0, 63.0)	58.0 (50.0, 64.0)	59.0 (49.0, 63.0)	57.0 (48.0, 65.0)	57.0 (51.0, 65.0)	57.0 (47.0, 62.0)	58.0 (50.0, 66.0)	56.0 (48.0, 63.0)	< 0.001
2020	58.0 (49.0, 64.0)	55.0 (46.0, 64.0)	57.0 (50.0, 64.0)	59.0 (47.0, 65.0)	57.0 (49.5, 64.0)	57.0 (45.0, 64.0)	56.0 (42.0, 63.0)	57.0 (48.0, 64.0)	58.0 (49.0, 65.0)	57.0 (47.0, 64.0)	58.0 (49.0, 64.0)	59.0 (48.0, 65.0)	< 0.001
Gender, *n* (%)													
2019													< 0.001
Male	380 (63.3)	390 (61.4)	415 (60.1)	375 (60.0)	345 (56.1)	445 (65.9)	425 (63.4)	495 (69.7)	440 (64.2)	450 (63.8)	375 (65.2)	350 (56.0)	
Female	220 (36.7)	245 (38.6)	275 (39.9)	250 (40.0)	270 (43.9)	230 (34.1)	245 (36.6)	215 (30.3)	245 (35.8)	255 (36.2)	200 (34.8)	275 (44.0)	
2020													0.037
Male	415 (65.4)	400 (61.1)	350 (62.5)	410 (68.9)	415 (59.3)	410 (57.7)	385 (57.5)	465 (66.9)	455 (65.9)	440 (67.7)	395 (59.4)	400 (58.4)	

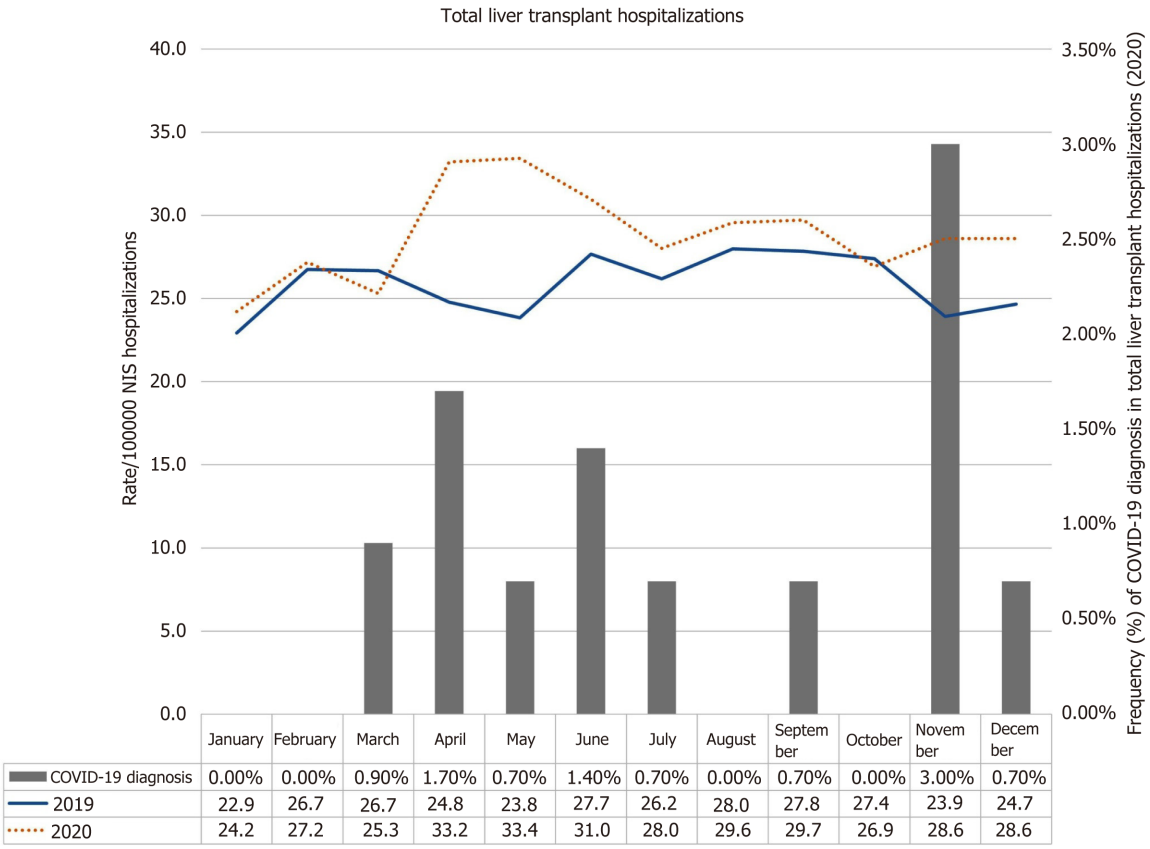
Female	220 (34.6)	255 (38.9)	210 (37.5)	185 (31.1)	285 (40.7)	300 (42.3)	285 (42.5)	230 (33.1)	235 (34.1)	210 (32.3)	270 (40.6)	285 (41.6)	
Median household income national quartile for patient ZIP Code, *n* (%)													
2019													< 0.001
1st (0-25th)	115 (20.4)	105 (17.1)	145 (21.8)	180 (29.0)	140 (22.8)	145 (21.8)	195 (29.8)	150 (21.6)	185 (27.6)	140 (20.0)	135 (24.1)	135 (22.1)	
2nd (26th-50th)	140 (24.8)	190 (30.9)	125 (18.8)	145 (23.4)	165 (26.8)	150 (22.6)	145 (22.1)	150 (21.6)	145 (21.6)	165 (23.6)	150 (26.8)	180 (29.5)	
3rd (51st-75th)	160 (28.3)	155 (25.2)	220 (33.1)	180 (29.0)	150 (24.4)	175 (26.3)	175 (26.7)	185 (26.6)	175 (26.1)	195 (27.9)	165 (29.5)	175 (28.7)	
4th (76th-100th)	150 (26.5)	165 (26.8)	175 (26.3)	115 (18.5)	160 (26.0)	195 (29.3)	140 (21.4)	210 (30.2)	165 (24.6)	200 (28.6)	110 (19.6)	120 (19.7)	
2020													< 0.001
1st (0-25th)	165 (26.4)	130 (20.2)	150 (26.8)	135 (23.1)	175 (25.5)	165 (23.6)	150 (22.6)	220 (32.1)	180 (26.1)	175 (27.6)	155 (23.5)	135 (20.6)	
2nd (26th-50th)	205 (32.8)	180 (27.9)	140 (25.0)	150 (25.6)	195 (28.5)	190 (27.1)	230 (34.6)	155 (22.6)	170 (24.6)	135 (21.3)	180 (27.3)	140 (21.4)	
3rd (51st-75th)	110 (17.6)	130 (20.2)	160 (28.6)	150 (25.6)	160 (23.4)	170 (24.3)	130 (19.5)	150 (21.9)	165 (23.9)	175 (27.6)	130 (19.7)	200 (30.5)	
4th (76th-100th)	145 (23.2)	205 (31.8)	110 (19.6)	150 (25.6)	155 (22.6)	175 (25.0)	155 (23.3)	160 (23.4)	175 (25.4)	150 (23.6)	195 (29.5)	180 (27.5)	
Primary payer, *n* (%)													
2019													< 0.001
Medicare	190 (33.0)	170 (28.3)	220 (33.3)	155 (25.4)	180 (30.8)	225 (34.9)	210 (31.8)	245 (36.0)	220 (33.6)	215 (32.6)	195 (36.8)	180 (30.0)	
Medicaid	85 (14.8)	100 (16.7)	95 (14.4)	120 (19.7)	95 (16.2)	105 (16.3)	110 (16.7)	110 (16.2)	110 (16.8)	120 (18.2)	65 (12.3)	85 (14.2)	
Private and other	300 (50.0)	330 (52.0)	345 (50.0)	335 (54.9)	310 (50.4)	315 (46.7)	340 (51.5)	339 (47.7)	340 (49.6)	347 (49.2)	293 (50.9)	349 (55.8)	
2020													< 0.001
Medicare	215 (35.0)	185 (30.8)	190 (35.5)	200 (35.1)	185 (27.8)	175 (25.7)	190 (30.4)	200 (29.9)	210 (32.1)	200 (32.3)	190 (29.2)	200 (29.9)	
Medicaid	90 (14.6)	135 (22.5)	60 (11.2)	90 (15.8)	105 (15.8)	105 (15.4)	115 (18.4)	140 (20.9)	95 (14.5)	110 (17.7)	100 (15.4)	115 (17.2)	
Private and other	310 (48.8)	280 (46.7)	285 (53.3)	280 (47.1)	375 (56.4)	400 (58.8)	320 (47.8)	330 (47.5)	350 (50.7)	310 (47.7)	369 (55.5)	355 (53.0)	
Inpatient mortality, *n* (%)													
2019	< 10	20 (3.1)	< 10	30 (4.8)	15 (2.4)	25 (3.7)	15 (2.2)	25 (3.5)	15 (2.2)	25 (3.5)	15 (2.6)	< 10	0.78
2020	< 10	25 (3.8)	< 10	45 (7.6)	15 (2.1)	25 (3.5)	15 (2.2)	25 (3.6)	15 (2.2)	15 (2.3)	20 (3.0)	30 (4.4)	0.55
Length of stay, median (IQR) (days)													

2019	12.5 (8.0, 25.5)	11.0 (7.0, 25.0)	11.0 (7.0, 23.0)	11.0 (7.0, 21.0)	11.0 (7.0, 17.0)	12.0 (7.0, 23.0)	14.0 (9.0, 25.0)	12.0 (7.0, 23.0)	11.0 (8.0, 23.0)	14.0 (7.0, 21.0)	11.0 (8.0, 24.0)	13.0 (8.0, 23.0)	< 0.001
2020	12.0 (7.0, 25.0)	12.0 (8.0, 21.0)	11.5 (7.0, 23.0)	13.0 (8.0, 24.0)	11.5 (8.0, 23.0)	11.5 (7.0, 21.0)	11.0 (7.0, 20.0)	15.0 (8.0, 26.0)	13.0 (8.0, 24.0)	14.5 (8.0, 30.0)	13.0 (8.0, 23.0)	13.0 (8.0, 25.0)	< 0.001
Total charges, median (IQR) (USD)													
2019	438680.5 (319902.0, 703305.0)	383767.0 (292185.0, 648388.0)	394906.0 (290243.0, 740556.0)	416119.0 (308253.0, 670906.0)	397547.0 (294459.0, 607369.0)	408327.0 (314639.0, 669496.0)	475886.0 (319526.0, 770702.0)	461861.0 (294480.0, 644659.0)	419143.0 (313531.0, 641207.0)	449383.0 (326746.0, 702840.5)	430862.0 (293962.0, 644716.0)	428974.0 (308548.0, 780206.0)	< 0.001
2020	442761.5 (303964.0, 677788.0)	465051.0 (340561.0, 685720.0)	442387.0 (329722.0, 705312.0)	476185.0 (340632.0, 652454.0)	435817.0 (328502.0, 714647.0)	457076.0 (347943.5, 676989.0)	456924.0 (331853.5, 664905.5)	515565.0 (369134.0, 806652.0)	481444.0 (327361.0, 726893.0)	523452.0 (339184.0, 951676.0)	505836.0 (330019.5, 796788.0)	451569.0 (325468.0, 754506.0)	< 0.001
COVID-19 Dx (2020 only), *n* (%)	0 (0.0)	0 (0.0)	< 10	< 10	< 10	< 10	< 10	0 (0.0)	< 10	0 (0.0)	20 (3.0)	< 10	0.10

According to the Healthcare Cost and Utilization Project Data Use Agreement, any individual table cell counts of ≤ 10 have been masked to ensure privacy and compliance. In such instances, data are designated as < 10.

meta-analysis also showed a cumulative incidence of graft dysfunction of 2.3% in LT recipients[24]. A prospective nationwide study also reported a graft dysfunction rate of 2.7% among LT recipients with COVID-19 infection[26]. In the early phase of the pandemic, a European multicenter prospective study showed that SARS-CoV-2 infection led to a reduction or cessation of immunosuppressive therapy in 39% and 7% of LT recipients, respectively[42]. Similarly, a French study revealed that antimetabolites, the mammalian target of rapamycin inhibitors (mTORI), and calcineurin inhibitors (CNI) were stopped in 41.9%, 30.0%, and 12.5% of LT recipients during their hospital stay, respectively[44]. Moreover, a multicenter analysis showed that immunosuppression required modifications in 49% of LT recipients who had COVID-19, mostly in cases requiring ICU transfer, mechanical ventilation, or vasopressors[19]. A prospective study showed that the immunosuppressive regimen containing mycophenolate was an independent predictor of mortality in LT recipients due to its synergistic effect with COVID-19 on host T cells[26]. They revealed a possible dose-dependent adverse effect with doses greater than 1000 mg/d (P = 0.003)[26]. However, CNI and mTORI may have either no adverse impact or may offer clinical benefit post-LT due to their antiviral actions and possible suppression of SARS-CoV-2 replication, respectively[52-54].

In our study, alterations in immunosuppressive regimens could have contributed to the increased rejection rates. While credible evidence continues to emerge, recommendations from experts are still crucial for clinical management[55]. Therefore, immunosuppressive drugs have been tailored on a case-by-case basis to meet the specific requirements of LT recipients with COVID-19. Patients with a mild infection do not need changes in immunosuppressive therapy. Reducing immunosuppression is often warranted in individuals with severe COVID-19 infection or those who are susceptible to the disease progression. In such clinical scenarios, it could be prudent to reduce the mycophenolate dosage preferentially. The recommendations by the major international liver associations also endorse such alterations in immunosuppression [56,57]. A meta-analysis showed that tacrolimus was found to be beneficial for COVID-19 in SOT recipients[58]. However, close monitoring of the drug levels is important, as COVID-19 may raise serum levels in these patients[52]. Moreover, mTORI and CNIs may have strong drug-drug interactions with Paxlovid. Therefore, concurrent administration of these agents should be avoided[59]. Patients with severe COVID-19 infections may also benefit from graft function monitoring, particularly after changes in immunosuppressive medications. It could help in the early identification of possible



	January	February	March	April	May	June	July	August	September	October	November	December
COVID-19 diagnosis	0.00%	0.00%	0.90%	1.70%	0.70%	1.40%	0.70%	0.00%	0.70%	0.00%	3.00%	0.70%
2019	22.9	26.7	26.7	24.8	23.8	27.7	26.2	28.0	27.8	27.4	23.9	24.7
2020	24.2	27.2	25.3	33.2	33.4	31.0	28.0	29.6	29.7	26.9	28.6	28.6

Figure 1 Monthly trend of liver transplant hospitalizations. The solid blue and dotted orange lines represent rates of liver transplant hospitalizations per 100000 hospitalizations documented in the United States National Inpatient Sample database before and during the coronavirus disease 2019 pandemic for 2019 and 2020, respectively. The bar graph indicates the frequency (%) of coronavirus disease 2019 diagnosed in liver transplant hospitalizations in 2020. COVID-19: Coronavirus disease 2019; NIS: National Inpatient Sample.

transplant rejection.

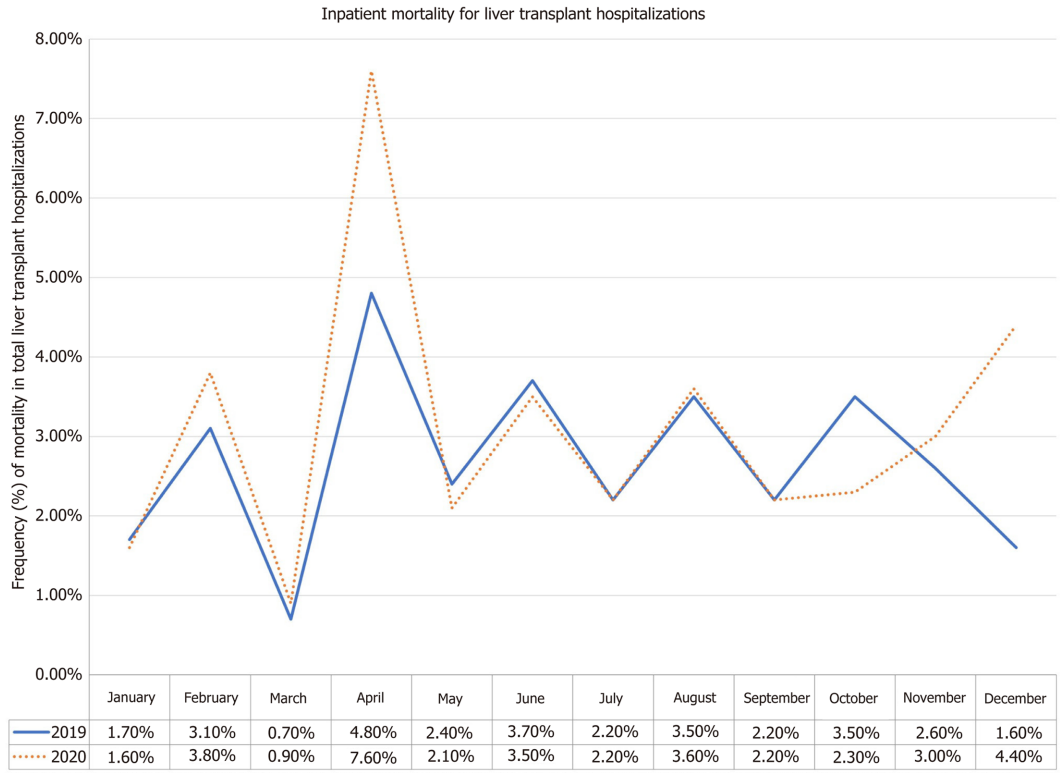
Our retrospective cohort study is a community-based analysis assessing hospitalization, transplant rejection, and in-hospital mortality in LT recipients during the COVID-19 pandemic. The majority of research on the effects of COVID-19 infection in the post-LT population is limited to smaller, single-center analyses. The results of these studies have restricted generalizability and cannot be applied broadly. In our research, the substantial sample size of the NIS made it feasible to perform an exhaustive, large-scale cohort analysis. Moreover, the 2020 NIS data allowed for a direct analysis of the impact of COVID-19 on LT hospitalizations, as it included the transition from pre-pandemic to pandemic time. It enabled an improved understanding of the differences in key variables between the two cohorts.

Limitations

There are a few limitations to our study. The retrospective nature of the study design lacks prospectiveness, which is crucial for proving causality. The NIS database uses data from a single hospitalization. Therefore, it is not possible to identify patients who had readmissions during the study period. The ICD-10 coding system may be susceptible to errors when applied to large databases. In addition, the ICD-10 code for COVID-19 infection (U07.1) was introduced in March 2020. Therefore, patients prior to March 2020 were not coded and thus missed out in our study. The first publicly available COVID-19 vaccine was not introduced until December 2020. Consequently, the impact of vaccination on LT recipients was not analyzed in our study. Nonetheless, studies showed that the risk of developing a serious SARS-CoV-2 infection was higher for SOT recipients, regardless of their vaccination status[60]. Specific data on COVID-19 severity or treatment are not available. The functional status of the grafts and the results of clinical or biological testing are also not available in the NIS. There was a risk of residual confounding due to the unavailability of the aforementioned variables, but it did not impact the primary and secondary objectives of our study.

CONCLUSION

This study has thoroughly analyzed the influence of COVID-19 pandemic on LT recipients using a multicenter database. The pandemic did not lead to an increase in hospitalizations among LT recipients. Our findings revealed that the COVID-19 pandemic had a negative impact on inpatient outcomes for LT recipients. Both inpatient mortality and transplant rejection rates increased during the pandemic. Specific therapeutic protocols are required for managing severe SARS-



	January	February	March	April	May	June	July	August	September	October	November	December
2019	1.70%	3.10%	0.70%	4.80%	2.40%	3.70%	2.20%	3.50%	2.20%	3.50%	2.60%	1.60%
2020	1.60%	3.80%	0.90%	7.60%	2.10%	3.50%	2.20%	3.60%	2.20%	2.30%	3.00%	4.40%

Figure 2 Monthly trends of inpatient mortality in liver transplant hospitalizations. The solid blue and dotted orange lines represent frequency (%) of inpatient mortality in total liver transplant hospitalizations before and during the coronavirus disease 2019 pandemic for 2019 and 2020, respectively.

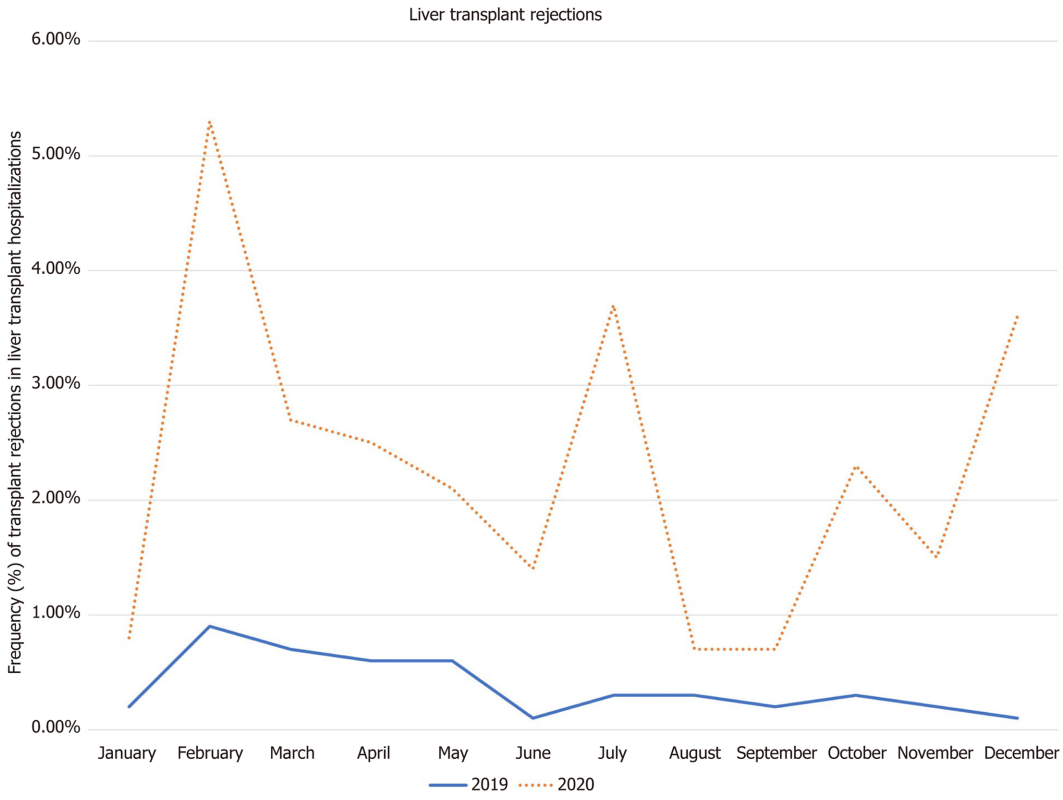


Figure 3 Monthly trends of transplant rejection in liver transplant hospitalizations. The solid blue and dotted orange lines represent frequency (%) of transplant rejections in liver transplant hospitalizations before and during the coronavirus disease 2019 pandemic for 2019 and 2020, respectively.

CoV-2 infection in post-transplant patients in order to decrease the risk of mortality and transplant rejection. In this regard, necessary adjustments to immunosuppressive regimens may be considered in severe cases. Further clinical evidence is required to evaluate the long-term impact of the COVID-19 infection on LT recipients.

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FOOTNOTES

Author contributions: Inayat F, Patel P, Ali H, Afzal A, Tahir H, and Chaudhry A concepted and designed the study, participated in the acquisition of data, interpretation of results, writing of the original draft, and critical revisions of the important intellectual content of the final manuscript; Ishtiaq R, Rehman AU, Darji K, Afzal MS, Nawaz G, and Giammarino A contributed to the analysis and interpretation of results and drafting of the manuscript; Satapathy SK reviewed, revised, and improved the manuscript by suggesting pertinent modifications; and all authors critically assessed, edited, and approved the final manuscript and are accountable for all aspects of the work.

Institutional review board statement: The data of patients was not acquired from any specific institution but rather open-access United States National Inpatient Sample (NIS) database. The NIS contains de-identified information, protecting the privacy of patients, physicians, and hospitals. Therefore, it was deemed exempt from the institutional review board (IRB).

Informed consent statement: Participants were not required to give informed consent for this retrospective cohort study since the analysis of baseline characteristics used anonymized clinical data.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Impact of payment source, referral site, and place of residence on outcomes after allogeneic transplantation in Mexico

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Abstract

BACKGROUND

The impact of social determinants of health in allogeneic transplant recipients in low- and middle-income countries is poorly described. This observational study analyzes the impact of place of residence, referring institution, and transplant cost coverage (out-of-pocket *vs* government-funded *vs* private insurance) on outcomes after allogeneic hematopoietic stem cell transplantation (alloHSCT) in two of Mexico's largest public and private institutions.

AIM

To evaluate the impact of social determinants of health and their relationship with outcomes among allogeneic transplant recipients in Mexico.

METHODS
In this retrospective cohort study, we included adolescents and adults ≥ 16 years who received a matched sibling or haploidentical transplant from 2015-2022. Participants were selected without regard to their diagnosis and were sourced from both a private clinic and a public University Hospital in Mexico. Three payment groups were compared: Out-of-pocket (OOP), private insurance, and a federal Universal healthcare program "Seguro Popular". Outcomes were compared between referred and institution-diagnosed patients, and between residents of Nuevo Leon and out-of-state. Primary outcomes included overall survival (OS), categorized by residence, referral, and payment source. Secondary outcomes encompassed early mortality, event-free-survival, graft-versus-host-relapse-free survival, and non-relapse-mortality (NRM). Statistical analyses employed appropriate tests, Kaplan-Meier method, and Cox proportional hazard regression modeling. Statistical software included SPSS and R with tidycmprsk library.

RESULTS
Our primary outcome was overall survival. We included 287 patients, n = 164 who lived out of state (57.1%), and n = 129 referred from another institution (44.9%). The most frequent payment source was OOP (n = 139, 48.4%), followed by private insurance (n = 75, 26.1%) and universal coverage (n = 73, 25.4%). No differences in OS, event-free-survival, NRM, or graft-versus-host-relapse-free survival were observed for patients diagnosed locally *vs* in another institution, nor patients who lived in-state *vs* out-of-state. Patients who covered transplant costs through private insurance had the best outcomes with improved OS (median not reached) and 2-year cumulative incidence of NRM of 14% than patients who covered costs OOP (Median OS and 2-year NRM of 32%) or through a universal healthcare program active during the study period (OS and 2-year NRM of 19%) (P = 0.024 and P = 0.002, respectively). In a multivariate analysis, payment source and disease risk index were the only factors associated with overall survival.

CONCLUSION
In this Latin-American multicenter study, the site of residence or referral for alloHSCT did not impact outcomes. However, access to healthcare coverage for alloHSCT was associated with improved OS and reduced NRM.

Key Words: Hematopoietic cell transplant; Social determinants of health; Geography; Haploidentical; Out-of-pocket; Financial toxicity; Survival; Health services and outcomes; Hematopoietic malignancy; Aplastic anemia

Core Tip: In our comprehensive analysis of allogeneic hematopoietic stem cell transplantation (alloHSCT) outcomes in Mexico, we underscore the pivotal role of insurance coverage. Patients with private insurance had superior survival rates compared to those relying on out-of-pocket or government programs. Intriguingly, geographical residence and referral sources did not significantly influence outcomes. This study underscores the profound implications of financial barriers in healthcare access and the urgent need for policy interventions. Our findings stress the importance of addressing socioeconomic disparities and emphasize the role of insurance status in enhancing alloHSCT outcomes in regions like Latin America.

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INTRODUCTION

The World Health Organization (WHO) defines social determinants of health as the "non-medical factors that influence outcomes"[1]. According to the WHO, these factors can account for 30%-55% of health outcomes, estimating that their contributions are more important than lifestyle choices or healthcare itself[1]. Allogeneic hematopoietic stem cell transplantation (alloHSCT) for hematological malignancies is a complex and expensive procedure that requires special pre- and post-transplant care. Not surprisingly, there is evidence that social determinants of health impact outcomes after alloHSCT. Most available data come from retrospective cohort analyses in the United States and other high-income countries. The impact of race, ethnicity, and socioeconomic status on outcomes after alloHSCT has been described in this setting. Low socioeconomic status has been reported to correlate with a higher risk of all-cause mortality and non-relapse mortality (NRM)[2]. Other factors associated with better quality of life and activity level include the ability to work, level

of education, and community health status[3,4].

To our knowledge, reports from Latin America on the influence of social determinants on outcomes after alloHSCT do not exist. The payment source in Latin America and other low and middle-income countries is a challenge, with most of the population relying on government-funded health systems that are limited in capacity. The Mexican health system consists of three main components: (1) Employment-based healthcare (40.4%); (2) public assistance services for the uninsured (43.5%); and (3) a private sector composed of out-of-pocket payments from patients and private insurance companies. Government-funded healthcare accounts for 58% of all healthcare financing, and less than 7.5% of the population has access to private insurance. The rest comes from out-of-pocket (OOP) expenses incurred by patients and their families[5,6].

Additionally, centers throughout the region are forced to refer patients to transplant centers in major cities due to a lack of local resources, forcing patients to travel and cover those costs, potentially increasing the risk of poorer outcomes. Specifically, reports analyzing the impact of the payment source, place of residence, and referral site are lacking in our setting. Therefore, our primary objective was to examine the association of the source of transplant payment, referral site, and place of residence on overall survival after alloHSCT for malignant hematological disorders in Mexico.

MATERIALS AND METHODS

This retrospective cohort included patients from two large transplant centers in Mexico: a private clinic and a public University Hospital with a FACT-JACIE accredited outpatient transplantation program. All patients ≥ 16 years old with hematologic malignancies that underwent alloHSCT from 2015-2022 were included. The University Hospital is open to all regardless of place of residence, referring institution, and healthcare access, but it requires OOP payment coverage to fund the procedure. From 2015 to 2019, a Universal healthcare program, "Seguro Popular," covered HSCT in our institution for otherwise uninsured patients across indications and populations but was terminated in 2019 by the current federal administration and is no longer available locally. Therefore, data from patients in the federal coverage program group, was exclusively from the period spanning 2015-2019, as no patients were eligible for coverage under the "Seguro Popular" program after 2019. The private clinic receives patients with private insurance and OOP regardless of the place of residence or referring institution. Patients are cared for by five transplant physicians who all trained at the university hospital; three worked in both institutions during the study period, sharing common practices and procedures. Thus, the outcomes of three payment coverage groups are compared in the entire cohort: OOP, privately insured patients, and patients who received care through the federal Universal healthcare program (2015-2019). Similarly, the outcomes of patients referred for transplant from another institution were compared to those diagnosed and treated in each institution before HSCT. Finally, the outcomes of patients who lived in Nuevo Leon *vs* those from out of state were also compared. The study was approved by the Institutional Review Board of both institutions and was performed according to the Declaration of Helsinki.

Conditioning and graft vs host disease prophylaxis

Conditioning regimens were similar in both medical centers. They included the following combinations: cyclophosphamide fludarabine and melphalan 140-200 mg/m^2, CyFlu plus busulfan (Bu) 8-12 mg/kg, CyFlu anti-thymocyte globulin for non-myeloablative regimens with or without 2 Gy total body irradiation for haploidentical transplant recipients. Graft-versus-host disease (GVHD) prophylaxis mainly included post-transplantation cyclophosphamide (PTCy) plus either PO cyclosporine or tacrolimus (CsA) and mycophenolate or CsA or tacrolimus plus methotrexate (CNI + MTX) tapered between day 100 until day 180 or after 1 year in patients with aplastic anemia.

Donor selection, mobilization, and cell procurement

Matched sibling donors were preferred across indications. During the study period, haploidentical family donors were considered acceptable alternatives for patients without matched sibling donors across indications since unrelated donors are highly expensive and of limited access in our country. When multiple haploidentical donors were available, younger donors with ABO compatibility and similar CMV seropositivity were selected. Donors were mobilized with filgrastim for 4 d, 10 ug/kg per day, and underwent peripheral blood apheresis with a target harvest of ≥ 5 × 10^6 CD34+ cells per kg of recipient weight. Cells were refrigerated and infused fresh without further manipulation on day 0.

Supportive care and follow-up

In the University Hospital, most patients underwent alloHSCT following a day-hospital outpatient strategy with ambulatory conditioning, cell infusion, and follow-up care extensively described by Gómez-Almaguer *et al*[7] with hospitalization indicated for complications associated with conditioning regimen toxicity and the need for intensive supportive care, infectious complications, or daily transfusion requirements. In the private setting, patients underwent a conventional in-patient strategy in a bone marrow transplant unit equipped with isolation rooms, independent air and water filtration systems, and positive pressure. Infectious disease prophylaxis was identical in both centers. It consisted of IV or PO levofloxacin 500 mg QD, itraconazole 100 mg BID or voriconazole 200 mg BID, acyclovir 400 mg BID, and trimethoprim/sulfamethoxazole 800/160 mg thrice weekly after engraftment. Filgrastim 5 μg/kg daily or pegfilgrastim 6 mg single dose was administered after day +5 until engraftment.

Outcomes

Our primary outcome was overall survival (OS) according to the place of residence (in-state *vs* out-of-state), referral (local diagnosis and treatment *vs* referral from another institution for HSCT), and transplant cost payment source (OOP *vs* universal coverage program *vs* private insurance). Secondary outcomes included early mortality, event-free survival (EFS), graft-versus-host-relapse-free survival (GRFS), and non-relapse mortality (NRM). OS was defined as the time between transplant and last follow-up or death. EFS was defined as the time between transplant and death, or relapse or progression of the underlying disease or last follow-up. GRFS was defined as the time between transplant and death, relapse or progression of the underlying disease, or the diagnosis of acute grade ≥ 3 GVHD or chronic GVHD requiring systemic treatment[8].

Statistical analysis

Patients' demographic and diagnostic characteristics, including sex, age, hematopoietic cell comorbidity index[9], and disease risk index (DRI)[10], were compared across interest groups. Similarly, transplant characteristics and immediate outcomes like donor HLA match, conditioning intensity[11], CD34+ cells infused, GVHD prophylaxis, neutrophil and platelet recovery, graft failure[12], and incidence and severity of acute or chronic GVHD were compared. Categorical variables were contrasted with the chi-square test, and continous variables were compared with Student's *t*-test, ANOVA, or the Mann Whitney *U* or Kruskal Wallis test according to normality. Survival outcomes were analyzed with the Kaplan-Meier method. Univariate and multivariate Cox proportional hazard regression modeling was performed to assess the potential impact of relevant co-variables on OS. The cumulative incidence of NRM was analyzed by considering death after relapse as a competing risk. Statistical analysis was performed with SPSS for Mac version 26 and R software and the *tidycmprsk* library. The statistical methods of this study were reviewed by Hector A Vaquera-Alfaro.

RESULTS

Baseline characteristics

Two hundred and eighty-seven patients were included, mostly a young population without comorbidities, n = 214 from the public and n = 73 from the private institution. Acute leukemia was the most common diagnosis, followed by aplastic anemia (n = 36, 12.5%) and non-Hodgkin lymphoma (n = 29, 10.1%) (Table 1). Regarding disease stage, n = 127 (44.2%) had a high or very high DRI with a median of 2 prior lines of treatment. Most patients received a haploidentical graft (n = 176, 61.3%); half received myeloablative conditioning (49.8%), and all patients received peripheral blood grafts. One hundred and sixty-four lived out of state (57.1%), and n = 129 were referred from another institution for HCT. Seventeen patients came from another country, most frequently from Central and South America. The most frequent payment source was OOP (n = 139, 48.4%), followed by private insurance (n = 75, 26.1%) and universal coverage (n = 73, 25.4%). The demographic information of our patient population is described in Table 1. The median follow-up of survivors/patients was 19.4 months.

Outcomes of in-state vs out-of-state residents

Out-of-state patients covered transplant costs more frequently OOP (56.7% *vs* 37.4%; P = 0.003) and had a worse DRI than local patients (high or very high 50.6% *vs* 35.7%; P = 0.02). No differences in HCT-CI, CD34 cells, myeloid recovery, aGVHD rates or early mortality were observed. Out-of-state patients received more frequent PTCy prophylaxis (81% *vs* 69.9%; P = 0.02) and experienced lower rates of severe cGVHD (2.4% *vs* 12.2%; P = 0.003). No statistical differences in OS, EFS, GRFS, or NRM were documented. Median OS was 31 months in state residents (95%CI: 1.9-32) *vs* 16.9 months in out-of-state residents (95%CI: 8.3-54.6) (Figure 1), with median EFS of 19.7 months (95%CI: 3.9-36.1) *vs* 12.1 (95%CI: 7.4-16.8) and identical median GRFS of 6.6 months (95%CI: 4.8-8.5 and 4.7-8.4, respectively). Two-year NRM was also similar, 26% (95%CI: 19%-33%) in out-of-state patients *vs* 21% (95%CI: 14%-29%) for in-state patients (P = 0.4). Place of residence was not associated with OS in the univariate Cox regression analysis (Table 2).

Outcomes in local vs referred patients

Patients who were diagnosed and treated elsewhere and referred to our institution for HCT had higher risk disease than local patients (high or very high DRI 49.4% *vs* 36.9%; P = 0.03). Also, they were more likely to reside out of state than local patients (78% *vs* 28.7%; P < 0.001) and cover transplant costs out-of-pocket (61.2% *vs* 31.1% P < 0.001). Patients had similar rates of aGVHD but higher rates of grades 3-4 acute GVHD (16.4% *vs* 6.8%; P = 0.03). No differences in engraftment, myeloid recovery, and early mortality in local *vs* referred patients were observed. Similarly, no statistical differences in OS, EFS, GRFS, or NRM were documented. Median OS was 20 months (95%CI: 5.3-35.6) *vs* 29.3 (95%CI: 14-44), median EFS was 20.6 months (95%CI: 2.2-38.9) *vs* 12.1 months (95%CI: 9.1-15.1) and median GRFS was 6.6 months (95%CI: 5.1-8.1) *vs* 6.9 months (95%CI: 5.3-8.5) in local *vs* referred patients, respectively (Figure 2). The two-year cumulative incidence of NRM was 26% (95%CI: 19%-33%) in local *vs* 20% (95%CI: 13%-27%) in referred patients (Figure 2). Univariate Cox regression analysis did not reveal the patient site of diagnosis and treatment (local *vs* referred) associated with OS (Table 2).

Outcomes according to payment source

Patients treated in the federal government coverage program were younger and received more frequent myeloablative conditioning regimens with calcineurin inhibitor and methotrexate GVHD prophylaxis than the private insurance and

Table 1 Baseline characteristics of 287 patients who received an allogeneic hematopoietic cell transplant

Variable		*n*	%
Sex	Male	168	58.6
	Female	119	41.5
Age	Median (years)	35	(16-79)
Country of origin	Mexico	270	94
	Other	17	6
State of origin	Nuevo Leon	123	42.9
	Other	164	57.1
Institution	Referral	165	57.5
	Local	122	42.5
Diagnosis	AML	77	26.8
	ALL	76	26.4
	AA	36	12.5
	NHL	29	10.1
	MDN	25	8.7
	HL	17	5.9
	CML	10	3.4
	CMML	6	2.1
	PMF	4	1.4
	CLL	4	1.4
	MM	3	1
Donor	Matched sibling	111	38.7
	Haploidentical	176	61.3
DRI	Non-malignant	36	12.6
	Intermediate	117	40.8
	High	100	34.8
	Very high	27	9.4
HCT-CI	Median	0	(0-5)
Treatment lines	Median	2	(0-6)
Payment source	Out-of-pocket	139	48.4
	Private insurance	75	26.1
	Universal coverage	73	25.4

DRI: Disease risk index; HCT-CI: Hematopoietic cell comorbidity index; AML: Acute myeloid leukemia; AA: Aplastic anemia; NHL: Non Hodgkin lymphoma; MDN: Myeldysplastic neoplasm; HL: Hodgkin lymphoma; CML: Chronic myeloid leukemia; CMML: Chronic myelomonocytic leukemia; MF: Myelofibrosis; CLL: Chronic lymphocytic leukemia; MM: Multiple myeloma.

OOP groups (Table 3). Patients who had private insurance experienced the best outcomes with a median OS not reached, while OOP patients did worse with a median OS of 16.9 months (95%CI: 11.2-22.7). Patients in the universal coverage program had a median OS of 26.3 months (95%CI: NC-63.5) (P = 0.024) (Figure 3). Median EFS was not statistically different, with 35.1 months (95%CI: 4-66.1), 13.1 months (95%CI: 1.1-25), and 11 months (95%CI: 7.1-14.9) in private, universal coverage, and OOP patients, respectively (P = 0.07). Similarly, GRFS was 7.1 months (95%CI: 4.1-10.2), 6.6 months (95%CI: 4.6-8.7), and 6.5 months (95%CI: 5.3-7.7) in private, universal coverage, and OOP patients, respectively (P = 0.54). In the univariate and multivariate analysis payment coverage was associated with OS, with access to private healthcare-associated to better survival. In the multivariate analysis, besides DRI, payment coverage was the only variable associated with overall survival (Table 2).

Table 2 Cox proportional hazards regression analysis of overall survival

		HR	95%CI	*P* value
Univariate analysis				
Age	Continuous	1	0.99-1.01	0.77
Sex	Female	1	0.71-1.4	0.98
DRI	Benign	0.66	0.36-1.19	**0.02**
	Low	0.15	0.02-1.08	
	Intermediate	0.66	0.46-0.94	
Treatment lines	Continuous	1.13	0.99-1.28	**0.06**
HCT-CI	Continuous	1.1	0.87-1.3	0.56
Place of residence	Out of state	0.94	0.67-1.31	0.7
Reference	Non-local	0.99	0.71-1.38	0.95
Coverage	Universal	0.76	0.51-1.13	**0.02**
	Private	0.55	0.35-0.86	
Donor	Haploidentical	1.48	1.03-2.1	**0.03**
Conditioning	NMA	0.94	0.53-1.67	0.92
	RIC	1.1	0.73-1.53	
GVHD prophylaxis	PTCy	1.6	0.89-3.01	**0.01**
Multivariate analysis				
DRI	Benign	0.64	0.3-1.37	0.25
	Low	0.15	0.02-1.12	0.06
	Intermediate	0.57	0.32-1	**0.05**
	High	0.9	0.52-1.58	0.72
Coverage	Federal	0.86	0.58-1.29	0.46
	Private	0.49	0.31-0.77	0.002
Donor	Haploidentical	0.93	0.56-1.53	0.78
GVDH prophylaxis	PTCy	1.64	0.89-3	0.11

DRI: Disease risk index; HCT-CI: Hematopoietic cell comorbidity index: GVHD: GRAFT versus host disease; NMA: Non-myeloablative; PTCy: Post-transplant cyclophosphamide.

DISCUSSION

Our analysis revealed a significant outcome contrast between patients with private insurance and those who paid OOP. Access to comprehensive insurance coverage may have a substantial positive impact on the post-alloHSCT journey. Patients who depend on OOP payments experienced the poorest outcomes. This finding emphasizes the critical role of financial barriers and highlights the challenges faced by individuals who lack adequate healthcare coverage. Interestingly, our analysis did not detect significant differences in outcomes between patients residing locally and those from out-of-state nor between patients referred from another institution and those with a local diagnosis. These findings suggest that geographical factors and referral sources are not significant determinants of outcomes in our population. We observed an increased rate of severe cGVHD in patients living in-state *vs* those living out of state (12.2 *vs* 2.4%). This finding may be explained by the fact that out-of-state patients received PTCy as GVHD prophylaxis more frequently. Similarly, patients diagnosed and treated locally had increased rates of grade III-IV aGVHD (16.4 *vs* 6.8%), but the reasons are unclear as GVHD prophylaxis strategies were similar between groups.

In our multivariate analysis, payment coverage emerged as a relevant factor associated with overall survival. Patients paying OOP exhibited an increased risk of mortality compared to those with private insurance. The association between payment coverage and OS highlights the significant role of insurance status in determining outcomes after alloHSCT. Several studies previously emphasized the economic burden of an alloHSCT. Over 40% of patients report selling or withdrawing money from accounts despite insurance coverage[13-15]. Fu *et al*[2] analyzed the long-term outcomes of patients who underwent alloHSCT for malignant and benign hematological disorders and had at least 1 year of remission. The authors reported that patients with a lower socioeconomic status (annual household income < $51000/

Table 3 Characteristics and outcomes of 287 patients who underwent allogeneic hematopoietic cell transplantation according to healthcare coverage and payment method

Variable		OOP		Universal		Private		*P* value
		n = 139	100%	*n* = 73	100%	*n* = 75	100%	
Sex	Male	81	58.3	41	56.2	46	61.3	0.81
	Female	58	41.7	32	43.8	29	38.7	
Age	Median (years)	35	(15-80)	29	(16-65)	43	(15-67)	**< 0.001**
Diagnosis	AML	37	26.6	15	20.5	25	33.3	**0.03**
	ALL	39	28.1	25	34.2	12	16	
	AA	20	14.4	10	13.7	6	8	
	NHL	8	5.8	10	13.7	11	14.7	
	MDN	10	7.2	4	5.5	11	14.7	
	HL	9	6.5	4	5.5	4	5.3	
	CML	7	5	3	4.1	0	0	
	CMML	3	2.2	1	1.4	2	2.7	
	PMF	3	2.2	0	0	1	1.3	
	CLL	3	2.2	1	1.4	0	0	
	MM	0	0	0	0	3	4	
Residence	In state	46	33.1	41	56.2	36	48	**0.003**
	Out of state	93	66.1	32	43.8	39	52	
Institution	Local	38	27.3	45	61.6	39	52	
	Referral	101	72.7	28	38.4	36	48	**< 0.001**
Donor	Identical	51	36.7	29	39.7	31	41.3	0.78
	Haploidentical	88	63.3	44	60.3	44	58.7	
Treatment lines	Median	2	(0-6)	2	(0-5)	1	(0-5)	0.62
DRI	Non-malignant	20	14.4	10	13.7	6	8	0.22
	Low	3	2.2	3	4.1	1	1.3	
	Intermediate	56	40.3	36	49.3	25	33.3	
	High	47	33.8	18	24.7	35	46.7	
	Very high	13	9.4	6	8.2	8	10.7	
HCT-CI	Median	0	(0-4)	0	(0-2)	1	(0-5)	0.08
Conditioning	MAC	57	41	51	69.8	35	46.7	**0.001**
	RIC	62	44.6	14	19.2	32	42.7	
	NMA	20	14.4	8	11	8	10.7	
CD34	Median	9	(1-16)	9	(2.4-19)	8	(1.8-23.7)	0.95
GVHD prophylaxis	PTCy	109	78.4	48	65.8	63	84	**0.03**
	CNI + MTX	30	21.6	25	34.2	12	16	
Recovery	ANC	15	(10-24)	14	(10-22)	15	(10-48)	0.66
	Platelet	15	(10-100)	14.5	(10-24)	15	(10-44)	0.83
Graft failure		17	13.1	13	18.3	8	12.2	0.5
aGVHD	Grades 1-2	46	37.1	23	38.3	23	31.9	0.7
	Grades 3-4	14	11.3	8	13.3	6	8.3	
cGVHD	Mild	14	14.9	11	19.6	15	23.8	0.09

	Moderate	13	13.8	13	23.2	13	20.6	
	Severe	3	3.2	6	10.7	5	7.9	
Early mortality	30 d	13	9.4	5	6.8	3	4	0.35
	60 d	24	17.3	7	9.6	6	8	0.12

DRI: Disease risk index; HCT-CI: Hematopoietic cell comorbidity index; GVHD: Graft versus host disease; AML: Acute myeloid leukemia; AA: Aplastic anemia; NHL: Non Hodgkin lymphoma; MDN: Myeldysplastic neoplasm; HL: Hodgkin lymphoma; CML: Chronic myeloid leukemia; CMML: Chronic myelomonocytic leukemia; MF: Myelofibrosis; CLL: Chronic lymphocytic leukemia; MM: Multiple myeloma; MAC: Myeloablative conditioning; CNI: Calcineurin inhibitor; MTX: Methotrexate; ANC: Absolute neutrophil recovery; PTCy: Post-transplant cyclophosphamide.

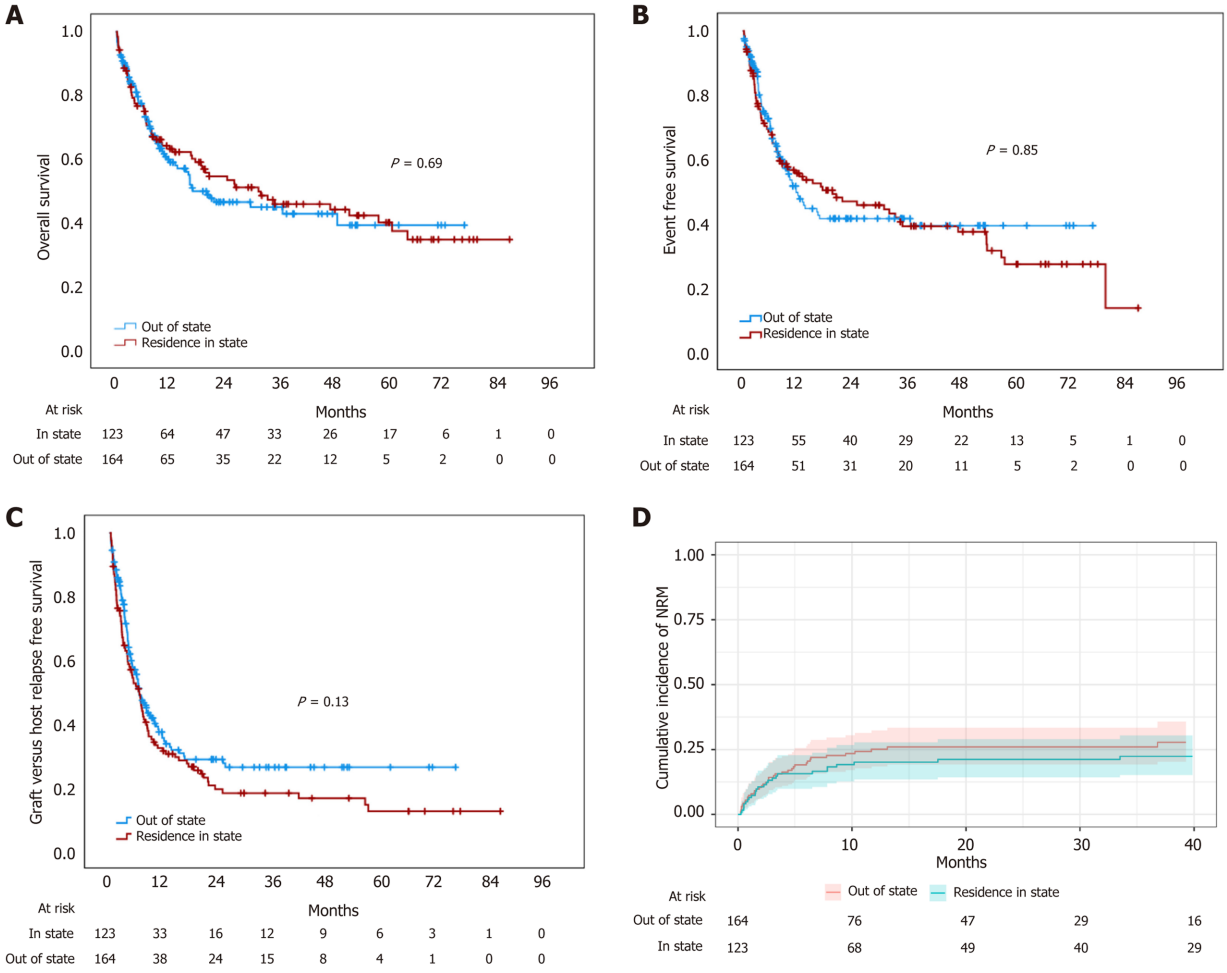

Figure 1 Outcomes after hematopoietic cell transplantation according to place of residence. A: Overall survival; B: Event-free survival; C: Graft-versus-host relapse-free survival; D: Non-relapse mortality.

year) have a higher risk of all-cause mortality and NRM. Hamilton *et al*[3] analyzed the impact of several SDH on chronic GVHD health outcomes, reporting that higher income, the ability to work, and having a partner were all associated with better chronic GVHD symptom scores (Lee score), although not survival. Higher income, the ability to work, and level of education were also associated with better quality of life and activity levels. As reported by Hong *et al*[4], patients with worse community health status, determined by several sociodemographic, environmental, and community indicators, have inferior survival after alloHSCT due to an increase in NRM. While we did not observe a significant difference in early mortality, we did observe an increase in NRM in OOP patients (Figure 3). Relevant transplant complications can generate additional expenses, increasing costs affecting patients who had an OOP payment, including conditioning regimen toxicities, GVHD, and bacterial and viral infections, which result in frequent consults and testing, hospital admissions, and the use of expensive drugs, which may be inaccessible and impact outcomes. Similarly, disease relapse or progression also requires significant use of resources, which may be limited for patients covering costs OOP and result in worse outcomes, as shown by the continuing separation of OS curves beyond the 12-month timepoint. This finding emphasizes the need for policy efforts to improve access to insurance coverage for alloHSCT patients, not only to access the procedure but throughout their entire journey, particularly in regions where financial barriers to care are prevalent.

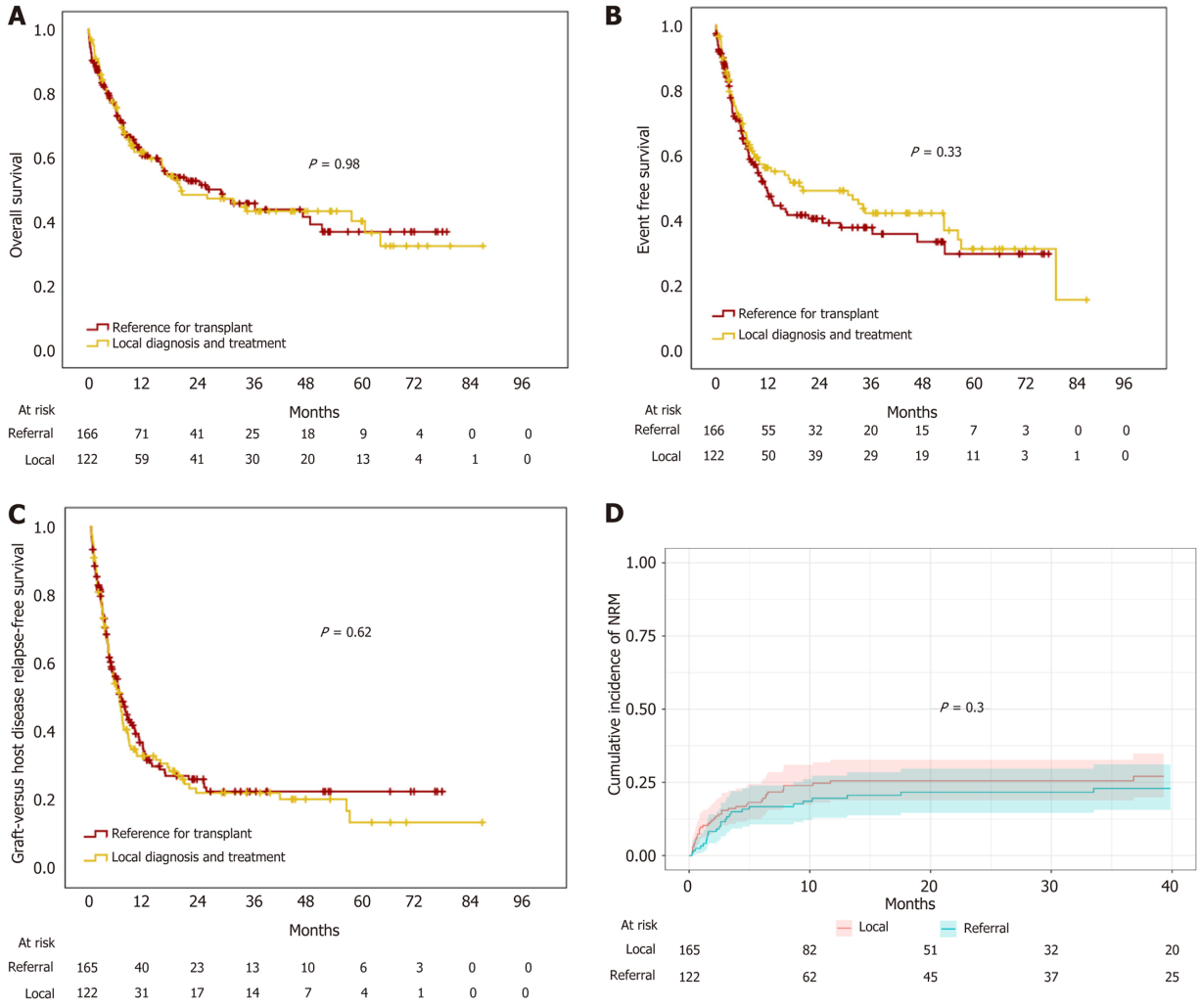

Figure 2 Outcomes after hematopoietic cell transplantation according to the site of diagnosis and treatment. A: Overall survival; B: Event-free survival; C: Graft-versus-host relapse-free survival; D: Non-relapse mortality.

To our knowledge, this analysis is the first to compare payment sources with outcomes in the Mexican population. A prior study assessed outcomes with regard to socioeconomic status, finding no difference between patient groups when social support is provided[16]. These results correlate with our findings since patients who had financial support during the times of the federal program had better outcomes than those who did not, demonstrating the positive effect of universal coverage for HSCT. Our findings have relevant implications for healthcare policymakers and practitioners. They may lead physicians to identify individuals facing economic and social marginalization and implement targeted interventions and organizations to advocate for the permanent inclusion of HSCT in government-funded programs, limiting the need for OOP coverage and avoiding financial toxicity.

Similarly, a study by Yanez *et al*[17] found that economic barriers were a main concern for the Latino population in the United States, a reflection of their counterparts in Latin America as they were overrepresented in low-income brackets and less likely to have health insurance coverage. Thus, addressing disparities in outcomes associated with payment coverage and healthcare access is fundamental. Developing intervention strategies to reduce economic inequity should be a priority everywhere, especially for underserved populations and those living in low- and middle-income countries. Initiatives that expand healthcare coverage and reduce financial barriers may improve survival rates and overall outcomes for alloHSCT patients. Our results emphasize the importance of ongoing efforts to study and address social determinants of health in healthcare delivery, particularly in regions where disparities may be more pronounced.

Certain limitations in our study need to be acknowledged. Our population may not represent all alloHSCT patients since it is based in a single region. Both transplant centers are high-volume reference centers that may not reflect the reality of the rest of the country. Access to private healthcare is also a surrogate for better social determinants of health in areas that may impact outcomes after alloHSCT, such as income, housing, education, nutrition, transportation, and a robust social support network, among others. The study is also limited by its retrospective nature and the lack of assessment of patient-level socioeconomic indices, as both institutions have distinct procedures that are not directly comparable. Future research is needed to understand better how social determinants of health interact with outcomes after alloHSCT.

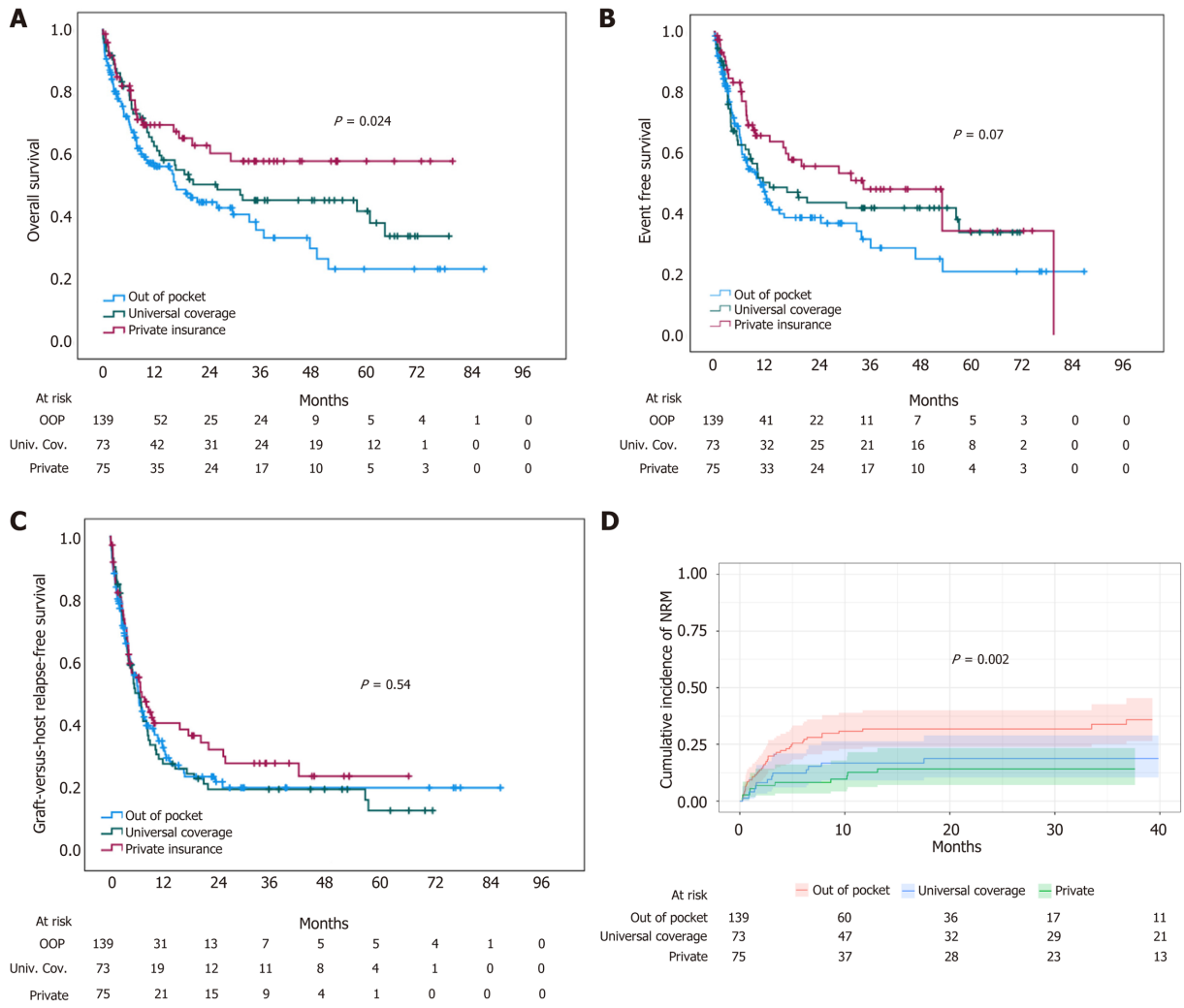

Figure 3 Outcomes according to payment coverage: out-of-pocket, private insurance, or universal coverage. A: Overall survival; B: Event-free survival; C: Graft-versus-host relapse-free survival; D: Non-relapse mortality. OOP: Out-of-pocket.

CONCLUSION

The site of residence or referral for HSCT did not impact outcomes. However, access to private insurance coverage for alloHSCT was associated with improved OS and reduced NRM compared to patients forced to cover expenses OOP or through government-funded programs.

ARTICLE HIGHLIGHTS

Research background

Despite the World Health Organization's recognition of the significance of non-medical factors in health outcomes, existing data primarily originates from high-income countries, leaving a lack of insight into Latin American specifics. The study aims to explore the association between social determinants—specifically, the source of transplant payment, site of referral, and place of residence—and overall survival after allogeneic hematopoietic stem cell transplantation (alloHSCT) in Mexico.

Research motivation

The motivation for this study lies in recognizing the potential impact of social determinants of health on alloHSCT outcomes, and the unique challenges faced by patients in Mexico.

Research objectives

To examine the association between the source of transplant payment, site of referral, and place of residence on overall survival after alloHSCT in Mexico. To compare outcomes based on payment source (out-of-pocket, private insurance, and government-funded programs), place of residence (in-state *vs* out-of-state), and referral source (local diagnosis and

treatment *vs* referred from another institution). To analyze the impact of social determinants, particularly financial barriers, on early mortality, event-free survival, graft-versus-host-relapse free survival, and non-relapse mortality after alloHSCT.

Research methods

Adopting a retrospective cohort design, this study includes patients from two major alloHSCT centers in Mexico, covering the period from 2015 to 2022. Statistical methods such as chi-square tests, t-tests, Kaplan Meier method, and Cox proportional hazard regression modeling were employed to analyze patient demographics, diagnostic characteristics, transplant procedures, and outcomes.

Research results

The study found that the site of residence or referral for hematopoietic stem cell transplantation (HSCT) did not significantly affect outcomes. However, access to private insurance coverage for allogeneic HSCT was associated with improved overall survival (OS) and reduced non-relapse mortality (NRM) when compared to patients covering expenses out-of-pocket or through government-funded programs.

Research conclusions

The study proposes that in allogeneic transplant recipients in low- and middle-income countries, the impact of social determinants of health, specifically the place of residence and transplant cost coverage, influences outcomes after hematopoietic cell transplantation. It suggests that access to healthcare coverage is associated with improved OS and reduced NRM.

Research perspectives

Future research in this field should focus on developing strategies to intervene and reduce economic barriers. Ongoing studies should continue to explore the broader impact of social determinants of health on healthcare delivery, especially in regions where disparities may be heightened.

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FOOTNOTES

Author contributions: Gómez-De León A conceptualized the research, gathered and analyzed data, and wrote the paper; López-Mora YA wrote the paper; García-Zárate V gathered and analyzed data; Varela-Constantino A gathered data and wrote the paper; González-Leal XJ gathered and analyzed data; Del Toro-Mijares R gathered data and wrote the paper; Rodríguez-Zúñiga AC gathered and analyzed data; Barrios-Ruiz JF gathered and analyzed data; Mingura-Ledezma V gathered and analyzed data; Colunga-Pedraza PR analyzed data and wrote the paper; Cantú-Rodríguez OG wrote the paper; Gutiérrez-Aguirre CH analyzed data and wrote the paper; Tarín-Arzaga L wrote the paper; González-López EE gathered and analyzed data; Gómez-Almaguer D supervised the research, analyzed data, and wrote the paper.

Institutional review board statement: The study was reviewed and approved by the Research Ethics Committee of the University Hospital "Dr. José Eleuterio González" (Approval No. HE19-00018).

Informed consent statement: Due to the nature of the research, which involved either no risk or minimal risk to participants, it was determined with prior approval from the Ethics Committee that obtaining informed consent was not deemed necessary. The absence of potential harm or discomfort to the participants warranted this decision. As such, the study received a waiver of the informed consent form requirement.

Conflict-of-interest statement: All authors have no conflicts of interest to disclose.

Data sharing statement: The original anonymous dataset is available on request from the corresponding author at dgomezalmaguer@gmail.com.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Safety and efficacy of Kaffes intraductal self-expanding metal stents in the management of post-liver transplant anastomotic strictures

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Abstract

BACKGROUND

Endoscopic management is the first-line therapy for post-liver-transplant anastomotic strictures. Although the optimal duration of treatment with plastic stents has been reported to be 8-12 months, data on safety and duration for metal stents in this setting is scarce. Due to limited access to endoscopic retrograde cholangiopancreatography (ERCP) during the coronavirus disease 2019 pandemic in our centre, there was a change in practice towards increased usage and length-of-stay of the Kaffes biliary intraductal self-expanding stent in patients with suitable anatomy. This was mainly due to the theoretical benefit of Kaffes stents allowing for longer indwelling periods compared to the traditional plastic stents.

AIM

To compare the safety and efficacy profile of different stenting durations using Kaffes stents.

METHODS

Adult liver transplant recipients aged 18 years and above who underwent ERCP were retrospectively identified during a 10-year period through a database query. Unplanned admissions post-Kaffes stent insertion were identified manually through electronic and scanned medical records. The main outcome was the incidence of complications when stents were left indwelling for 3 months *vs* 6 months. Stent efficacy was calculated *via* rates of stricture recurrence between patients that had stenting courses for ≤ 120 d or > 120 d.

RESULTS
During the study period, a total of 66 ERCPs with Kaffes insertion were performed in 54 patients throughout their stenting course. In 33 ERCPs, the stent was removed or exchanged on a 3-month interval. No pancreatitis, perforations or deaths occurred. Minor post-ERCP complications were similar between the 3-month (abdominal pain and intraductal migration) and 6-month (abdominal pain, septic shower and embedded stent) groups - 6.1% *vs* 9.1% respectively, $P = 0.40$. All strictures resolved at the end of the stenting course, but the stenting course was variable from 3 to 22 months. The recurrence rate for stenting courses lasting for up to 120 d was 71.4% and 21.4% for stenting courses of 121 d or over ($P = 0.03$). There were 28 patients that were treated with a single ERCP with Kaffes, 21 with removal after 120 d and 7 within 120 d. There was a significant improvement in stricture recurrence when the Kaffes was removed after 120 d when a single ERCP was used for the entire stenting course (71.0% *vs* 10.0%, $P = 0.01$).

CONCLUSION
Utilising a single Kaffes intraductal fully-covered metal stent for at least 4 months is safe and efficacious for the management of post-transplant anastomotic strictures.

Key Words: Liver transplantation; Cholangiopancreatography; Endoscopic retrograde; Constriction; Pathologic; Self expandable metallic stents; Bile duct diseases; Cholestasis

Core Tip: Biliary strictures are the most common complication post orthotopic liver transplantation. This retrospective study evaluates the safety and efficacy of managing such strictures using intraductal fully-covered metal stent (Kaffes) for different durations. The results show that a single Kaffes stent indwelling for at least 4 months is safe and effective for treating post liver transplant anastomotic strictures.

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INTRODUCTION

Biliary anastomotic strictures are the most common complication post liver transplant (LT)[1], affecting 5%-13% of cases [2]. Post-transplant anastomotic strictures (PTAS) typically occur within 5-8 months post-operatively, although occasionally these have been reported to appear between 7 d and 11 years following LT[3]. While early onset strictures tend to be due to technical issues during surgery such as duct size mismatch, postoperative bile leak and excessive cauterization for haemostasis[4]; delayed strictures usually are a consequence of ischemia, rejection or fibrosis[5].

Regardless of its timing, endoscopic management is the first-line therapy in most cases, due to superior success rates and less invasive nature compared to radiological approaches, as well as lower complication rates compared to surgical interventions[1,3,6-10].

Over time, the initial strategy focused mainly on endoscopic retrograde cholangiopancreatography (ERCP)-guided balloon dilatation has been superseded by a combination of balloon dilatation and serial stenting with improved stricture resolution (30% *vs* 75%)[11], and reduced recurrence rates (31% *vs* 62%)[12]. The current standard of care involves 3-monthly treatments of stricture dilation/stepwise upsizing of multiple plastic stents (MPS) until the cholangiogram confirms stricture resolution[13], which typically follows a 12-month stenting course[14]. Following adequate endoscopic management of the stricture, there is enduring patency of up to 90%[11,12,15], and both graft and patient survival rates approximate those without a history of PTAS[16].

Due to challenges arising from the coronavirus disease 2019 (COVID-19) pandemic, in 2020, our cohort of patients were faced with delays in scheduled replacements of their stents. At this point, discussions within our Endoscopy Unit around how to address this challenging scenario had begun. While traditional self-expanding metal stents (SEMS) would potentially offer a longer occlusion-free indwelling time, they were limited by migration risk of up to 75%[17].

However, the unique intraductal fully covered SEMS (FCSEMS) with an antimigration waist named Kaffes stent (Niti-S Kaffes, Taewoong Medical, Gyeonggi-do, South Korea) was already in use at our centre, with good anecdotal outcomes and other groups reporting excellent PTAS resolution and reduced risk of stent migration[18-20]. Routinely, this stent was replaced at 3 monthly intervals at our centre prior to COVID-19, similarly to the plastic stenting protocol.

During the COVID–19 pandemic, our unit recommendation shifted to removing these fully-covered intraductal SEMS in 6 rather than 3 months based on reassuring data from the literature[2,3,21,22]. We hence aim with this retrospective

study to evaluate the safety of different stent indwelling periods and efficacy of different stenting course durations using intraductal FCSEMS (Kaffes).

MATERIALS AND METHODS

Study design

In this single centre retrospective cohort study, we investigated the safety profile of Kaffes FCSEMS *via* assessing post-ERCP complications, and then evaluated efficacy by appraising the stricture resolution and recurrence rates. Finally, a subanalysis was performed on stent courses where a single Kaffes FCSEMS was utilised upfront.

Patients

Adult LT recipients (> 18 years) who underwent ERCPs for PTAS between December, 2012 and May, 2023 at the sole LT hospital in the state of Victoria (located in Melbourne, Australia) were retrospectively identified through an endoscopy reporting software (Provation). All encounters that involved a Kaffes stent were included. All Kaffes encounters were cross matched manually by three of the authors (Sarraf B, Lim C and Ng J), through electronic and scanned medical records, and divided into two groups based on the intended duration of Kaffes indwelling time of 3- *vs* 6-months. All unplanned readmissions occurring within 30 d of any Kaffes insertion procedures were identified and assessed for post-ERCP complications.

Data on the same cohort of LT recipients who underwent Kaffes insertion were then reorganised based on stenting courses. Each stenting course commenced when a biliary stent was inserted for PTAS where there was no indwelling biliary stent at the start of the procedure; and concluded when the biliary stent was removed after PTAS resolution (defined as lack of resistance on sweeping biliary tree and lack of waist on cholangiogram), and at the end of the procedure the patient was left unstented. These stenting courses commonly included consecutive intervening stent changes, but in some cases consisted of a single stent staying in place for the whole stenting course duration. In the event of stricture recurrence, subsequent endoscopic stenting was considered a fresh stenting course.

When assessing for stent efficacy (stricture resolution and recurrence), atypical stent courses with mixed aetiology strictures and prematurely terminated courses were excluded. Non-PTAS strictures commonly present as multi-level strictures that would not be amenable to Kaffes stenting, and have a different pathophysiology that may pose as a confounding factor. One of the stent courses terminated prematurely due to graft failure from other causes, resulting in stent removal together with the explanted organ, therefore making it impossible to analyse the effect of Kaffes stenting on stricture progress. It was noted that in the remaining stent courses, it appeared that most of the stricture recurrences occurred in cases where Kaffes stent was left indwelling for less than 121 d. Subsequently, these remaining stent courses were divided into separate groups of ≤ 120 d *vs* > 120 d. To better analyse the effect of Kaffes stenting, a subanalysis was performed on these courses where Kaffes was inserted upfront.

Data collection

Demographic data including age at the time of the ERCP, gender, indication for transplantation and time between LT and ERCP were collected.

ERCP procedure characteristics were extracted from clinical notes, intra-operative and anaesthetic records, medication charts and ERCP reports generated at the time of the procedure. Specifically, ERCP-related information was retrieved including indication, intervention details and stent characteristics. Readmission data included time between the ERCP and readmission, length of stay, reason for readmission and procedural-related complications leading to readmission.

Defining post-ERCP complications

Post-ERCP pancreatitis was defined as per the Atlanta criteria[23]. Episodes of pancreatitis fulfilling these criteria and occurring within 14 d after ERCP were included. Cholangitis was defined following the 2018 Tokyo Guidelines[21]. Abdominal pain was defined as any non-specific abdominal pain that could not be attributed to any other known cause such as post-ERCP pancreatitis. Bleeding was defined as clinical evidence of bleeding, haematemesis and/or melaena, or a drop in haemoglobin by 2 g/L without other cause. Perforation was defined by evidence of gas or luminal content outside the gastrointestinal tract as determined by imaging. Mortality was tracked over 30 d following ERCP.

Statistical analysis

Statistics were calculated using SPSS 26.0.0.0 (IBM SPSS Statistics© Copyright IBM Corporation 1989, 2019, Armonk, NY, United States). Normality was assessed with the Shapiro-Wilk test and showed outcomes analysed were not normally distributed. Hence, Mann Whitney tests were used for statistical analyses. Median and interquartile ranges (IQR) were used for continuous variables. Frequencies and percentages were used for categorical variables.

Ethics

This study was reviewed and granted approval by the Austin Health Office for Research.

RESULTS

Patients

54 LT recipients who met our study's criteria were identified, and 10 of these had more than one ERCP procedures for Kaffes stent insertion, with a total of 66 unique Kaffes stent insertion encounters for biliary PTAS (Figure 1). All LT recipients received deceased donor grafts, and the most common indication was hepatoma (Table 1). Median time between transplant and Kaffes stent insertion was 79 wk in the 3-month group (IQR 33-149 wk) and 80 wk in the 6-month group (IQR 18–240 wk). Median duration of ERCPs for Kaffes insertion was 24 min (IOR 17-30).

Kaffes-insertion encounters were divided equally into two groups of 33 based on the intended duration of Kaffes stent indwelling time of 3- *vs* 6-months (see Table 2 for details). 23 cases in the 3-month group, and 6 cases in the 6-month group, were performed prior to the COVID-19 lockdown movement control orders.

Comparing the 3-month-indewelling group *vs* the 6-month-indewelling group, 7 *vs* 16 (21.2% *vs* 48.5%) of these patients had known duct mismatch following transplant, and 66.7% *vs* 36.4% had a history of rejection. Both groups had similar frequencies of history of bile leak and hepatic artery thrombosis, and more than 90% in both groups had known PTAS prior to ERCP (Table 1).

Safety assessment

There were no cases of post-ERCP pancreatitis, perforation, or death within 30 d of Kaffes stent deployment/removal in either arm (Table 3). Patients in both arms only received rectal indomethacin in < 20% of cases, mostly due to a history of prior sphincterotomies. While one patient in each arm had inadvertent pancreatic duct cannulation, only the case from the 3-month group received prophylactic pancreatic stent. More than 85% of patients from both groups were administered prophylactic antibiotics during stent insertion.

Comparing the 3-month to the 6-month group, there were similar numbers of minor post-ERCP complications (6.1% *vs* 9.1%, P = 0.40) as follows. One patient from each group were admitted overnight for observation of self-limiting abdominal pain. One patient from the 3-month group was noted to have downstream migration of Kaffes stent when presenting for planned stent removal, at which point stricture had resolved and patient was asymptomatic, concluding the stent course. In the 6-month group, one patient with a history of septic showers post-ERCP developed transient cholangitis within 24 h of elective observatory admission despite prophylactic antibiotics; another patient experienced difficulty in removal of Kaffes stent which was partly embedded. After sweeping the biliary tree, another Kaffes stent was placed stent-in-stent to induce local pressure necrosis, and a pigtail stent was placed alongside the 2nd Kaffes to permit biliary drainage. 3 wk later all 3 stents were easily retrieved, followed by balloon dilation and a switch to MPS strategy, with the total stenting course duration being 22 months – there has not been recurrence since.

Efficacy assessment

Of the 66 encounters of Kaffes stent insertion above, two encounters were part of the same stenting course (Kaffes replaced by another Kaffes). Two stenting courses were not included in the efficacy analysis (recurrence), one due to presence of complex mixed anastomotic and ischemic strictures and ongoing stenting was determined as being related mostly to the ischaemic component; and the other underwent a redo LT in the middle of the course for graft cirrhosis and failure with ischemic strictures hence hindering assessment of the end of the stenting course.

Of the remaining 63 ERCP encounters, 31 Kaffes indwelling time of 3 months, and 32 involved Kaffes indwelling time of 6 months. Median duration of follow up was 860 d (IQR 531–1533 d). Looking at all episodes of Kaffes insertion, 30 out of 31 in the 3-month-group and 30 out of 32 in 6-month group had stricture resolution on fluoroscopy and were hence left unstented (*i.e.*, concluded the stenting course), regardless of the total stenting course duration (Table 4).

Stenting courses ranged from 3 to 22 months, and were split into two groups: ≤ 120 d or > 120 d. While there was no statistical difference in stricture resolution on Kaffes removal between the two groups (100.0% *vs* 89.3%, P = 0.66), there was a higher rate of recurrence when stent course lasted less than 121 d (71.4% *vs* 21.4%, P = 0.03) (Table 5). The time-to-recurrence was close to 8 months in the former group and over one year for the later. When considering only the stent courses where Kaffes was the final stent, results were similar (Table 6).

In the subanalysis of 28 patients that were treated with a single ERCP with Kaffes stent, 7 had stent removal within 120 d and 21 over 120 d. Median duration of stent courses were 95 d (90-116 d) *vs* 183 d (167-193 d). Recurrence rate was statistically higher when the stenting course with a single Kaffes had it removed within 120 d (71.0% *vs* 10.0%, P = 0.01). Median d to recurrence was numerically higher but did not reach statistical difference (Table 7).

DISCUSSION

While current guidelines recommend a treatment protocol of 3-monthly sequential dilatation/stenting of PTAS, there is no data specifically looking into 3 *vs* 6 months of FCSEMS placement[24]. To our knowledge, this is the first study reporting on the safety of 6-month stenting interval in the LT setting. Despite theoretical concerns about risks of secondary localised ischemic stricture formation, our study demonstrated similar stricture resolution in both the 3- and 6-month stent indwelling groups when compared to previous publications[18,19,25]. Stricture recurrence rates amongst the 6-month indwelling group was less than those reported in the literature (Table 8). Our study also showed reduced stent migration rates compared to previous studies[26-28], and the only case with migration in our study likely occurred due to early stricture resolution.

Table 1 Patient demographics

Demographic data of patients	Stent indwelling time	
	3 months	6 months
Median age at the time of Kaffes stent insertion, yr (IQR, yr)	57 (48-64)	61 (53-69)
Gender, *n* (%)		
Male	20 (60.6)	19 (57.6)
Female	13 (39.4)	14 (42.4)
Transplant indication, *n* (%)[1]		
Hepatoma	8 (14.3)	9 (16.1)
Non-alcoholic steatohepatitis	9 (16.1)	5 (8.9)
Alcoholic cirrhosis	6 (10.7)	7 (12.5)
Hepatitis C	8 (14.3)	7 (12.5)
Hepatitis B	4 (7.1)	1 (1.8)
Autoimmune hepatitis	3 (5.4)	6 (10.7)
Cryptogenic cirrhosis	6 (10.7)	3 (5.4)
Acute liver failure	2 (3.6)	3 (5.4)
Primary biliary cirrhosis	2 (3.6)	3 (5.4)
Primary sclerosing cholangitis	2 (3.6)	3 (5.4)
Polycystic liver	2 (3.6)	3 (5.4)
Alpha 1 antitrypsin deficiency	2 (3.6)	3 (5.4)
Other	2 (3.6)	3 (5.4)
Graft size, *n* (%)		
Complete liver graft	31 (93.9)	31 (93.9)
Partial liver graft	2 (6.1)	2 (6.1)
Biliary anastomosis anatomy, *n* (%)		
End to end	33 (100.0)	31 (93.9)
End to side	0 (0.0)	2 (6.1)
Transplant complications, *n* (%)		
History of rejection	19 (63.3)	12 (36.4)
History of bile leak	5 (16.7)	6 (18.2)
History of hepatic artery thrombosis	1 (3.3)	2 (6.1)
History of previous anastomotic stricture	28 (93.3)	31 (93.9)
Time between transplant and Kaffes insertion, wk (IQR, wk)	79 (33-149)	80 (18-240)

[1]30 Liver transplant recipients had more than 1 indication for transplant.
IQR: Interquartile range.

The unique design of Kaffes intraductal FCSEMS likely accounts for the low rate of migration and improved recurrence rate. Compared to conventional stents, Kaffes has a mid-stent waist which produces a radial force towards the stent centre, and nestles entirely within the biliary duct, protecting it from being dragged vertically. Also, the Kaffes stents were able to provide continuous dilation to the maximum diameter soon after deployment, compared to plastic stents that were only able to achieve target diameter within the final 3 months of the stenting course.

The most reported complications following endoscopic treatment of PTAS are cholangitis (7%-40%) pancreatitis (5%) and perforation (up to 2%)[18,19]. Despite our study's retrospective nature and relatively small number of patients treated, our cohort of patients did not demonstrate a significantly different complication rate regardless of prolonged or standard duration for stent indwelling time. Antibiotic coverage and stenting the pancreatic duct following inadvertent duct cannulation likely conferred a protective effect.

Table 2 Endoscopic retrograde cholangiopancreatography details

ERCP characteristics	3 months	6 months
Indication for ERCP, *n* (%)[1]		
Stricture	31 (93.9)	31 (93.9)
Choledocolithiasis	3 (9.1)	5 (15.2)
Cholangitis	2 (6.1)	8 (24.2)
Other[2]	12 (36.4)	6 (18.2)
ERCP setting, *n* (%)		
Inpatient	11 (33.3)	12 (36.4)
Outpatient	22 (66.6)	21 (63.6)
Imaging prior to ERCP, *n* (%)		
Ultrasound	13 (39.4)	16 (48.5)
CT abdomen	15 (45.5)	18 (54.5)
Magnetic resonance cholangiopancreatography	19 (57.6)	22 (66.7)
At least one of the above modalities	28 (84.8)	29 (87.9)
Technical details, *n* (%)		
Sphincterotomy	2 (6.1)	2 (6.1)
Dilatation	8 (24.2)	8 (24.2)
Previous stent in situ, *n* (%)		
Nil	15 (45.5)	20 (60.6)
Plastic	18 (54.5)	13 (39.4)
Indication for Kaffes, *n* (%)		
New stricture	9 (27.3)	16 (48.5)
Persistent stricture, failed plastic stent program	20 (60.6)	15 (45.5)
Persistent stricture, failed metal stent program	0 (0.0)	1 (3.0)
Persistent stricture, failed combination stents	1 (3.3)	0 (0.0)
Migration of previous stent	0 (0.0)	0 (0.0)
Stricture recurrence	3 (9.1)	1 (3.0)

[1]Note a portion of patients had multiple indications for endoscopic retrograde cholangiopancreatography (ERCP).
[2]Other indications for ERCP include: Deranged liver function tests, abdominal pain and bile leak follow up.
ERCP: Endoscopic retrograde cholangiopancreatography; CT: Computed tomography.

When considering the efficacy of Kaffes stenting to manage PTAS, rates of stricture resolution on stent removal were similar regardless of duration of stent indwelling time or sequence of stent type throughout the stent course. However, recurrence rates were statistically less when stents were indwelling for at least 4 months. Even when Kaffes stent was placed upfront and utilised as the sole stent during the stenting course, this finding holds true. This suggests that placing a Kaffes stent for at least 4 months would be the ideal duration for PTAS management, negating the need for multiple repeated courses of ERCPs.

CONCLUSION

This study suggests that a 6 monthly schedule utilising intraductal FCSEMS to manage PTAS is both safe and efficacious, and offers an exciting alternative approach to the current standard of care. In particular, a single course of Kaffes stenting for at least 4 months (121 d) is sufficient if there is stricture resolution on removal fluoroscopy, and has low risk of stricture recurrence. Larger randomized control trials should be considered to explore the promising results of this retrospective study.

Table 3 Post-endoscopic retrograde cholangiopancreatography complications

Post-ERCP complications	3 months	6 months	*P* value
Any complication, *n* (%)	3 (6.1)	3 (9.1)	0.40
Pancreatitis, *n* (%)			
Episodes	0 (0.0)	0 (0.0)	1.00
During Kaffes insertion			
Prophylactic rectal indomethacin	2 (6.1)	4 (12.1)	0.40
Pancreatic duct cannulation	1 (3.0)	1 (3.0)	1.00
Pancreatic duct stent insertion[1]	1 (3.0)	0 (0.0)	0.32
Cholangitis, *n* (%)			
Episodes	0 (0.0)	1 (3.0)	0.32
Prophylactic antibiotics at Kaffes insertion	30 (90.9)	29 (87.9)	0.69
Piperacillin/Tazobactam	20 (60.6)	25 (75.8)	
Ciprofloxacin	1 (3.0)	0 (0.0)	
Ceftriaxone	8 (24.2)	0 (0.0)	
Other	1 (3.1)	4 (12.1)	
Bleeding[2]	1 (3.3)	0 (0.0)	1.00
Admission[3]	2 (6.7)	3 (9.1)	0.31
Stent migration	1 (3.3)	0 (0.0)	0.29

[1]Pancreatic duct stent inserted for same patient who had inadvertent duct cannulation.
[2]Bleeding due to gastric ulcer, unrelated to endoscopic retrograde cholangiopancreatography (ERCP) procedure.
[3]Case with bleeding was included even though unrelated to ERCP procedure.
ERCP: Endoscopic retrograde cholangiopancreatography.

Table 4 Stricture recurrence data based on Kaffes indwelling time, regardless of stent course duration

Stricture outcomes	3 months	6 months	*P* value
Stricture resolution on stent extraction, *n* (%)	30 (96.8)	30 (93.8)	0.72
Stricture recurrence, *n* (%)	14 (42.4)	3 (9.1)	0.01[a]
Median days to recurrence since stent removal, d (IQR, d)	273 (73-1192)	431 (7-617)	

[a]Stricture recurrence was significantly less when Kaffes was inserted for 6 months.
IQR: Interquartile ranges.

Table 5 Stent efficacy based on stent course duration (all stent courses involving Kaffes insertion, regardless of Kaffes indwelling time)

Stricture outcomes	≤ 120 d	> 120 d	*P* value
n	7	56	
Median duration of stent course, d (IQR, d)	95 (90-116)	196 (176-296)	
Stricture resolution on Kaffes removal, *n* (%)	7 (100.0)	50 (89.3)	0.66
Recurrence			
n (%)	5 (71.4)	12 (21.4)	0.03[a]
Median days to recurrence (IQR)	248 (104–812)	368 (259-1084)	0.33

[a]Stricture recurrence was significantly less when Kaffes was inserted for > 120 d.

IQR: Interquartile ranges.

Table 6 Stent efficacy (stent courses where Kaffes stent was the final stent)

Stricture outcomes	≤ 120 d	> 120 d	*P* value
n	7	50	
Median duration of stent course, d (IQR, d)	95 (90-116)	193 (178-281)	
Stricture resolution at end of course, *n* (%)	7 (100.0)	50 (100.0)	1.00
Recurrence			
n (%)	5 (71.4)	9 (18.0)	0.02[a]
Median days to recurrence (IQR)	248 (104-812)	431 (264-1522)	0.24

[a]Stricture recurrence was significantly less in stent courses where Kaffes stent was the final stent and left indwelling for >120 d.
IQR: Interquartile ranges.

Table 7 Stent efficacy (stent courses where Kaffes stent was the only stent used)

Stricture outcomes	≤ 120 d	> 120 d	*P* value
n	7	21	
Median duration of stent course, d (IQR, d)	95 (90-116)	183 (167-193)	
Stricture resolution on Kaffes removal, *n* (%)	7 (100.0)	20 (95.0)	1.00
Recurrence			
n (%)	5 (71.0)	2 (10.0)	0.01[a]
Median days to recurrence (IQR)	248 (27-812)	1139 (785-1493)	0.19

[a]Stricture recurrence was significantly less when Kaffes stent was used upfront and left indwelling for >120 days.
IQR: Interquartile ranges.

Table 8 Intraductal fully covered self-expanding metal stents studies (18, 19, 22, 26, 27, 28)

Ref.	Sissingh *et al*[22], 2023	Warner *et al*[18], 2020	Martins *et al*[27], 2018	Tal *et al*[26], 2017	Cote *et al*[28], 2016	Kaffes *et al*[19], 2014
n	80	62	59	48	73	20
FCSEMS removal protocol, months	6	3	6	4-6	6-12	3
Median stent indwelling time, months	NA	10	5	6	6	4
Stricture resolution (%)	93	96	83	100	89	100
Stricture recurrence (%)	33	25	32	21	15	30
Migration rate (%)	16	NA	10	21	45	0
Acute pancreatitis (%)	7	5	13	NA	6	NA
Cholangitis rate (%)	7	4	2	NA	3	10
Bile duct perforation (%)	0	2	NA	NA	NA	NA

FCSEMS: Fully covered self-expanding metal stents; NA: Not available.

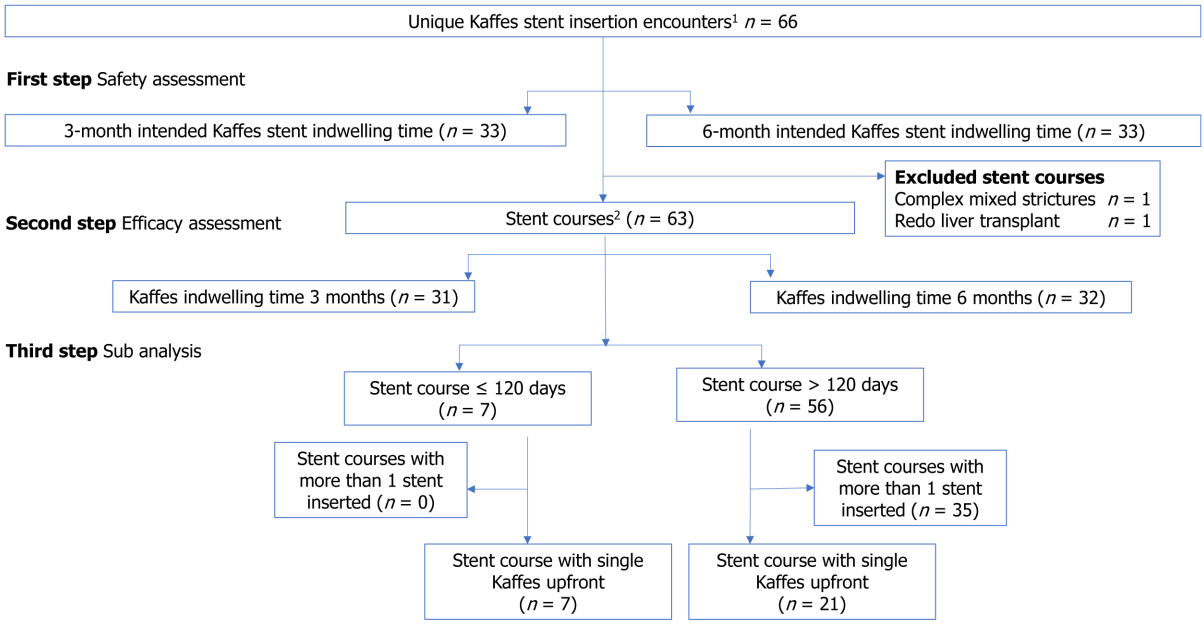

Figure 1 Flowchart of study design. [1]54 Liver transplant recipients identified (10 having more than one endoscopic retrograde cholangiopancreatography procedures for Kaffes stent insertion); [2]One stent course comprised of two stent insertion encounters.

FOOTNOTES

Author contributions: Chandran S, Efthymiou M and Vaughan R formulated the research question; Chandran S designed the study; Lim C, Ng J and Sarraf B conducted the research; Lim C and Zorron Cheng Tao Pu L analyzed and interpreted the data; Lim C and Zorron Cheng Tao Pu L wrote the manuscript. All authors have read and approve the final manuscript.

Institutional review board statement: The project has been reviewed by Austin Health Office for Research against the principles of the National Statement on Ethical Conduct in Research (2007, updated 2018) and approved. (Approval Number: Audit/22/Austin/43).

Informed consent statement: This is an informed consent exemption statement. This application is a clinical audit project involving the collection, use and disclosure of the data in a de-identified format to be conducted at Austin Health. Such data is to be accessed by an Austin Health employee only.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Frequency of and reasons behind non-listing in adult patients referred for liver transplantation: Results from a retrospective study

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Abstract

BACKGROUND

Few studies have evaluated the frequency of and the reasons behind the refusal of listing liver transplantation candidates.

AIM

To assess the ineligibility rate for liver transplantation and its motivations.

METHODS

A single-center retrospective study was conducted on adult patients which entailed a formal multidisciplinary assessment for liver transplantation eligibility. The predictors for listing were evaluated using multivariable logistic regression.

RESULTS

In our center, 314 patients underwent multidisciplinary work-up before liver transplantation enlisting over a three-year period. The most frequent reasons for transplant evaluation were decompensated cirrhosis (51.6%) and hepatocellular carcinoma (35.7%). The non-listing rate was 53.8% and the transplant rate was 34.4% for the whole cohort. Two hundred and five motivations for ineligibility were collected. The most common contraindications were psychological (9.3%), cardiovascular (6.8%), and surgical (5.9%). Inappropriate or premature referral accounted for 76 (37.1%) cases. On multivariable analysis, a referral from another hospital (OR: 2.113; 95%CI: 1.259–3.548) served as an independent predictor of

non-listing.

CONCLUSION
A non-listing decision occurred in half of our cohort and was based on an inappropriate or premature referral in one case out of three. The referral from another hospital was taken as a strong predictor of non-listing.

Key Words: Controindication; Eligibility; Evaluation; Referral; Personalized medicine

Core Tip: Because of organ shortage and the need to optimize graft survival, patient candidates for liver transplantation must undergo an intensive multidisciplinary work-up to determine their suitability for registration on the waitlist. Few studies have evaluated the ineligibility rate for liver transplantation and its motivations. In this single-center, retrospective cohort study, the observed non-listing rate was 53.8% and about one out of three non-listing reasons was an inappropriate or premature referral. The external referral was a predictor of non-listing, so the betterment of the education and the training of referring physicians is recommended.

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INTRODUCTION

Because of organ shortage and the need to optimize graft survival, patient candidates for liver transplantation must undergo an intensive multidisciplinary work-up to determine their suitability for registration on the waitlist[1]. The primary purpose of the evaluation process is to select candidates with a projected 5-year post-transplant survival rate of more than 50%[2]. The American Association for the Study of Liver Diseases guidelines[3] consider the following medical and non-medical non-listing reasons for liver transplantation: A Model for End-stage Liver Disease (MELD) Score < 15 (without other exceptions)[4], severe cardiac or pulmonary disease[5,6], Acquired Immuno-Deficiency Syndrome[7], ongoing alcohol or illicit substance abuse[8], hepatocellular carcinoma (HCC) with metastatic spread[9], uncontrolled sepsis[10], anatomic abnormality that precludes liver transplantation[11], intrahepatic cholangiocarcinoma[12], extra-hepatic malignancy[13], acute liver failure (ALF) with sustained intracranial hypertension[14], hemangiosarcoma[15], persistent noncompliance or the lack of an adequate social support system[16,17]. Few studies have evaluated the ineligibility rate for liver transplantation and its motivations. This study aims to assess the ineligibility rate for liver transplantation and its motivations among potential candidates for liver transplantation.

MATERIALS AND METHODS

This is a retrospective cohort study that has been conducted at Fondazione Policlinico Universitario A. Gemelli IRCCS (Rome, Italy). All adult patients with liver diseases who were referred for a formal multidisciplinary assessment of eligibility for liver transplantation from 1 January 2015 to 31 December 2017 were included in the study. The primary outcome was the percentage of evaluations that resulted in non-listing for liver transplantation (non-listing rate).

Our transplant center is included in the transplant program of the Lazio region; according to the program's rules[18], only patients with a MELD sodium (MELD Na) score ≥ 15[19] or with the HCC within the up-to-7 criteria[20] are eligible for liver transplant waitlist. Moreover, our transplant center serves as a referral center for patients in the Abruzzo and Molise regions in a "hub-and-spoke" network. Hence, we admit a high percentage of patients who are referred from other hospitals (approximately 30%).

All patients were identified from a clinical referral database that contains information on all patients who are referred for liver transplant evaluation. We collected demographic and baseline clinical data on patients who were waitlisted and non-waitlisted for liver transplantation during the study period. In patients who suffered from more than one disease that led to liver dysfunction, we considered all possible components. In patients with more than one reason behind non-listing, we recorded all the non-listing reasons. The reasons behind the non-listing of patients were categorized as follows: Contraindications, incorrect indication, patient decision, and complications during the evaluation process.

Multidisciplinary evaluation process

The evaluation work-up was carried out on either an outpatient or an inpatient basis, according to the patient's clinical

conditions. All patients underwent an evaluation of their complete medical history and physical examination, including risk-appropriate cardiopulmonary evaluation. Laboratory work-up included the following: Complete blood count, coagulation tests, blood chemistry, ABO-Rh blood group determination, tumor markers, thyroid function, serologic tests for hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV), cytomegalovirus, Epstein-Barr virus, Herpes-simplex virus, Herpes-zoster virus, Syphilis, Toxoplasma, Rubella, molecular HBV-DNA, and HCV-RNA assays, both tuberculin skin test and QuantiFERON test for latent tuberculosis infection and both bacterial and fungal culture on blood, urine, stool and throat swab.

The cardiovascular work-up included electrocardiography, echocardiography, exercise or pharmacologic stress myocardial perfusion imaging by single-photon emission computed tomography (CT), followed by coronary angiography if it was indicated. Respiratory work-up included acid-base-balance, spirometry, and pulmonary artery systolic pressure estimation by echocardiography. The patients underwent total body CT scan with contrast medium to assess the anatomical variants of abdominal vessels, the possible presence of arcuate ligament syndrome, the possible presence and staging of portal vein thrombosis, the diagnosis and staging of HCC, and the search for lesions or occult abscesses in other districts. They also underwent portal vein Doppler ultrasound, supra-aortic vessels and vascular access Doppler ultrasound, electroencephalogram, gastroscopy, and colonoscopy if their age was more than 50 years. The nutritional consultant and the dietitian carried out nutritional assessment and education. Additionally, the women underwent a Papanicolaou smear screening test, transvaginal echography, and mammography, while the men underwent a prostate-specific antigen screening test. All patients underwent alcohol disorder evaluation conducted by a dedicated consultant (Addolorato G) and assessment by a dedicated psychologist (Calia R); subsequent psychiatric consultation was performed on a case-to-case basis. The dental evaluation included digital panoramic radiography, visits, and extractions if they were needed. In conclusion, patients underwent anesthesia and surgical assessment.

Patients with a diagnosis of ALF[21] were evaluated according to an accelerated protocol for possible listing in case of the urgent need for transplantation (status 1, according to the United Network for Organ Sharing). The accelerated protocol includes only a recapitulation of medical history and physical examination, complete blood count, coagulation tests, blood chemistry, ABO-Rh blood group determination, serologic tests for HAV, HBV, HCV, HIV, Cytomegalovirus, Epstein-Barr Virus, hepatitis E virus, electrocardiography, echocardiography, urgent cardiology consultation, and total body CT scan with a contrast medium.

Statistical analysis

Continuous data were expressed by mean ± SD and categorical data were expressed by frequencies and percentages. Independent samples student's *t*-test and χ^2 test were used for group comparisons wherever it was appropriate. Multivariable logistic regression was used to evaluate the predictors for listing. The differences were reported as statistically significant if the *P* value was less than 0.05. Statistical analysis was performed using SPSS version 17.0 (SPSS Inc., Chicago, IL).

RESULTS

In the 2015–2017 timeframe, 327 adult patients were referred to our center for liver transplant evaluation. Most patients (75%) were male and their mean age was 54.6 years. Since for 13 of the patients, a listing decision had not yet been taken as of 31 December 2017, our study cohort included 314 patients for whom the evaluation process for being registered in the liver transplantation waitlist was completed (Table 1). The most common reason behind the indication of listing was decompensated cirrhosis in 162 (51.6%) patients, followed by HCC in 112 (35.7%) patients, confirmed or suspected to be ALF in 34 (10.8%) patients, and other indications in 6 (1.9%) patients (5 patients for polycystic liver disease and 1 patient for portal hypertensive biliopathy). Most patients (87.3%) had liver cirrhosis; the most common etiologies were alcoholic liver disease (41.4%), HCV (22.3%), and non-alcoholic steatohepatitis (13.7%). Other etiologies are described in Table 2.

Among the 314 evaluated patients, 145 (46.2%) patients were listed. Their final outcome was transplantation in 108 (34.4%) patients, still on the waitlist as of 31 December 2017 in 21 (6.7%) patients, and delisting in 16 (5.1%) patients (9 patients because of complications during waitlist, 3 because of HCC progression, 2 because of non-compliance and 2 after liver function improvement). In 169 patients, the decision to non-listing for the 2015–2017 period was made and, hence, the non-listing rate was 53.8% in our cohort.

Table 3 reports the reasons behind non-listing. The presence of contraindications accounted for 44.4% of the non-listing reasons; in particular, liver transplant contraindications were more frequently psychological (9.3%), cardiovascular (6.8%), and surgical (5.9%). An inappropriate or premature referral summed up for 37.1% of non-listing reasons and included 16.1% of cases where the patient had a low MELD Na score (below < 15), 10.2% of cases of recovery after conservative management for confirmed or suspected ALF and 7.8% cases of HCC beyond the up-to-7 criteria that were not amenable for downstaging. Moreover, there were 7.8% of cases where patients refused transplantation, 2.9% where people chose another center, and 1.5% where patients lost to follow-up. Finally, 6.3% of patients developed complications during the evaluation process and subsequently died. In 30 patients, there was more than one reason behind non-listing. Hence, we recorded 205 non-listing reasons out of our cohort of 169 patients.

According to patient features between the listed and non-listed patients (Table 2), we showed that male sex, the presence of HCC, past-HBV infection, and the presence of TIPS were significantly more frequent in patients who were listed, while a working diagnosis of confirmed or suspected ALF or a referral from another hospital were significantly more frequent in patients who were non-listed. In the multivariable analysis (Table 4), only the referral from another hospital (OR: 2.113; 95%CI: 1.259–3.548) and past HBV infection (OR: 0.373; 95%CI: 0.164–0.852) were confirmed to be

Table 1 Adult patients evaluated for liver transplantation by year

	2015	2016	2017	2015-2017
Non listed	29	60	80	169 (53.8%)
On waitlist (on 31/12)[1]	17	28	21	21 (6.7%)
Drop-out from waitlist	5	5	6	16 (5.1%)
Transplanted	30	36	42	108 (34.4%)
Total (column)	81	129	149	314

[1]These data were provided only to illustrate the distribution of patients in the individual years of the study. For the final calculation of the three-year study period, only those patients who were on the active waitlist as of 31 December 2017 were considered.

Table 2 Clinical features of patients

	All patients (*n* = 314)	Listed (*n* = 145)	Non-listed (*n* = 169)	*P* value
Age (yr)	54.6 ± 11.5	54.4 ± 10.1	54.7 ± 12.6	NS
Male sex	236 (75.1%)	118 (81.4%)	118 (69.8%)	0.018
Alcohol	130 (41.4%)	61 (42.1%)	69 (40.8%)	NS
HCC	112 (35.7%)	63 (43.4%)	49 (29%)	0.008
Active HBV	35 (11.1%)	19 (13.1%)	16 (9.5%)	NS
Past HBV	32 (10.2%)	22 (15.2%)	10 (5.9%)	0.007
HCV	70 (22.3%)	36 (24.8%)	34 (20.1%)	NS
PBC/PSC	23 (7.3%)	15 (10.3%)	8 (4.7%)	NS
Autoimmune	9 (2.9%)	3 (2.1%)	6 (3.6%)	NS
Non-Alcoholic Steatohepatitis	43 (13.7%)	25 (17.2%)	18 (10.6%)	NS
Other indications[1]	27 (8.6%)	14 (9.6%)	13 (7.7%)	NS
Confirmed or suspected ALF[2]	34 (10.8%)	8 (5.5%)	26 (15.3%)	0.011
Portal vein thrombosis	52 (16.6%)	28 (19.3%)	24 (14.2%)	NS
TIPS	20 (6.4%)	14 (9.7%)	6 (3.6%)	0.027
Referred from another hospital	102 (32.5%)	33 (22.8%)	69 (40.8%)	0.001

[1]Include 6 hepatitis D virus coinfection, 5 polycystic liver disease, 3 re-transplantation, 3 iron overload, 2 secondary biliary cirrhosis, 2 Budd-Chiari Syndrome, 2 Alagille Syndrome, 1 Caroli Syndrome, 1 Wilson disease, 1 drug-induced liver disease, 1 portal hypertensive biliopathy.
[2]Include: 10 drug-related, 6 indeterminate, 5 hepatitis B virus, 4 hepatitis A virus, 2 hepatitis E virus, 2 iatrogenic, 1 autoimmune, 1 malignant infiltration, 1 amanita phalloides, 1 Hemolysis Elevated Liver enzymes and Low Platelet count syndrome, 1 acute hepatic artery thrombosis.
Data has been presented as the number of patients (%) or mean ± SD. Analysis has been conducted by either a χ^2 test or independent samples student's *t*-test. HCC: Hepatocellular carcinoma; HBV: Hepatitis B virus; HCV: Hepatitis C virus; PBC: Primary biliary cholangitis; PSC: Primary sclerosing cholangitis; ALF: Acute liver failure; TIPS: Transjugular intrahepatic portosystemic shun; NS: Not significant.

significant predictors of non-listing and listing, respectively.

DISCUSSION

In this study, the observed non-listing rate was 53.8%. Few studies have evaluated the frequency of and the reasons behind a candidate's refusal to enlist for liver transplantation. A single-center retrospective cohort study on 309 adult patients, evaluated in Singapore in the 1990–2001 timeframe, reported a non-listing rate of 65.7%[22]. The transplant center of Pisa (Italy), by adopting a step-by-step approach (preemptive evaluation, preliminary evaluation, and complete evaluation), obtained a non-listing rate of 73.7% in the 1996–2004 timeframe[23]. Another single-center retrospective cohort study among 314 adult patients completely evaluated in the British Columbia transplant center, Canada, in the 1997–2001 timeframe reported a non-listing rate of 46.8%[24]. The non-listing rate of Mayo Clinic (United States) in 2005, after the institution of the MELD scoring system for organ allocation, was found to be 53.1%[25]. A cohort study on 337

Table 3 Reasons behind non-listing for liver transplantation

Non-listing categories	Non-listing motivations	N°			
Contraindications	Psychological[1]	19	9.3%	91	44.4%
	Cardiovascular[2]	14	6.8%		
	Surgical[3]	12	5.9%		
	Ongoing alcohol abuse[4]	10	4.9%		
	Infectious[5]	10	4.9%		
	Obesity (BMI > 35)	9	4.4%		
	Respiratory[6]	7	3.4%		
	Extrahepatic malignancy[7]	6	2.9%		
	Malnutrition[8]	4	1.9%		
Incorrect indication	MELD Na < 15[9]	33	16.1%	76	37.1%
	Recovery after conservative management for confirmed or suspected ALF	21	10.2%		
	HCC beyond up-to-7 criteria and not amenable to downstaging	16	7.8%		
	Low Mayo Risk Score	4	2.0%		
	HCC successfully treated (T0)	2	1.0%		
Patient decision	Refused transplantation	16	7.8%	25	12.2%
	Chose another center	6	2.9%		
	Lost to follow-up	3	1.5%		
Complications during evaluation		13	6.3%	13	6.3%
Total		205	100%	205	100%

[1]6 cases of psychiatric comorbidities, 5 cases of neurological comorbidities, 3 cases of persistent non-compliance, 5 cases of the lack of an adequate support system.
[2]8 cases of ischemic heart disease, 4 cases of valvular heart disease, 1 case of arrhythmia, 1 case of pulmonary hypertension.
[3]5 cases of portal vein thrombosis Yerdel III-IV, 6 cases of previous gastrointestinal surgery with arterial axil alteration, 1 case of high-risk re-transplantation.
[4]abstinence period < 6 months and negative evaluation by alcohol-disorders specialist.
[5]4 cases of pneumonia, 2 cases of sepsis, 2 cases of HIV infection, 1 case of active tuberculosis, 1 case of osteomyelitis.
[6]5 cases of severe chronic obstructive pulmonary disease, 1 case of severe restrictive pattern, 1 case of interstitial lung disease.
[7]2 cases of breast cancer, 1 case of ovarian cancer, 1 case of lung cancer, 1 case of pancreatic cancer, 1 case of lymphoma.
[8]Based on the opinions of the nutritional consultant and the subsequent multidisciplinary (transplant hepatologist, transplant surgeon, and anesthesist) decision.
[9]After the antiviral treatment or alcoholic abstinence.
MELD-Na: Model for end-stage liver disease-sodium; ALF: Acute liver failure; HCC: Hepatocellular carcinoma; BMI: Body mass index.

adult patients evaluated in London Ontario, Canada, in the 2009–2011 timeframe documented a non-listing rate of 49.3% [26]. According to the report by Mount Sinai Medical Center in New York, its non-listing rate was 58% in the 2000–2012 timeframe, reaching a rate of 82% in the HIV-positive population[27]. These older studies refer to an era in which the effect of anti-HBV and anti-HCV antiviral treatments had not yet been routinely applied; in recent years, waitlist registrations for HBV and HCV patients have been drastically reduced because of decompensation, persisting only registrations because of HCC, HDV co-infection or HBV-related ALF[28,29]. Our study confirms a non-listing rate of approximately 50% in a population predominantly suffering from alcohol-based and metabolic liver disease.

In our study, about one out of three non-listing reasons was inappropriate or premature referral. This is in line with other experiences[22-27] including those reported in a study in Tampa (United States) that was conducted among 242 evaluated candidates who were not listed for liver transplantation during the 2004–2006 period; retrospectively, the most common reasons behind non-listing were early referrals, psychosocial factors, and medical contraindications[30]. On the one hand, early referral undoubtedly entails a cost (for patients, family members, and healthcare providers) and subtracts the availability of resources from other candidates. On the other hand, it provides some benefits such as the optimization of patient care and monitoring, strengthens the doctor-patient relationship, and improves their understanding of the surgery. As per the reports by Mayo Clinic, many patients who were initially refused for liver transplant listing because of too early referral or because of psychosocial reasons, were subsequently re-presented and listed for liver transplantation. The authors concluded that early referral was beneficial for patients because the management of end-stage liver disease could consequently be initiated, and the psychosocial issues could be timely manner. Despite these

Table 4 Multivariate analysis of predictors for listing

Variable	*P* value	OR (95%CI)
Referred from another hospital	0.005	2.113 (1.259–3.548)
Past HBV infection	0.019	0.373 (0.164–0.852)
HCC	0.068	0.623 (0.374–1.037)
Male sex	0.067	1.699 (0.964-2.994)
TIPS	0.116	0.439 (0.157–1.226)
ALF/Severe acute hepatitis	0.310	1.584 (0.651–3.852)

Analysis has been conducted by using multivariate logistic regression. HBV: Hepatitis B virus; HCC: Hepatocellular carcinoma; TIPS: Transjugular intrahepatic portosystemic shunt; ALF: Acute liver failure.

observations, it is currently unclear whether early referrals influence (either positively or negatively) clinical outcomes and liver transplantation programs.

Moreover, it is unclear whether non-listing rates relate to the appropriateness of referrals from providers and/or to the effectiveness of the screening of referrals in the liver transplantation program. According to the multivariable analysis, the referral from another hospital was a significant predictor of non-listing. Given that our center has decided not to provide a preemptive evaluation, a possible explanation behind this decision is related to the heterogeneity of the spoke centers regarding the balance of potential contraindications to liver transplant. A potential perspective of our study is to implement better training of the spoke centers to optimize the referral process.

The main limitation of our study is that this is a single-center study and its external validity may be limited. A potential perspective of our study is to perform a multicenter study, possibly endorsed by a scientific society, to overcome this limitation and provide data that better reflect the national (or preferably international) state-of-the-art of liver transplant evaluation.

CONCLUSION

In conclusion, even in the post-Direct Antiviral Agents era, a final decision of ineligibility for liver transplantation was observed in half of our cohort. Inappropriate or premature referral occurred in one case out of three, but this did not necessarily amount to a flaw. Since the referral from other hospitals was considered a strong predictor of non-listing, the betterment of the education and the training of referring physicians is recommended.

FOOTNOTES

Author contributions: Biolato M designed the study and wrote the paper; Marrone G, and Tarli C collected the data; Liguori A and Miele L analyzed the data; Calia R, Addolorato G, Pompili M, Agnes S, Gasbarrini A, and Grieco A revised the manuscript with an important intellectual contribution.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Incidence, risk factors and clinical outcome of multidrug-resistant organisms after heart transplantation

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Abstract

BACKGROUND

Transplant recipients commonly harbor multidrug-resistant organisms (MDROs), as a result of frequent hospital admissions and increased exposure to antimicrobials and invasive procedures.

AIM

To investigate the impact of patient demographic and clinical characteristics on MDRO acquisition, as well as the impact of MDRO acquisition on intensive care unit (ICU) and hospital length of stay, and on ICU mortality and 1-year mortality post heart transplantation.

METHODS

This retrospective cohort study analyzed 98 consecutive heart transplant patients over a ten-year period (2013-2022) in a single transplantation center. Data was collected regarding MDROs commonly encountered in critical care.

RESULTS

Among the 98 transplanted patients (70% male), about a third (32%) acquired or already harbored MDROs upon transplantation (MDRO group), while two thirds

did not (MDRO-free group). The prevalent MDROs were *Acinetobacter baumannii* (14%), *Pseudomonas aeruginosa* (12%) and *Klebsiella pneumoniae* (11%). Compared to MDRO-free patients, the MDRO group was characterized by higher body mass index (P = 0.002), higher rates of renal failure (P = 0.017), primary graft dysfunction (10% *vs* 4.5%, P = 0.001), surgical re-exploration (34% *vs* 14%, P = 0.017), mechanical circulatory support (47% *vs* 26% P = 0.037) and renal replacement therapy (28% *vs* 9%, P = 0.014), as well as longer extracorporeal circulation time (median 210 *vs* 161 min, P = 0.003). The median length of stay was longer in the MDRO group, namely ICU stay was 16 *vs* 9 d in the MDRO-free group (P = 0.001), and hospital stay was 38 *vs* 28 d (P = 0.006), while 1-year mortality was higher (28% *vs* 7.6%, log-rank-χ^2: 7.34).

CONCLUSION

Following heart transplantation, a predominance of Gram-negative MDROs was noted. MDRO acquisition was associated with higher complication rates, prolonged ICU and total hospital stay, and higher post-transplantation mortality.

Key Words: Heart transplantation; Multi drug resistant organisms; Transplantation complications; Transplantation outcome

Core Tip: We evaluated multidrug-resistant organisms (MDROs) in heart transplantation and their impact on patient outcome. Carbapenem-resistant Gram-negative bacteria predominated, in line with the epidemiologic pattern in south-eastern Europe. Among comorbidities, renal failure and higher body mass index were shown to be important risk factors pre-transplantation. Surgical and medical complications were shown to be predictive of MDRO acquisition, while no association was shown for the type of cardiomyopathy, for the mode of admission [from home, ward or intensive care unit (ICU)] or for previous cardiac surgery. MDRO presence was associated with longer ICU and hospital length of stay, and higher ICU-mortality and 1-year mortality.

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INTRODUCTION

In the south-eastern European countries, a higher prevalence of multidrug-resistant organisms (MDROs) is annually being reported in comparison to the northwest of Europe, pertaining mainly to multidrug-resistant (MDR) Gram-negative organisms[1]. High MDRO prevalence is strongly correlated with nosocomial infections[2]. Previous publications suggest an increased mortality in transplanted patients with MDRO colonization or bacteremia[3,4]. In concert with the patient safety guidelines of the World Health Organization, MDRO infections represent the occurrence of avoidable harm: Therefore MDRO prevalence must be recorded and its effects on patients measured[5].

There is a gap of knowledge on the impact of MDRO acquisition on heart transplant recipients in intensive care unit (ICU) environments with a high burden of gram-negative pathogens displaying advanced resistance patterns, for which limited treatment options are available.

We investigated whether MDRO presence negatively affects heart transplantation outcomes and constitutes a valid concern for patient safety, with an emphasis on the Gram-negative MDR pathogens, which are endemic in ICU environments in south-eastern Europe.

MATERIALS AND METHODS

Study design

This is a retrospective 10-year study conducted at the Onassis Cardiac Surgery Center, a referral hospital for cardiomyopathies and heart failure. The hospital hosts the national heart transplantation program in Greece. The post-surgical care of heart transplant patients takes place in the 16-bed cardiac surgery ICU. The study protocol received approval from the hospital scientific and ethics committee (P.E.E 787/16.10.2023).

Pathogen identification

As per ICU microbiological surveillance protocol, colonization cultures were obtained from transplanted patients daily

during the first week post transplantation, followed by three times per week during ICU stay. Nasal, pharyngeal and rectal swabs, bronchial secretions and urine samples were taken. Blood cultures were drawn as per clinical indication, *i.e.* following the occurrence of signs consistent with an inflammatory response or circulatory compromise. A specific pathogen isolated from sequential cultures from the same patient was analyzed as a single occurrence, given that recurrent identification of the same pathogen in the ICU is generally ascribed to pathogen tolerance and persistence mechanisms, rather than reinfection[6,7].

The MDROs reviewed were those frequently encountered in ICU care, which are currently under active monitoring (epidemiological surveillance), as per national and European guidelines[8]. These include carbapenem-resistant organisms, namely *Acinetobacter baumannii, Klebsiella pneumoniae* and *Pseudomonas aeruginosa* isolates, as well as *methicillin-resistant Staphylococcus aureus* (MRSA) and *vancomycin-resistant Enterococcus sp* (VRE).

Study population

The study comprised all 98 consecutive patients who underwent heart transplantation in our unit between 1/1/2013 and 31/12/2022 (10 years). Group comparison was carried out according to MDRO isolation from patient samples, *i.e.* patients were separated into two groups as per MDRO presence or MDRO absence.

Risk factors and outcomes

The variables reviewed were: (1) Patient demographic characteristics; (2) Clinical pre-transplantation characteristics: Cause of cardiac failure, presence of ventricular assist device (VAD), comorbidities and acute physiologic derangement *e.g.* continuous renal replacement treatment (CRRT); (3) Route of admission at transplantation: Ambulant patient/admission from home; inotrope-dependent patient/admission from hospital ward; mechanical circulatory support patient/admission from cardiac ICU; (4) Operating procedure data: Duration of general anesthesia, duration of extracorporeal circulation, aorta closure time, transfusion requirements; (5) Post-transplantation clinical data: Days of mechanical ventilation, use of nitric oxide (NO) as a marker for refractory post-transplantation hypoxemia, days of CRRT, major medical and surgical complications; and (6) Microbiology data: Type of MDRO, MDRO presence upon transplantation or acquisition during ICU stay, donor-acquired MDRO. Outcome measures were ICU length of stay and total hospital length of stay post-transplantation, as well as ICU mortality and early (30-d) and late (1-year) mortality.

Statistical analysis

SPSS v.25 software was employed for statistical analysis. Categorical values are given as absolute numbers and percentages (relative frequency). The Kolmogorov-Smirnoff test was used to check whether continuous variables conformed to a normal distribution. Normally distributed continuous variables, namely weight, height and body mass index (BMI), are given as mean values with SD. Continuous variables non-normally distributed are given as median with percentiles (25-75th). Demographic and comorbidity data prior to transplantation were explored through descriptive statistics. The Chi-square test was used for the analysis of categorical variables. The Mann-Whitney test was used for the comparison of means of continuous variables with a non-normal distribution, while the *t*-test was used for normally distributed continuous variables. The Kaplan-Meier curve was used for 1-year post-transplantation survival analysis.

RESULTS

Demographics

The population of heart transplant recipients consisted of 98 Caucasian patients, of whom 69 were male (70.4%) (Table 1). The median age was 49.5 years (range: 15-66 years). The mean patient BMI was 25.1 (range: 15.1-33); six patients fell within the cachexia range (BMI < 18.5), and seven patients within the obesity range (BMI ≥ 30). When comparing patients with or without MDRO presence, a statistically significant association between higher body weight/BMI and MRDO presence was found (P = 0.001), while age was not shown to have an impact.

Clinical characteristics

The reason for transplantation was non-ischemic cardiomyopathy in 76 patients (77.5%) and ischemic cardiomyopathy in 22 patients (22.4%). Of the former, 60 cases (61%) pertained to dilated cardiomyopathy, 10 cases (10.2%) to hypertrophic obstructive cardiomyopathy and 6 (6.1%) to other non-ischemic cardiomyopathies. Previous chemotherapy for hematologic neoplasia, mostly lymphoma, was the underlying cause for dilated cardiomyopathy in 9 patients (9.2%).

Over half of the patients (54/98 or 55%) were supported by a VAD on transplantation, equally divided between left ventricular and biventricular support (left ventricular assist device and bi-VAD respectively). Apart from these patients, an additional number of 8 patients had undergone cardiac surgery before transplantation, namely coronary artery bypass or valvular surgery. Therefore, the total number of patients with a history of cardiac surgery added up to 62 patients (63.3%).

Most patients were ambulant on admission (admitted from home: 65/98, 66.3%), of whom 16 were supported by a VAD (16.3% of total transplantations, 24.6% of home admissions). Upon transplantation, 33 patients were already hospitalized (33.7%). Of these, 15 were admitted from a cardiology ward (15.3% of total patients, 45% of hospitalized recipients), while 18 were admitted from the cardiac ICU (18.4% of total patients, 54.5% of hospitalized recipients). The patients admitted from a hospital ward had a median pre-transplantation hospitalization of 16 d (range: 2-520 d), while 9/15 (60%) were supported by a VAD. The patients admitted from a cardiac ICU had a median pre-transplantation ICU stay of

Table 1 Selected characteristics of heart transplant recipients according to multidrug-resistant organism presence

Heart transplant recipients	Total (*n* = 98)	MDRO presence (*n* = 32)	MDRO-free (*n* = 66)	*P* value
Demographics				
Age (yr)	50 (37-56)	51 (41-56)	45.5 (35.5-56)	0.48
Sex (male)	69 (70.4)	25 (78.1)	44 (66.7)	0.24
Height (cm), SD	172 (9)	174 (8)	172 (9)	0.25
Body weight (kg), SD	75 (15)	81 (11)	72 (16)	0.002
BMI (kg/m^2), SD	25.1 (3.8)	26.9 (3)	24.3 (3.9)	0.001
Heart failure etiology				
Non-ischemic cardiomyopathy	75 (76.5)	23 (71.9)	52 (78.8)	0.45
Ischemic cardiomyopathy	22 (22.4)	8 (25)	14 (21.2)	0.67
Comorbidities				
Diabetes mellitus	21 (21.4)	8 (25)	13 (19.7)	0.54
CRF (eGFR ≤ 60 mL/min/m^2)	13 (13.3)	8 (25)	5 (7.6)	0.017
Vasculopathy	40 (40.8)	17 (53.1)	23 (34.8)	0.08
COPD	5 (5.1)	2 (6.3)	3 (4.5)	0.72
Previous cardiac surgery	18 (18.4)	24 (75)	38 (57.6)	0.09
Smoking history	55 (56.7)	21 (65.6)	34 (52.3)	0.21
Status at transplantation				
VAD	54 (55.1)	22 (68.8)	32 (48.5)	0.06
Admitted from home	65 (66.3)	20 (62.5)	45 (68.2)	0.10
Admitted from ward	15 (15.3)	5 (15.6)	10 (15.2)	0.95
Admitted from ICU	18 (18.4)	7 (21.9)	11 (16.7)	0.53
Operating room				
General anesthesia (hours)	7 (6-8)	6.5 (6-8)	7 (6-8)	0.84
Extracorporeal circulation (min)	168 (144-229)	210 (146-271)	161 (141-193)	0.003
Aorta closure (min)	115 (77-198)	115 (85-130)	115 (67-211)	0.94
Transfusion (RBC units)	4 (2-10)	9.5 (4-13)	4 (2-7)	0.001
Post transplantation				
Primary graft dysfunction	13 (13.3)	10 (31)	3 (4.5)	0.001
Surgical re-exploration	20 (20.4)	11 (34)	9 (13.6)	0.017
Ventilator days	2 (1-5)	5 (3-3.5)	1.3 (1-3)	0.001
NO for refractory hypoxemia	25 (25.5)	14 (43.8)	11 (16.7)	0.04
CRRT for renal failure	15 (15.3)	9 (28)	6 (9)	0.014
Post Tx mechanical circulatory support	32 (32.7)	15 (46.9)	17 (25.8)	0.037
ATG treatment (days)	5 (4-7)	6 (5-8)	5 (4-6)	0.08
Outcomes				
ICU stay, days	10 (7-17)	15.5 (10-26)	9 (7-12)	0.001
Post transplantation total hospital stay, days	30 (24-41)	38 (25-62)	28 (21-39)	0.006
Early mortality (30 d)	9 (1)	6 (18.8)	3 (4.5)	0.02
Late mortality (1-year)	14 (14.3)	9 (28.1)	5 (7.6)	0.006
Died in ICU	12 (12.2)	8 (25)	4 (6)	0.003

Categorical values are given as absolute numbers and percentages. Normally distributed continuous variables (weight, height, body mass index) are given as mean values with SD. Continuous variables non-normally distributed are given as median with percentiles (25-75th). ATG: Anti-thymocyte globulin; BMI: Body mass index; CRRT: Continuous renal replacement treatment; ICU: Intensive care unit; NO: Nitric oxide; VAD: Ventricular assist device; COPD: Chronic obstructive pulmonary disease; MDRO: Multidrug-resistant organism; CRF: Chronic renal failure.

47 d (26-429), while 2/18 (11%) had a VAD in place, 14/18 (77.8%) were on circulatory support by intra-aortic balloon pump (IABP) and 1/98 was on Extracorporeal Membrane Oxygenation (ECMO) support and mechanically ventilated.

The type of cardiomyopathy, the presence of VAD or the mode of admission (home/ward/ICU) were not shown to differ between patients with MDROs and MDRO-free patients.

Comorbidities

Pertaining to comorbidities, peripheral vasculopathy was the most prevalent condition (40.8%), followed by diabetes mellitus (21.4%) and chronic renal failure (13.3%). An additional 10% of patients had arterial hypertension without vasculopathy. Chronic obstructive pulmonary disease and sleep apnea was present in 5.1%. Nearly a quarter of patients (24.5%) had suffered a cerebrovascular accident prior to transplantation. The prevalence of dyslipidemia was 23.4%, while 56% of patients had a smoking history.

Renal failure was the only comorbidity shown to be related to MDRO presence in the recipient.

Surgical procedure

The median duration of general anesthesia was 7 h (range: 4-18), the median duration of extracorporeal circulation was 168 min (range: 99-413) and median aorta closure time was 115 min (range: 36-283). The median number of packed-red-cell units transfused was 4 (range: 0-41).

Extracorporeal circulation time was shown to differ across comparison groups, namely longer duration was associated with a greater MDRO prevalence in heart recipients. Similarly, larger transfusion requirements, a marker of surgical complications, were associated with a greater MDRO prevalence. No difference was shown for general anesthesia duration or mean aorta closure time.

Post-transplantation events

Primary graft dysfunction occurred in 13 patients (13.3%). Mechanical circulatory support was required in 32 patients (32.7%). Of the latter, 26/32 (81%) were supported by IABP (median duration: 4 d, range: 1-39 d), of whom 7/26 (26.9%) died in ICU. ECMO support was needed for 11/32 patients (34%, median duration: 13.5 d, range: 1-26 d), of whom 8/11 (72.7%) died in ICU.

Major surgical complications occurred in 32 patients (32.7%). Surgical re-exploration was needed in 21/32 cases (65.6%), mainly due to hemorrhage (16/21, 76.2%) or tamponade (5/21, 23.8%). Delayed sternal closure was necessary in 18 patients (median open chest duration: 2 d, range: 1-20). Sternal wound debridement was carried out in 18/32 patients (18.4%), of whom 12 were open chest cases.

Major medical complications included acute renal failure requiring CRRT in 15 patients (median duration: 13 d, range: 1-33), major thromboembolism in 6 patients (6.1%) and multiple organ failure in 11 patients (11.2%). Septic shock occurred in 7 patients, of whom 5 had MDRO bacteremia.

Ventilator support exceeded 48 h post-surgery in 48/98 patients (49%), while re-intubation was necessary in 16/98 patients (16.3%). Post-transplantation refractory hypoxemia requiring treatment with inhaled NO was noted in 25/98 patients (25.5%). Median post-transplantation sedation was 40 h (range: 5-650). Median chest tube days were 7.5 (range: 6-39). Tracheostomy was performed on 8 patients (median duration: 12.5 d, range: 3-83).

Induction anti-thymocyte globulin (ATG) was used in all but 4 patients (96%, median duration: 6 d, range: 1-13).

Ventilator days, sedation hours and NO administration for refractory hypoxemia, right ventricle support were all associated with MDRO presence in the recipient. This was also true for primary graft dysfunction, post-transplantation mechanical circulatory support and any major surgical or medical complication, such as surgical re-exploration and renal replacement (CRRT). No impact was shown for the administration of ATG or its duration.

Microbiology

MDRO presence pertained almost exclusively to Gram-negative carbapenemase producing pathogens (94,8% of MDRO presence and 100% of MDRO bacteremias, Figure 1). Carbapenem-resistant *Acinetobacter baumannii* was the prevalent MDRO (36% of MDROs isolated), found in 14 patients (14.3% of all transplanted patients). Half of those already harbored *Acinetobacter* upon transplantation, five more acquired the organism in the ICU (median length of ICU stay before MDRO acquisition: 11 d, range: 8-33 d), while two acquired the pathogen from a donor subsequently found to have been bacteremic (blood cultures had been drawn from the donor upon organ procurement).

Carbapenem-resistant *Pseudomonas aeruginosa* followed in frequency (30.8% of MDROs isolated), found in 12 recipients (12.2%). Of those, 10 patients acquired the organism in ICU (median length of ICU stay for acquisition: 20 d, range: 2-31 d), one patient was already a carrier upon transplantation, while one acquired the pathogen from the donor.

Carbapenem-resistant *Klebsiella pneumoniae* (28.2% of MDROs isolated) was found in 11 patients (11.2%). All patients acquired the organism in ICU (median length of ICU stay for acquisition: 8 d, range: 3-40 d).

Overall, regarding the timeline of Gram-negative pathogen acquisition within the ICU, *Klebsiella* ICU acquisition generally preceded *Acinetobacter* acquisition, while *Pseudomonas* acquisition was a delayed event (median acquisition day:

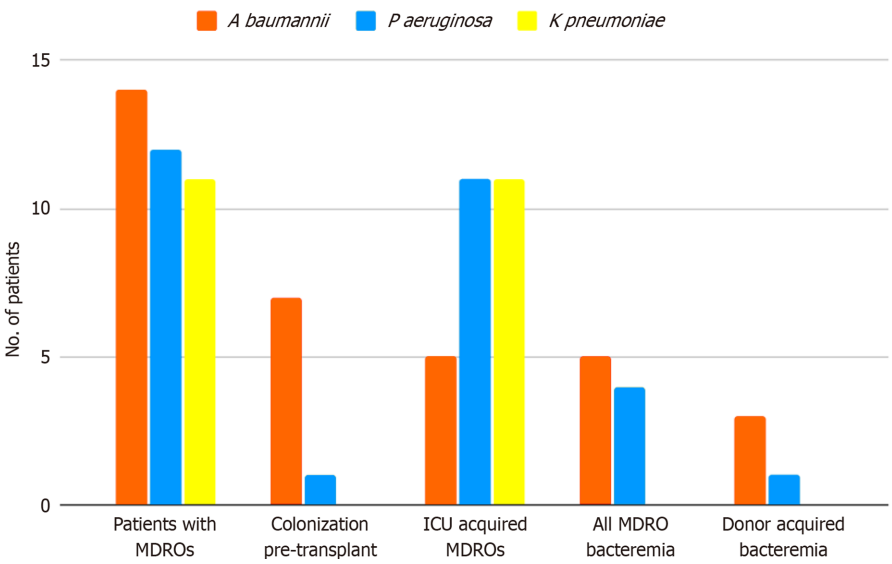

Figure 1 Multidrug-resistant organism carriage and bacteremia in heart transplantation patients (*n* = 98). Transplanted patients with multidrug-resistant organisms (MDROs): *Acinetobacter baumannii* was the most prevalent MDRO, followed by *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*. MDRO acquisition: Half of the patients with *Acinetobacter* and a single patient with *Pseudomonas* were already colonized pre-transplantation, while most *Pseudomonas* strains and all *Klebsiella* strains were intensive care unit acquired. MDRO bacteremia was noted in about a third of *Acinetobacter* and *Pseudomonas* carriers. Four cases of MDRO bacteremia were donor-acquired (the donor was subsequently found to have been bacteremic at the time of organ procurement). All MDRO bacteremias were due to Gram-negative pathogens. MDRO: Multidrug-resistant organism.

8th for *Klebsiella*, 11th for *Acinetobacter* and 20th for *Pseudomonas*).

Two patients were found to harbor MRSA, acquired on days 2 and 5 of ICU hospitalization respectively. No VRE cases were recorded.

Gram-negative MDRO bacteremia occurred in 11 patients (11.2%): 5 were caused by *A. baumannii*, 4 by *P. aeruginosa* and 2 by *K. pneumoniae*. Four out of eleven bacteremic patients had received a graft from a donor subsequently found to be bacteremic on the day of procurement (3 cases of *A. baumannii*, 1 case of *P. aeruginosa*).

However, not all recipients of bacteremic donors developed bacteremia post transplantation: Four additional patients having received a heart from a donor with MDRO bacteremia (2 cases of *A. baumannii* and 2 cases of *K. pneumoniae*) did not develop bacteremia during the first month post transplantation. In total, eight patients received a heart from a MDRO bacteremic donor; half of these developed bacteremia by that pathogen. The characteristics and outcomes of these patients are summarized in Table 2. No bacteremia was recorded by gram-positive MDROs.

Outcomes

Median ICU stay for all patients was 10 d (range: 3-22), while the median total hospital stay post transplantation was 30 d (range: 6-198). In total, 11 patients died in ICU, of whom 9 during the first 30 d (median survival: 26 d, range: 6-60 d). One male patient died in the operating room. Two more patients died within one year, following a long course of frequent readmissions with poor functional status (survival: 190 and 337 d respectively). Early mortality (30 d), ICU mortality and late mortality (1-year) were higher in the MDRO group (1-year mortality: 28% *vs* 7.6%, log-rank-χ^2 = 7.34, Figure 2).

DISCUSSION

MDRO presence occurred frequently in heart transplant recipients and was associated with surgical or medical complications post-transplantation. MDRO presence had a negative impact on patient outcomes, with a longer ICU and hospital stay, as well as an increased early and late mortality rate.

In patients with *Acinetobacter*, the organism was already present upon transplantation in about half of the cases, while *Pseudomonas* and *Klebsiella* were ICU acquired. Pre-transplantation hospitalization was not shown to be a predictor of MDRO presence upon transplantation, *i.e.* hospitalization at the time of transplantation did not seem to impact MDRO prevalence, as compared to patients admitted from home. However, most advanced cardiac failure patients are intermittently admitted in hospital, a fact which may account for this finding[9].

Among comorbidities, peripheral vasculopathy prevailed, but only renal failure and higher BMI was significantly higher in MDRO patients.

Bacteremia occurred in about a third of patients with MDRO presence. Moreover, bacteremia cases (36%) were donor acquired. This is a remarkably high percentage, which could be attributed to a delay in decision making about brain death declaration and organ procurement, resulting in donor increased length of stay in the ICU, a MDRO burdened environment[10].

Table 2 Patients who received a heart from a bacteremic donor and developed multidrug-resistant organism bacteremia post-transplantation

Patient	1	2	3	4
Diagnosis	DCM	DCM	DCM	DCM
Age (yr)	21	53	58	61
Sex	M	F	M	M
Device pre-transplant	BiVAD	IABP	LVAD	LVAD
Comorbidities	-	DM	-	CRF, vasculopathy
Admitted from (days of stay pre-transplant)	Ward (3 d)	Cardiac ICU (123 d)	Home	Ward (36 d)
Recipient MDRO colonization pre-transplant	No	No	No	No
MDRO donor bacteremia	*Acinetobacter baumannii*	*Acinetobacter baumannii*	*Acinetobacter baumannii*	*Pseudomonas aeruginosa*
Post-transplant complications	Re-exploration for hemorrhage	IABP (3 d)	IABP (9 d), re-exploration for hemorrhage	-
Septic shock	No	No	Yes	No
Post-transplant ICU stay	10 d	8 d	27 d (death)	11 d
Post-transplant total hospital stay	35 d	50 d	27 d (death)	34 d
Outcome (1 yr)	Fully functional at home	Fully functional at home	Death (day 27) due to thromboembolism/MOF	Partially dependent at home, frequent readmissions

BiVAD: Bi-ventricular assist device; CRF: Chronic renal failure; DCM: Dilated cardiomyopathy; IABP: Intra-aortic balloon pump; ICU: Intensive care unit; LVAD: Left ventricular assist device; MOF: Multiple organ failure; MDRO: Multidrug-resistant organism.

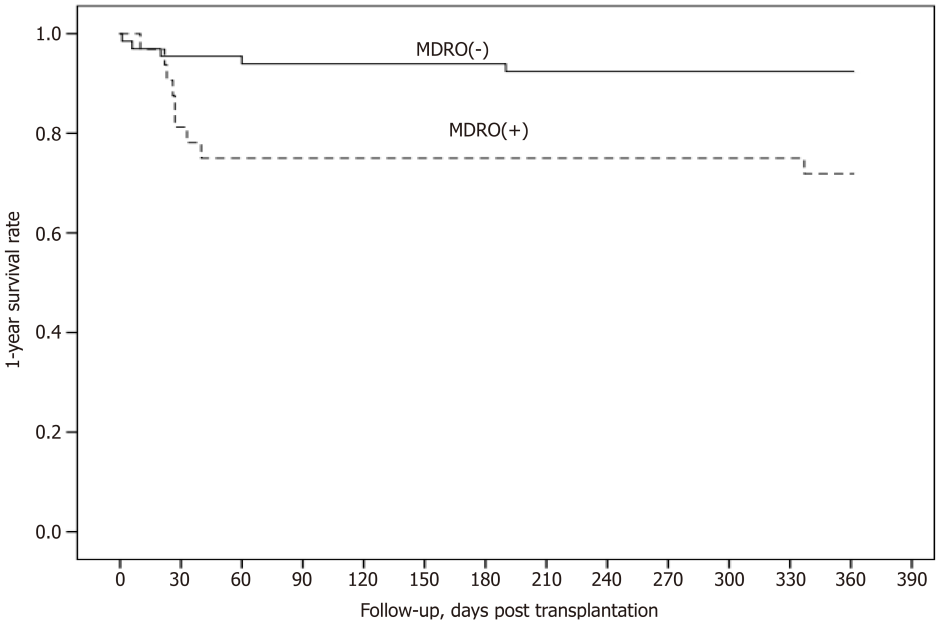

Figure 2 Post-transplantation 1-year survival according to multidrug-resistant organism status. 1-year survival was 72% in heart transplant recipients with multidrug-resistant organism (MDRO) presence (MDRO+) *vs* 92% in MDRO-free (MDRO-) recipients ($P < 0.01$). MDRO: Multidrug-resistant organism.

Particularities of MDRO prevalence

ICUs harbor a distinct pathogen ecosystem arising through ongoing antimicrobial selection pressure[11,12]. As compared to other acute hospital settings, the ICU endemicity pattern comprises MDROs, which carry genes entailing evolving resistance to advanced antimicrobial agents[13]. In referral hospitals and specialty ICUs, patient previous inter-hospital transfers are an additional source of MDR pathogen importation[14].

In Europe, a geographical north-to-south and west-to-east gradient of bacterial resistance exists, with higher rates observed in the southeast: The selected bacteria surveyed in this study are the most prevalent microorganisms in ICU environments in south-eastern Europe, where carbapenem-resistant gram-negative pathogens prevail[15]. These pathogens are accordingly deemed relevant for hospital infection surveillance purposes in Greece, in consonance with the National Action Plan for Antimicrobial Resistance. The Action Plan draws on the antimicrobial resistance reporting protocol issued by the European Center for Disease Control (ECDC)[8].

Acinetobacter baumannii, the prevailing MDRO in our study, is characterized by the capacity to acquire and harbor a battery of determinants of antimicrobial resistance and environmental persistence[16]. In low-prevalence ICU environments, *e.g.* in the north and west of Europe, *Acinetobacter* outbreaks are usually monoclonal and can be traced to an index transmission event; in contrast, high prevalence ICU environments, similar to those of south-eastern Europe, are marked by a diversity of polyclonal isolates and entail an increased complexity regarding the pathways of transmission [17]. In this setting, accelerated evolution of resistance *via* plasmid transfer between different isolates has been documented[18]. In a similar manner, mobile genetic elements, including plasmids or phages, play a critical role in *Klebsiella* ICU clusters, *via* horizontal transmission between polyclonal strains[19].

Remarks on MDRO colonization of heart transplant patients

Heart transplant candidates constitute a heterogenous patient group. Considering the most frequent underlying diagnoses, patients with dilated cardiomyopathy in our cohort were younger, while patients with ischemic cardiomyopathy were middle-aged. Both in this cohort and as a general rule, the latter group is relatively more burdened by comorbidities, such as hypertension, diabetes, peripheral vasculopathy and renal disease[20]. Patients re-transplanted for graft vasculopathy represent a small, but challenging subgroup[21].

Candidates for heart transplantation share numerous risk factors for MDRO acquisition pre-transplant. Notably, heart failure is a leading cause of hospitalization, while asymptomatic colonization of patients with MDRO is a recognized consequence of frequent admissions[22]. Further, a subgroup of heart transplantation candidates (about a third of patients in our study) is confined to the inpatient setting in a state of "dependent stability", *i.e.* in need of continuous inotrope infusion (15.3%) and/or support with an IABP (14.3%). A small group of patients pertains to a hyper-acute state, such as ECMO support (one patient in our study).

A feature particular to heart transplantation candidates is the presence of VAD (55% in our study). VAD at the time of transplantation confers an increased risk of MDRO colonization, usually at the driveline entry point (5.5% of patients in our study)[23]. VAD entry point infection occasionally spreads across the driveline (mediastinitis)[24,25]. However, active VAD-related bacterial infection in the transplant recipient does not constitute a contraindication to transplantation[26]. Given that heart transplantation is never a scheduled procedure, bacteremia secondary to active device infection cannot always be accurately excluded at the time of transplantation. Further, weight-gain in patients on VAD is not infrequent. Among VAD patients subsequently transplanted, increased BMI was associated with post-transplantation complications [27].

Regarding the timing of MDRO acquisition, MDRO pathogens in our study were mainly acquired post-transplantation in the ICU, rather than already present at transplantation. Patients in the ICU become colonized *via* cross-contamination between patients, *via* direct or indirect contact due to environmental MDRO persistence, or *via* acquisition of resistant strains in the patient's gut or skin following prolonged antimicrobial exposure[28,29].

Indeed, newly transplanted patients are commonly being treated with long courses of antimicrobials, even in the absence of complications or clinical indications of infection[30]. To address the use of antimicrobials out of proportion to infection prevalence, current guidelines recommend the discontinuation of prophylactic antimicrobials 24-48 h post transplantation[31]. Nevertheless, the familiarity of common practice prevails over best available evidence; it is notably difficult to de-implement customary treatments and practices devoid of an evidence-based foundation[32]. This effect is further enhanced by the fluctuating post-surgical physiological state of transplanted patients, generating uncertainty about whether antimicrobials may be safely discontinued or even de-escalated.

Infection control strategies and antimicrobial stewardship need to be constantly promoted in the ICU, to improve patient outcomes. However, even when relevant policies are in place, high workload may act as a hindrance to guideline implementation[33]. Our cardiac surgery ICU has a 100% occupancy, while the average nurse-to-patient ratio is 0.7, becoming 1 for transplanted patients. The steadily high bed occupancy rate entails an increased work volume per nurse, a possible impediment to optimal infection prevention practices[34].

Post-transplantation MDRO bacteremia

In the ICU, bacteremia arising from vascular catheter colonization is an important cause of patient destabilization[35]. MDRO bacteremia, in particular, is a recognized cause of sepsis in the ICU[36,37]. Sepsis-related mortality remains high in ICUs, although increasing attention is being given to the prompt recognition and control of septic episodes, and despite the availability of incrementally advanced and precise diagnostics[38].

Due to concerns for post-transplantation bacteremia, MDRO presence in the donor or the recipient was formerly listed as a contraindication for transplantation[39,40]. Indeed, MDRO bacteremias are mostly encountered in the early post-transplantation period, when transplanted patients recover from major surgery, while being treated with high dose immunosuppression[41]. In our unit, immunosuppressive treatment comprises ATG, corticosteroids, mycophenolate and tacrolimus.

Further, an increased propensity for bacterial translocation to the blood through the gut mucosa is noted in heart transplant patients, given that hemodynamic instability is common in the early post-transplantation period, even in the absence of graft dysfunction[42].

All post-transplantation bacteremia episodes in our study were caused by Gram-negative MDROs. Globally, the epidemiology of bacteremia in transplanted patients has shifted from Gram-positive to Gram-negative pathogens, matched with a rising emergence of resistant strains[43].

In this study MDRO acquisition preceded bacteremia episodes, a finding in accordance with other studies[44,45], although MDRO bacteremia without previous colonization has been previously reported[35]. Due to the limited number of post transplantation bacteremia episodes, the study was underpowered to support a valid analysis of the impact of MDRO bacteremia on patient outcomes.

Outcomes: Mortality and ICU length of stay

Whether the presence of MDROs in the ICU has a measurable impact on patient ICU mortality remains an unsettled question. Different studies report opposing results, both positive[43-45] and negative[46]. When matched immunocompetent patients serve as a control group, solid organ transplantation patients generally experience more bacteremia episodes during hospitalization, but mortality does not seem to be greater[47]. Therefore, while MDRO colonization was previously listed as a contra-indication for transplantation, presently, donor or recipient MRDO colonization no longer constitutes an exclusion criterion *per se* for organ procurement and allocation[48,49]. Rather, comprehensive recipient evaluation and effective interinstitutional communication channels are recommended, so that information about MDRO presence can be rapidly communicated and managed at the time of transplantation[50,51].

In our study, immediate post-transplantation mortality (within 10 days) was due to primary graft dysfunction and surgical complications. Indeed, immediate post transplantation mortality is generally not attributed to microbial causes [52]. However, ICU mortality, 30-d mortality and 1-year mortality were higher in patients harboring MDROs. Therefore, while heart transplant recipients with MDROs are not more likely to die when compared with matched non-transplanted ICU patients, they have a higher mortality rate when compared with MDRO-free transplant recipients. It is unclear whether this association represents a direct causal relation, given that MDRO presence may be either a consequence of medical and surgical complications of the transplantation procedure, or a marker of prolonged poor status, rather than a direct cause of death[53].

A longer ICU stay and total hospital stay were clearly correlated with MDRO presence. Given the detrimental impact of prolonged ICU stay on patient functional status and hospital resource allocation, it becomes clear that infection control practices need to be constantly revisited, so that patient MDRO colonization can be prevented. Teamwork is essential for infection prevention effectiveness, *i.e.* nurses daily inspecting indwelling devices (venous, arterial and urinary catheters, tracheal tubes *etc.*), physicians reassessing the need for such devices, and cleaning staff implementing surface disinfection. Antimicrobial stewardship support is decisive for discontinuation of antimicrobials as appropriate[54]. Best efforts for adequate ICU staffing and continuing staff education and support must be made by the hospital administration[55].

Strengths and limitations of the study, and future directions: Although this was a retrospective study, which constitutes a limitation *per se*, all transplanted patients were consecutively included in the study, and data completeness was 100% for all the variables studied. Despite the relatively low sample size, the study demonstrated a statistically significant association between MDRO presence and patient outcomes. However, the study was underpowered to support a valid analysis of infrequent events, such as receiving a heart from a donor subsequently proven to have been bacteremic at the time of organ procurement. In the future, these parameters need to be re-evaluated by pooling data from several transplantation centers.

Although the study was conducted in a single transplantation center, the pattern of resistance observed is representative of the prevailing resistance pattern in south-eastern Europe (high prevalence of carbapenemase producing MDROs/high level of resistance). Given the geographical epidemiological differences, the results may not be generalizable for institutions in the north-west of Europe, where the pathogen resistance pattern is characterized by a predominance of Gram-positive MDROs or by the prevalence of ESBL-producing Gram-negative MDROs with lower level of resistance[56].

Finally, in this study, bacterial isolation and identification was based on classic microbiological detection methods. In the future, novel sequencing techniques may provide more information on MDRO clonal spread and virulence characteristics. Different patient outcomes may be influenced by dissimilar virulence capacity among distinct isolates of the same pathogen[57,58]. Therefore, molecular pathogen data may clarify phenomena, such as the persistence of colonizing MDRO strains and their interaction with the transplanted host, as well as the way these phenomena determine transplantation outcomes.

CONCLUSION

This single center retrospective study showed that heart transplant recipients had a high incidence of MRDO presence with a clear predominance of Gram-negative carbapenemase-producing pathogens, a pattern characteristic of south-eastern Europe. MDROs were mainly ICU acquired during the early post-transplantation period, rather than already present at transplantation. Higher BMI and pre-existing renal failure were shown to be risk factors pre-transplant, while medical and surgical complications upon transplantation were shown to be risk factors of MDRO acquisition post-transplant. MDRO acquisition was associated with prolonged ICU and total hospital stay, as well as early and late post transplantation mortality.

FOOTNOTES

Author contributions: Hatzianastasiou S performed the research and wrote the paper; Vlahos P, Stravopodis G, Chilidou D and Koukousli A retrieved patient data and contributed to the analysis; Elaiopoulos D, Papadopoulos K, Soulele T, Kolovou K, Chamogeorgakis T, Gkouziouta A, Bonios M and Adamopoulos S provided clinical advice; Papaparaskevas J supervised the report, and Dimopoulos S designed the research, supervised the report and gave the final approval.

Institutional review board statement: This study was reviewed and approved by the Ethics Committee of the Onassis Cardiac Surgery Center.

Informed consent statement: Patients were not required to give informed consent to the study, because the analysis used anonymous clinical data that were obtained after each patient agreed to heart transplantation by written consent.

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ORIGINAL ARTICLE

Retrospective Study

Does the use of double hormone replacement therapy for trauma patient organ donors improve organ recovery for transplant

Eden M Gallegos, Tanner Reed, Paige Deville, Blake Platt, Claudia Leonardi, Lillian Bellfi, Jessica Dufrene, Saad Chaudhary, John Hunt, Lance Stuke, Patrick Greiffenstein, Jonathan Schoen, Alan Marr, Anil Paramesh, Alison A Smith

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Abstract

BACKGROUND

With an ongoing demand for transplantable organs, optimization of donor management protocols, specifically in trauma populations, is important for obtaining a high yield of viable organs per patient. Endocrine management of brain-dead potential organ donors (BPODs) is controversial, leading to heterogeneous clinical management approaches. Previous studies have shown that when levothyroxine was combined with other treatments, including steroids, vasopressin, and insulin, BPODs had better organ recovery and survival outcomes were increased for transplant recipients.

AIM
To determine if levothyroxine use in combination with steroids in BPODs increased the number of organs donated in trauma patients.

METHODS
A retrospective review of adult BPODs from a single level 1 trauma center over ten years was performed. Exclusion criteria included patients who were not solid organ donors, patients who were not declared brain dead (donation after circulatory death), and patients who did not receive steroids in their hospital course. Levothyroxine and steroid administration, the number of organs donated, the types of organs donated, and demographic information were recorded. Univariate analyses were performed with $P < 0.05$ considered to be statistically significant.

RESULTS
A total of 88 patients met inclusion criteria, 69 (78%) of whom received levothyroxine and steroids (ST/LT group) *vs* 19 (22%) receiving steroids without levothyroxine (ST group). No differences were observed between the groups for gender, race, pertinent injury factors, age, or other hormone therapies used ($P > 0.05$). In the ST/LT group, 68.1% ($n = 47$) donated a high yield (3-5) of organ types per donor compared to 42.1% ($n = 8$) in the ST group ($P = 0.038$). There was no difference in the total number of organ types donated between the groups ($P = 0.068$).

CONCLUSION
This study suggests that combining levothyroxine and steroid administration increases high-yield organ donation per donor in BPODs in the trauma patient population. Limitations to this study include the retrospective design and the relatively small number of organ donors who met inclusion criteria. This study is unique in that it mitigates steroid administration as a confounding variable and focuses specifically on the adjunctive use of levothyroxine.

Key Words: Organ donation; Trauma; Brain death; Levothyroxine; Hormone replacement therapy; Steroids; Organ donor; Retrospective

Core Tip: The present study considers the impact of combination endocrine management on the number of solid organs donated in brain-dead organ donors. Specifically, we focused on the use of steroids alone or steroids and levothyroxine in organ donors of the trauma patient population from a single level 1 trauma center. We showed a significant association between a high yield of organs donated per donor and the use of combination hormone replacement therapy as compared to steroids alone. These data complement published literature on combination endocrine management and highlight the role of levothyroxine on the number of organs recovered per organ donor.

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INTRODUCTION

Aggressive organ donor management has been shown to yield positive outcomes for organ donation[1-4]. With an ongoing demand for transplantable organs, optimization of donor management protocols, specifically in trauma populations, is important for obtaining a high yield of viable organs per patient. Hormone replacement therapy is an area of intensive care protocols that the Society of Critical Care Medicine has advised, however there is little evidence supporting its efficacy[1,4,5]. Hormone therapy may preserve the potential for organ donation in patients that have experienced non-survivable catastrophic brain injuries or after brain death declaration, but protocols for implementing these interventions are ill-defined[1,6]. The value of combination steroid and thyroid hormone replacement in hemodynamically stable or unstable patients is still under debate, as studies looking at the beneficial effects of these interventions show mixed results[4,7].

The goal of this study was to assess the role of double hormone replacement therapy, including steroid and levothyroxine administration, in organ donation outcomes (organs transplanted per donor). Steroids are routinely utilized for potential brain-dead organ donors in the trauma population. However, the current literature lacks in consistently controlling for steroid use when comparing outcomes between combination therapies[1,4,8,9]. We hypothesized that levothyroxine with steroids administered in trauma patients with catastrophic brain injuries or confirmed brain death

would increase the number of organs donated.

MATERIALS AND METHODS

A retrospective review of adult patients who were eligible for organ donation from a level 1 trauma center between July 2012 and March 2021 was performed. The trauma registry was used to find patients meeting the inclusion criteria. Inclusion criteria were as follows: Patients 18 years of age or older who were declared brain dead, were solid organ donors and were administered steroids (methylprednisolone, hydrocortisone, or both) during their hospital course. These patients underwent chart review using electronic medical records and records from the associated organ procurement organization. Exclusion criteria were patients younger than 18 years of age, patients who were not solid organ donors, patients who were not declared brain dead (such as patients who donated after circulatory death), and patients who did not receive steroids (methylprednisolone, hydrocortisone, or both) in their hospital course (Figure 1). Brain death determination was made using two confirmatory brain death exams and, in some cases, ancillary tests including cerebral perfusion scans. The Institutional Review Board approved this study, and a waiver of informed consent was obtained. There were no set trauma intensive care unit guidelines for management of potential organ donors, and management was left to the discretion of the attending physician.

Demographic data such as age, race, and gender were collected. Pertinent injury factors were recorded, including injury severity score, type of injury (blunt or penetrating), and presence of traumatic brain injury (TBI). A donated organ was defined as any organ recovered by the organ procurement organization. The type of solid organs donated, including lungs, kidneys, heart, liver, and pancreas, were recorded. The types of solid organs donated were then summed to range between 1-5 organ types per donor. For example, two donated kidneys would still only be counted as one type. A high yield of organs recovered per donor was defined as 3-5 organ types donated by an individual donor.

Data on treatment for other endocrine disorders, such as diabetes insipidus (DI) and hyperglycemia, were also collected. DI treatment was identified as desmopressin or vasopressin administration following suspected DI due to polyuria (> 2.5-3 mL/h/kg), hypernatremia (> 150 mEg/L), high serum osmolarity (> 295 mOsm/L), and/or low urine osmolarity (< 200 mOsm/L)[10]. Insulin requirement was recorded as hyperglycemia treatment.

Patients were then divided into two groups: Those receiving levothyroxine plus steroids (ST/LT group) *vs* those only receiving steroids without levothyroxine (ST group). Data was analyzed using statistic analysis system (SAS) version 9.4 (SAS Institute Inc, Cary, NC, United States). Variables collected are reported as either median and minimum and maximum for not normally distributed count variables or proportions for categorical variables. Univariable analyses were conducted to compare demographic and clinical donors' characteristics and donated organs between two groups (ST *vs* ST/LT) using the χ^2 test or the exact test when comparing proportions and the Mann-Whitney *U* test when comparing medians. A two-sided *P* value less than 0.05 indicated statistical significance.

RESULTS

Study population

Of the patients reviewed, a total of eighty-eight organ and tissue donors met the study inclusion criteria (Figure 1). Of these organ donors, 78% received levothyroxine and steroids (ST/LT group, $n = 69$) *vs* 22% receiving steroids alone (ST group, $n = 19$).

Study demographics

No significant differences were observed between the two groups in the reported patients' demographical and clinical characteristics (Table 1). Patients' ages ranged from 18 years-75 years old in the ST group and 20 years-75 years old in the ST/LT group, with the majority in each being male (68.4% *vs* 81.2%, $P = 0.232$, respectively). In the ST compared to the ST/LT group, 31.6% *vs* 46.4% were African American/Black, 57.9% *vs* 43.5% were Caucasian/White, and 10.5% *vs* 10.1% were of a different racial background, respectively ($P = 0.483$). Regarding clinical characteristics of the patients, the median injury severity score was 25 (4–54) in the ST group and 29 (9-75) in the ST/LT group ($P = 0.911$). Blunt injuries occurred in 73.7% ($n = 14$) of the ST group patients and 60.9% of the ST/LT group patients, with 26.3% and 39.1%, respectively, having penetrating injuries ($P = 0.304$). In the ST group, 84.2% of patients had a TBI, and in the ST/LT group, 94.2% had a TBI ($P = 0.169$). Other than LT and ST, endocrine protocols used were insulin administration for hyperglycemia treatment and desmopressin or vasopressin administration for DI treatment. Insulin was administered in 57.9% of ST group patients and 55.1% of ST/LT patients ($P = 0.826$). Finally, DI was treated in 31.6% of ST group patients and 40.6% of ST/LT group patients ($P = 0.476$) (Table 1).

Organ donation

Organ donation summaries for the patients are reported in Table 2. The median number of organ types donated [median (min-max)] was not significantly different between the two groups and were 2 (1-5) for the ST group and 3 (1-5) for the ST/LT group ($P = 0.068$, Table 2). A significantly higher proportion of patients with a high yield of organs (3-5 organ types per donor) was observed in the ST/LT group compared to the ST group (68.1% *vs* 42.1%, $P = 0.038$, Table 2). No individual organ type was donated at a significantly higher proportion between the treatment groups ($P > 0.05$, Table 2). Furthermore, although non-statistically significant, all organs were donated at a numerically higher proportion for the

Table 1 Demographic and clinical characteristics of adult donors by hormone therapy usage, *n* (%)

Item	ST (*n* = 19)	ST/LT (*n* = 69)	*P* value
Age (yr), median (min–max)	36 (20–75)	32 (18–75)	0.214
Gender			0.232
Male	68.4 (13)	81.2 (56)	
Female	31.6 (6)	18.8 (13)	
Race			0.483
African American/Black	31.6 (6)	46.4 (32)	
Caucasian/White	57.9 (11)	43.5 (30)	
Other	10.5 (2)	10.1 (7)	
Injury type			0.304
Blunt	73.7 (14)	60.9 (42)	
Penetrating	26.3 (5)	39.1 (27)	
ISS, median (min–max)	25 (4–54)	29 (9–75)	0.911
TBI	84.2 (16)	94.2 (65)	0.169
Insulin	57.9 (11)	55.1 (38)	0.826
DI	31.6 (6)	40.6 (28)	0.476

ISS: Injury severity score; TBI: Traumatic brain injury; DI: Diabetes insipidus treated; ST/LT: Levothyroxine and steroids; ST: Steroids.

Table 2 Donated organs by hormone therapy usage, *n* (%)

Item	ST (*n* = 19)	ST/LT (*n* = 69)	*P* value
Total number, median (min-max)	2 (1–5)	3 (1–5)	0.068
Donation of 3 or more organs	42.1 (8)	68.1 (47)	0.038
Organ type			
Heart	42.1 (8)	59.4 (41)	0.179
Kidney	94.7 (18)	91.3 (63)	0.624
Liver	79.0 (15)	92.8 (64)	0.079
Lung	21.1 (4)	39.1 (27)	0.144
Pancreas	26.3 (5)	36.2 (25)	0.419

Total number of organ types donated of five: Heart, liver, lung, kidney, and/or pancreas. ST/LT: Levothyroxine and steroids; ST: Steroids.

ST/LT group compared to the ST group, except for kidneys, which had a very high donation rate (> 90% in both treatment groups, Table 2).

DISCUSSION

Meeting the demand for transplantable organs remains an ongoing challenge, making the optimization of interventional protocols, specifically in trauma populations, an essential part of maximizing the number of organs obtained per patient. Steroids are routinely used for potential brain-dead organ donors in the trauma population. However, the current literature lacks in consistently controlling for steroid use when comparing outcomes between combination therapies[4,8,11,12].

The present study compared steroids in adjunct with levothyroxine to steroids alone in brain-dead potential organ donors (BPODs) and found an increase in high-yield organ donation per donor (*i.e.*, 3-5 organ types donated per donor) in the ST/LT group compared to the ST group. There was no difference in the total number donated or the number of individual organs donated between the groups. Notably, there was no decrease in organs donated in the ST/LT group

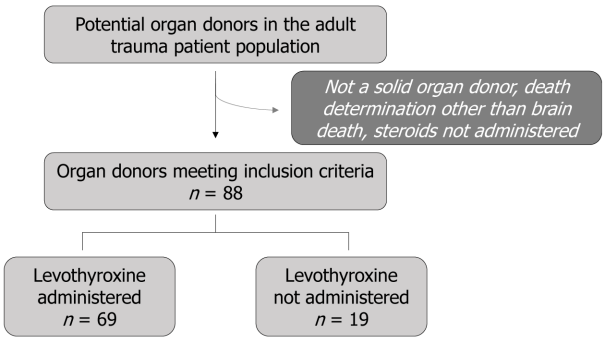

Figure 1 Study design flowchart showing inclusion criteria and final groups. Excluded patients are signified by the unmet criteria in the dark gray box.

compared to the ST group, suggesting there was no identifiable negative association of LT treatment in this cohort of organ donors in the trauma patient population.

The history of research on including levothyroxine as an intervention for potential organ donors has been mixed[1,7]. For a recent review of the literature on levothyroxine's role in hormone replacement therapy, see Turco *et al*[5], 2019. In short, circulating levothyroxine was shown to decrease after brain death in several studies, and pre-clinical studies indicated a potential role of levothyroxine replacement in maintaining perfusion of organs *via* increased hemodynamic stability[5,13]. Following these findings, numerous clinical studies ranging from small prospective to large retrospective studies identified levothyroxine alone or in combination hormone replacement therapy as beneficial in regards to donor hemodynamic status or organ retrieval rates and outcomes[11,12,14,15]. Clinical trials studying levothyroxine, however, have failed to elucidate a beneficial effect of levothyroxine therapy on the organs of brain-dead donors[7,16-19]. Limitations to these studies include inconsistent outcome measures and, in the case of randomized controlled trials (RCTs), small numbers of hemodynamically unstable patients[19,20]. In addition, quality RCTs evaluating the benefit of combination hormone replacement therapy are lacking[21]. An ongoing multicenter randomized controlled trial including 800 brain-dead, hemodynamically unstable organ donors may clarify whether heart donation, heart function, and/or vasopressor requirements are impacted specifically by intravenous thyroxine treatment[22]. However, as organ procurement organizations are allowed to continue their other individual standard donor management protocols, it is not yet clear how or whether the contributions of other hormone replacement therapies, such as steroids, will be considered [22]. Still, a comparative study showed evidence that levothyroxine intervention before brain death was beneficial in increasing the number of organs donated[23]. One other study identified the timing of hormone replacement therapy as an important factor after catastrophic brain injury, but few studies have been able to give clear guidance on when hormone intervention should be initiated[6]. Timing, then, may also impact the findings in RCTs based on whether levothyroxine treatment was initiated before or after brain death and how long the patients were exposed to the treatment. Similarly, understanding the optimal timing of levothyroxine administration in relation to when steroid interventions are started will aid in determining appropriate endocrine protocols for BPODs in the trauma patient population. In summary, the proper usage of levothyroxine or combination replacement therapy in catastrophic brain injury or after brain death is still under debate. Still, previous literature, as well as the present study, highlight the potential benefits of LT and combination therapy in increasing organ donation after brain death.

While the present study did not focus on stability parameters of the patient population, prospective studies may be able to better differentiate the impact of levothyroxine and steroid therapies on stable compared to unstable patients. Study limitations include its retrospective and single-center nature. Other potential confounders of the results include the vasopressor requirements, cardiovascular stability, timing of hormone therapy administration, and length of time on the therapy. Future prospective studies controlling for these factors may elucidate other important aspects of treating potential organ donors in cases of imminent or confirmed brain death. With multiple cohort studies indicating significant impacts of combination therapy, more clinical trials with sufficient power investigating combination instead of single therapy are warranted.

CONCLUSION

In conclusion, this retrospective study showed an increase in high-yield organ donation per donor when levothyroxine was adjunctively administered with steroids in BPODs as compared to BPODs administered steroids alone. These results, along with previous reports from RCTs, call for further investigation of the use of levothyroxine in adjunct with steroids for the management of brain-dead organ donors.

FOOTNOTES

Author contributions: Gallegos EM wrote the first draft and revisions of the manuscript; Gallegos EM, Smith AA, Reed T, Paramesh A, Bellfi L, and Dufrene J contributed to the research design of this manuscript; Gallegos EM, Reed T, and Chaudhary S contributed to the

performance of the research; Gallegos EM, Deville P, Platt B, Leonardi C, and Smith AA contributed to data analysis; Paramesh A, Smith AA, Deville P, Platt B, Leonardi C, Hunt J, Stuke L, Greiffenstein P, Schoen J, and Marr A provided critical revisions of the manuscript.

Institutional review board statement: The Louisiana State University Health Sciences Center-New Orleans Institutional Review Board approved this study (#1966), and a waiver of informed consent was obtained.

Informed consent statement: Informed consent was waived by the ethics committee because this was an observational retrospective study.

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ORIGINAL ARTICLE

Retrospective Study

Transarterial embolization is an acceptable bridging therapy to hepatocellular carcinoma prior to liver transplantation

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Abstract

BACKGROUND

Hepatocellular carcinoma (HCC) is an aggressive malignant neoplasm that requires liver transplantation (LT). Despite patients with HCC being prioritized by most organ allocation systems worldwide, they still have to wait for long periods. Locoregional therapies (LRTs) are employed as bridging therapies in patients with HCC awaiting LT. Although largely used in the past, transarterial embolization (TAE) has been replaced by transarterial chemoembolization (TACE). However, the superiority of TACE over TAE has not been consistently shown in the literature.

AIM

To compare the outcomes of TACE and TAE in patients with HCC awaiting LT.

METHODS

All consecutive patients with HCC awaiting LT between 2011 and 2020 at a single center were included. All patients underwent LRT with either TACE or TAE. Some patients also underwent percutaneous ethanol injection (PEI), concomitantly or in different treatment sessions. The choice of LRT for each HCC nodule

was determined by a multidisciplinary consensus. The primary outcome was waitlist dropout due to tumor progression, and the secondary outcome was the occurrence of adverse events. In the subset of patients who underwent LT, complete pathological response and post-transplant recurrence-free survival were also assessed.

RESULTS

Twelve (18.5%) patients in the TACE group (only TACE and TACE + PEI; n = 65) and 3 (7.9%) patients in the TAE group (only TAE and TAE + PEI; n = 38) dropped out of the waitlist due to tumor progression (P log-rank test = 0.29). Adverse events occurred in 8 (12.3%) and 2 (5.3%) patients in the TACE and TAE groups, respectively (P = 0.316). Forty-eight (73.8%) of the 65 patients in the TACE group and 29 (76.3%) of the 38 patients in the TAE group underwent LT (P = 0.818). Among these patients, complete pathological response was detected in 7 (14.6%) and 9 (31%) patients in the TACE and TAE groups, respectively (P = 0.145). Post-LT, HCC recurred in 9 (18.8%) and 4 (13.8%) patients in the TACE and TAE groups, respectively (P = 0.756). Posttransplant recurrence-free survival was similar between the groups (P log-rank test = 0.71).

CONCLUSION

Dropout rates and posttransplant recurrence-free survival of TAE were similar to those of TACE in patients with HCC. Our study reinforces the hypothesis that TACE is not superior to TAE as a bridging therapy to LT in patients with HCC.

Key Words: Hepatocellular carcinoma; Transarterial embolization; Transarterial chemoembolization; Liver transplantation; Locoregional therapy; Bridging

Core Tip: Hepatocellular carcinoma (HCC) is an aggressive malignant neoplasm, and the treatment of choice is liver transplantation (LT). Because the waiting time is often unpredictable, locoregional therapy is used to halt HCC progression until an organ is available. Although largely replaced by transarterial chemoembolization (TACE), transarterial embolization (TAE) or bland embolization is an alternative with a lower cost and safer adverse event profile. Our findings, in conjunction with those of previous studies, provide evidence of non-superiority of TACE over TAE, thereby encouraging a more liberal use of TAE for bridging HCC to LT.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is an aggressive malignant neoplasm that arises in the presence of cirrhosis. Unless appropriate treatment is administered, HCC may progress, rupture, or metastasize[1-3]. In the presence of cirrhosis and portal hypertension, liver transplantation (LT) is the treatment of choice for HCC[4,5].

The Milan criteria is widely used to identify patients likely to benefit from LT[6,7]. Although some organ allocation systems may prioritize patients with HCC for LT[8], most of these patients face a long waiting period. Thus, locoregional therapy (LRT) is indicated for this patient population to halt tumor progression beyond the acceptable limits of the Milan criteria (bridging therapy)[9].

Although the main LRT options are transarterial chemoembolization (TACE) and radiofrequency ablation (RFA), other modalities such as transarterial radioembolization, percutaneous ethanol injection (PEI), microwave ablation, and transarterial embolization (TAE) are also employed worldwide. Recently, our group demonstrated that PEI is an acceptable bridging therapy to LT in patients with HCC[10,11]. The choice of LRT is influenced by tumor size, number, and location, liver function, and individual center experience[10-12].

Although widely used in the past, TAE has been replaced by TACE. The potential advantage of TACE over TAE may be the addition of a chemotherapeutic agent. However, because HCC expresses a *multidrug resistance* gene, it is resistant to most chemotherapeutic agents available[13]. Furthermore, the advantages of TACE over TAE have not been confirmed in clinical practice. A recent systematic review and meta-analysis comparing randomized control trial (RCT) data on TAE and TACE use among patients with unresectable HCC detected no superiority of TACE over TAE in terms of disease-free survival[14].

Only one study till date has compared the outcomes of TAE *vs* TACE in terms of dropout rates of patients with HCC on the transplant list[15]. Thus, the aim of this study was to analyze the outcomes of TAE and TACE as an LRT for

patients with HCC awaiting LT. The dropout rates and post-transplant outcomes of both techniques have been compared.

MATERIALS AND METHODS

This study was a retrospective analysis of a prospectively filled dataset from the Hospital de Clínicas de Porto Alegre (HCPA) Liver Transplant Program. All adults (aged > 18 years) with cirrhosis and HCC who were enlisted for orthotopic liver transplantation (OLT) between 2011 and 2020 at the authors' institution and had undergone TACE or TAE for bridging or downstaging were included. Patients with HCC who met the Milan criteria were included in this analysis. Patients who did not meet the Milan criteria were included only after downstaging HCC using LRT to meet the Milan criteria.

The choice of LRT for each HCC nodule was determined by a consensus among LT surgeons, hepatologists, and interventional radiologists. Because RFA is not available in the Brazilian public health system, PEI was preferred for lesions ≤ 3 cm in size and accessible *via* percutaneous ultrasound-guided liver puncture. For tumors > 3 cm in size, TACE or TAE were preferred. Until 2013, TAE was the only modality of embolization available in the Brazilian public health system[16]. Since then, TACE is preferred over TAE. However, even after 2013, some patients underwent TAE because of contraindications to doxorubicin or unavailability of the drug. For some patients with more than one tumor, PEI was performed in addition to TACE or TAE, either in the same treatment session or in different sessions. Patients who underwent PEI only or RFA were not included in this study.

TACE and TAE were performed by one of the two experienced interventional radiologists (Scaffaro LA and Farenzena M) *via* the femoral route under sedation. A 5-F Cobra or Mikaelson catheter was used to achieve selective catheterization and perform an arteriogram of the celiac trunk and superior mesenteric artery. The tumor feeding artery was selectively catheterized using a 2.8-F microcatheter (Progreat; Terumo). For each TACE session, doxorubicin-lipiodol emulsion followed by polyvinyl alcohol (PVA) or microspheres with particle size 100 μm–300 μm were infused. For TAE, only PVA or microspheres with particle size 100 μm–300 μm were infused without the addition of a chemotherapeutic agent. PEI was also performed by one of the same two experienced interventional radiologists under computed tomography (CT) or ultrasound guidance. The tumor was punctured percutaneously using a 20-gauge needle under sedation.

Follow-up imaging [contrast-enhanced CT or magnetic resonance imaging (MRI)] was performed 6 wk–8 wk after each procedure. The need for subsequent therapy was decided on the basis of residual contrast enhancement in the lesion region, which indicated the presence of residual tumor. The imaging follow-up protocol remained the same throughout the study period.

Contrast-enhanced CT or MRI was used to characterize preprocedural disease extent, including the size and number of lesions. Because 74% of LIRADS 4 lesions and 94% of LIRADS 5 lesions are HCCs[17], both were considered as HCC tumors. Biopsy of the lesions was not routinely performed. Based on the tumor size and number of lesions, tumor burden was classified according to the Barcelona Liver Clinic staging system[5]. The Model for End-Stage Liver Disease (MELD) score was calculated as described in the study by Malinchoc *et al*[18]. Preprocedural alpha-fetoprotein (AFP) level was defined as the AFP level immediately before the first LRT. The following patient demographic data were collected: Age, sex, cirrhosis etiology, calculated MELD score, preprocedural AFP level, number of lesions, diameter of the largest tumor, and number of procedures.

According to the LRT chosen, the study patients were divided into four groups: Only TAE, only TACE, TAE + PEI and TACE + PEI. The primary study outcome was waitlist dropout due to tumor progression beyond the limits of the Milan criteria. The secondary outcomes were as follows: (1) Pathological response; (2) side effects of LRT, as graded by the Clavien–Dindo classification[19]; and (3) post-transplant HCC recurrence, as evaluated by post-transplant recurrence-free survival. Patients were followed until their death, waitlist dropout, or the end of the study on June 30, 2023.

For the main outcome measure (waitlist dropout), the date of the first LRT session of each patient enlisted for LT was defined as day zero of the follow-up. Dropout due to tumor progression was considered an event. Time to dropout due to tumor progression was defined as the number of days between the first LRT and the dropout date. The dropout rate was analyzed using the Kaplan–Meier method in a time-to-event manner. Patients who underwent LT or dropped out due to any cause other than tumor progression (*e.g.*, clinical or psychosocial dropout) were excluded on the transplant or dropout day, respectively.

For the evaluation of post-transplant recurrence-free survival in a subset of the cohort's patients who underwent LT, the transplant day was defined as day zero of the follow-up. The analysis of post-transplant recurrence-free survival included HCC recurrence or death due to any cause as the events. Patients lost to follow-up were censored.

The pathological response and vascular invasion by the tumor were assessed by a dedicated liver pathologist. Complete or near-complete pathological response was defined as 90% tumor necrosis on histopathological examination of the explanted liver of patients who underwent OLT.

Categorical variables were compared using the Fisher's exact test. The normality of the continuous variables was estimated using the Shapiro–Wilk test. Continuous variables were analyzed using the Mann–Whitney test or Student's t-test as appropriate. Time-to-event data (time to dropout due to tumor progression and recurrence-free survival) were estimated using the Kaplan–Meier method and compared using the log-rank test. For all the analyses pertaining to waitlist dropout, follow-up day zero in patients whose HCC was downstaged to meet the Milan criteria was set to when they were enlisted. All comparisons were two-sided with a level of significance of 0.05. All analyses were performed using R for microwave-assisted, continuous-flow organic synthesis (version 4.0.3; R Foundation for Statistical Computing, Vienna, Austria)[20]. The statistical methods used in the study were reviewed by a biomedical statistician from HCPA.

RESULTS

From 2011 to 2021, 183 patients with HCC were placed on the LT waiting list. Of these, 80 patients were excluded for the following reasons: No LRT was performed (n = 17), RFA was performed (n = 6), and PEI alone was performed (n = 57). One hundred and three patients with HCC who were enlisted for LT underwent LRT with TAE or TACE. Of these, 65 (63.1%) patients underwent TACE and 38 (36.9%) underwent TAE. There was no statistically significant difference between the groups in terms of patient, tumor, and treatment characteristics (Table 1).

Dropout due to tumor progression

Dropout due to tumor progression occurred in 7 (17.5%), 5 (20%), 2 (9.5%), and 1 (5.9%) patients who underwent only TACE (n = 40), TACE + PEI (n = 20), only TAE (n = 21), and TAE + PEI (n = 17), respectively (Table 2). The difference among the four treatment groups was not statistically significant (P = 0.565). The overall dropout due to tumor progression was 12 (18.5%) and 3 (7.9%) in the TACE (only TACE and TACE + PEI, n = 65) and TAE (only TAE and TAE + PEI, n = 38) groups, respectively (P = 0.162). In a time-to-event analysis using the Kaplan–Meier method (Figure 1A), no significant difference in dropout rates was detected between the TACE and TAE groups (P log-rank test = 0.29).

Adverse events

Of the 65 patients who underwent TACE, adverse events occurred in 8 (12.3%) patients, of which 7 were classified as Clavien–Dindo Grade 2 or lower. The remaining patient died following a combined TACE + PEI procedure due to hemorrhage. Of the 38 patients who underwent TAE, adverse events occurred in 2 (5.3%) patients. Both events were classified as Clavien–Dindo Grade 1. The difference between adverse events in the TACE and TAE groups was not statistically significant (P = 0.316).

Post-transplant outcomes

The demographic and treatment characteristics of patients who underwent OLT are listed in Table 3. In total, 77 (74.8%) of the 103 included patients underwent LT. Forty-eight (73.8%) of the 65 patients in the TACE group and 29 (76.3%) of the 38 patients in the TAE group underwent LT (P = 0.818). No statistically significant difference in the study variables was detected between the groups.

After transplantation, HCC recurred in 9 (18.8%) of the 48 patients in the TACE group and 4 (13.8%) of the 29 patients in the TAE group (P = 0.756). The recurrence-free survival curves are shown in Figure 1B. No statistical difference was detected in the recurrence-free survival between TACE and TAE (P log-rank test = 0.71).

DISCUSSION

The present study evaluated the outcomes of TACE and TAE in patients with HCC on the LT waitlist. Neither the proportion of patients who underwent LT nor the dropout rate due to tumor progression beyond the limits of the Milan criteria differed between the groups. Moreover, in patients who later underwent LT, recurrence-free survival was similar regardless of the bridging therapy employed. Adverse events were not statistically different between the TAE and TACE groups. However, a higher incidence of adverse events was observed in the TACE group (12.3%) than in the TAE group (5.3%).

Whether the addition of a chemotherapeutic agent to TAE has a significant clinical effect has been the subject of several studies. The first RCT on this issue suggested that TACE was superior to TAE in patients with unresectable HCC, a patient group that is different to the one analyzed in the present study[21]. However, that trial was discontinued because preliminary results demonstrated the benefit of TACE over no treatment, precluding a more precise comparison between TACE and TAE. Since then, three RCTs have failed to demonstrate improved overall or progression-free survival of TACE over TAE in patients with HCC who are unsuitable for curative treatment[22-24]. Additionally, two recent meta-analyses of RCTs suggested that there were no benefits of TACE over TAE in patients with unresectable HCC[14,25].

Only one case-control study by Kluger *et al*[15] directly compared TACE with TAE in patients with HCC on the LT waitlist. Similar to our findings that study also demonstrated no difference in dropout rates, complete pathological response, and recurrence-free survival between TAE and TACE as a bridging therapy to LT. Tsochatzis *et al*[26] demonstrated that either TACE or TAE improved post-transplant outcomes in comparison to no pre-transplant treatment. Most patients in the study by Tsochatzis *et al*[26] underwent TAE instead of TACE. Although a direct comparison between TACE and TAE regarding clinical outcomes was not performed, there was no difference in terms of histological response in the explanted livers. Another study found a higher rate of histological necrosis in patients who underwent TACE than in patients who underwent TAE[27]. However, that study did not report the dropout rate. Furthermore, its small sample size (n = 16) precludes a conclusion regarding post-transplant outcomes.

In our study, the rate of complete or near-complete tumor necrosis was relatively low in both groups (TACE 14.6% *vs* TAE 31%). This may be attributed to the fact that our pathology report only considered complete tumor necrosis when no viable tumor was observed in the entire liver explant. The rate of complete or near-complete tumor necrosis was similar between the TACE and TAE groups, with a trend toward a higher rate in the TAE group. A similar trend in complete pathological response was observed in the study by Kluger *et al*[15] (TAE 36% *vs* TAE 26%). Conversely, Nicolini *et al*[27] found more tumor necrosis in patients who underwent TACE than in those who underwent TAE (77% *vs* 27.2%). Given the conflicting results, it remains controversial whether there is a difference between TACE and TAE in terms of complete tumor necrosis.

Table 1 Patient, tumor, and treatment characteristics, *n* (%)

Variables	TACE	TAE	*P* value
Number	65	38	
Age (yr), median (IQR)	60 (55, 65)	61.5 (55, 64)	0.962
Male sex	40 (61.5)	23 (60.5)	> 0.99
Diagnosis			0.889
HCV	51 (78.5)	32 (84.2)	
HBV	4 (6.2)	2 (5.3)	
Alcohol	4 (6.2)	3 (7.9)	
NASH	4 (6.2)	1 (2.6)	
Other	2 (3.1)	0	
Calculated MELD score, median (IQR)	9 (8, 12)	11 (9, 12)	0.122
Preprocedural AFP level, median (IQR)	22.5 (5.6, 68.3)	15.75 (6.8, 94.5)	0.992
Number of lesions			0.652
1	37 (56.9)	22 (57.9)	
2	18 (27.7)	11 (28.9)	
3	10 (15.4)	4 (10.5)	
≥ 4	0	1 (2.6)	
Largest tumor diameter, median (IQR)	3 (2.4, 3.8)	3.3 (2.4, 3.9)	0.634
Milan-out	10 (15.4)	8 (21.1)	0.591
Use of PEI	25 (38.5)	17 (44.7)	0.541
Number of procedures, median (IQR)	2 (1, 3)	2 (1, 2.75)	0.914

Milan-out refers to patients beyond the limits of the Milan criteria. TACE: Transarterial chemoembolization; TAE: Transarterial embolization; HCV: Hepatitis-C virus; HBV: Hepatitis-B virus; MELD: Model for End-Stage Liver Disease; AFP: Alpha-feto protein; PEI: Percutaneous ethanol injection; IQR: Interquartile range; NASH: Non-alcoholic steatohepatitis.

Table 2 Dropout due to tumor progression in the treatment groups, *n* (%)

	Dropout due to tumor progression		
		No	Yes
TACE	TACE only	33 (82.5)	7 (17.5)
	TACE + PEI	20 (80)	5 (20)
	Overall TACE	53 (81.5)	12 (18.5)
TAE	TAE only	19 (90.5)	2 (9.5)
	TAE + PEI	16 (94.1)	1 (5.9)
	Overall TAE	35 (92.1)	3 (7.9)

Fisher's exact test for comparison of the four groups [transarterial chemoembolization (TACE) only, TACE + percutaneous ethanol injection (PEI), transarterial embolization (TAE) only, and TAE + PEI]: $P = 0.565$. Fisher's exact test for comparison of the two groups (Overall TACE *vs* overall TAE): $P = 0.162$. TACE: Transarterial chemoembolization; TAE: Transarterial embolization; PEI: Percutaneous ethanol injection.

In this study, the rate of adverse events, which included one death, was higher in the TACE group than in the TAE group (prevalence, 12.3% *vs* 5.3%). This difference was not statistically significant, which may be attributable to the small sample size (type II error). Two meta-analyses found increased toxicity after TACE than after TAE[14,27]. In a study evaluating the use of TAE in patients on the LT waitlist, the incidence of major complications (Clavien–Dindo Grade 3 or higher) was considerably low (2.6%)[28]. In our study, the two adverse events (5.3%) in the TAE group were minor (Clavien–Dindo Grade 1).

Table 3 Patient, tumor, and treatment characteristics of patients who underwent liver transplantation, *n* (%)

Variables	TACE	TAE	*P* value
Number	48	29	
Age (yr), median (IQR)	60.5 (55.75, 65.25)	62 (53, 63)	0.458
Male sex	30 (62.5)	19 (65.5)	0.812
Diagnosis			0.385
HCV	37 (77.1)	25 (86.2)	
HBV	4 (8.3)	1 (3.4)	
Alcohol	3 (6.2)	3 (10.3)	
NASH	4 (8.3)	0	
Other	0	0	
Calculated MELD score, median (IQR)	9 (8, 11.25)	11 (9, 12)	0.109
Pretransplant AFP, median (IQR)	11.7 (4.77, 46)	9.1 (4.4, 31.95)	0.668
Number of lesions			0.704
1	29 (60.4)	16 (55.2)	
2	12 (25)	8 (27.6)	
3	7 (14.6)	4 (13.8)	
≥ 4	0	1 (3.4)	
Largest tumor diameter, median (IQR)	2.8 (2.3, 3.8)	3.3 (2.5, 3.6)	0.333
Milan-out	5 (10.4)	8 (27.6)	0.064
Use of PEI	19 (39.6)	15 (51.7)	0.348
Complete pathological response	7 (14.6)	9 (31)	0.145
Vascular invasion	8 (16.7)	4 (13.8)	> 0.99

Milan-out refers to patients beyond the limits of the Milan criteria. TACE: Transarterial chemoembolization; TAE: Transarterial embolization; HCV: Hepatitis-C virus; HBV: Hepatitis-B virus; MELD: Model for End-Stage Liver Disease; PEI: Percutaneous ethanol injection; IQR: Interquartile range; NASH: Non-alcoholic steatohepatitis.

The ultimate goals of HCC bridging therapies are to prevent dropout due to tumor progression beyond the limits of the Milan criteria and to ensure long-term recurrence-free survival after LT. As there seems to be no superiority of TACE over TAE regarding those clinical outcomes, evidence of TACE's superiority over TAE in this group of patients is lacking. Given the tendency of increased toxicity and the indisputable higher cost of TACE when compared with TAE, we believe that our study findings, in conjunction with those of the study by Kluger *et al*[15], should encourage a more liberal use of TAE for bridging therapy to LT in patients with HCC.

Our study has some limitations. It was a retrospective study. However, the data were extracted from a prospectively filled database. In addition, most patients underwent PEI in addition to TACE or TAE, which might have confounded the interpretation of the study results. Nevertheless, the proportion of patients who underwent PEI was similar between the groups. Several patients with HCC on the LT waitlist have more than one tumor with different features that render them suitable for different types of LRTs. Thus, we believe that the addition of patients who underwent an ablation procedure makes our sample more similar to "real-life" patients, thereby improving the external validity of the study.

CONCLUSION

In conclusion, the use of TAE in patients with HCC who are on the LT waitlist produced similar outcomes as the use TACE in terms of dropout rate, transplant rate, pathological necrosis, and post-transplant recurrence-free survival. Our study further reinforces that TACE is not superior to TAE for the treatment of HCC. Thus, TAE may be employed in scenarios in which the use of chemotherapeutic agents is contraindicated, such as intolerance to antineoplastic drugs, and in frail patients in whom its concomitant use with PEI or RFA is required.

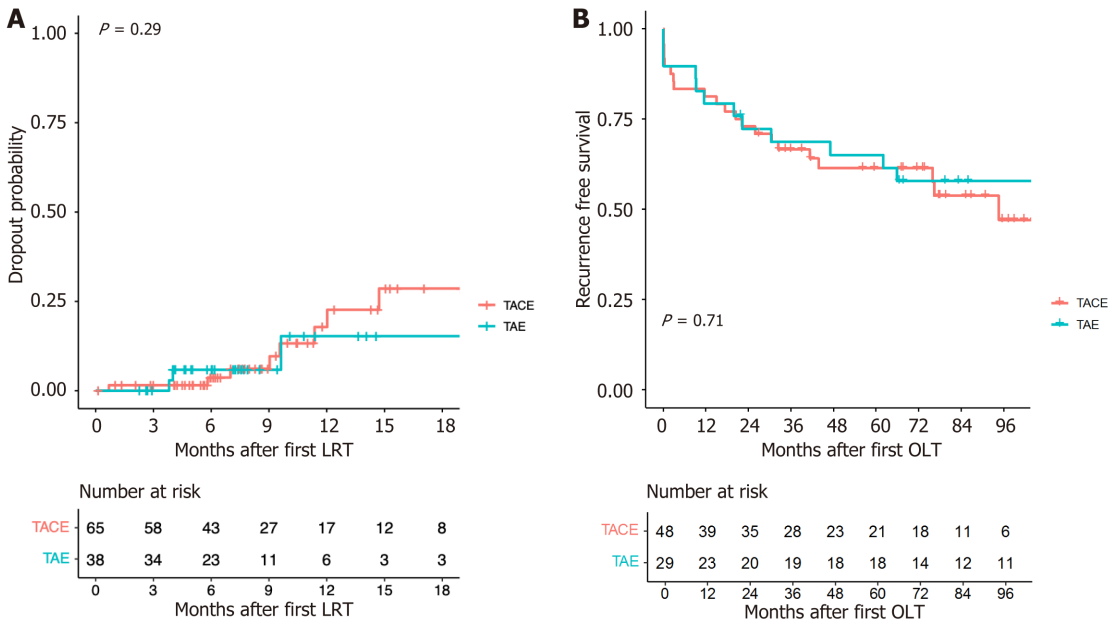

Figure 1 Kaplan–Meier analysis. A: Waitlist dropout due to tumor progression according to locoregional therapy performed. Log-rank test for the comparison between the two groups: *P* = 0.29; B: Post-transplant recurrence-free survival according to locoregional therapy performed. Log-rank test for the comparison between the two groups: *P* log-rank test = 0.71. TACE: Transarterial chemoembolization; TAE: Transarterial embolization; LRT: Locoregional therapy; OLT: Orthotopic liver transplantation.

FOOTNOTES

Author contributions: Lazzarotto-da-Silva G and Chedid MF participated in the research design, data collection, data analysis, and writing of the manuscript; Scaffaro LA, Farenzena M, Feier FH, Grezzana-Filho TJM, Rodrigues PD, de Araujo A, Alvares-da-Silva MR, Marchiori RC, and Kruel CRP participated in the research design and revision of the final version of the manuscript; Prediger L and Silva RK participated in data collection and writing of the manuscript.

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ORIGINAL ARTICLE

Retrospective Study

Portal vein arterialization in 25 liver transplant recipients: A Latin American single-center experience

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Abstract

BACKGROUND

Portal vein arterialization (PVA) has been used in liver transplantation (LT) to maximize oxygen delivery when arterial circulation is compromised or has been used as an alternative reperfusion technique for complex portal vein thrombosis (PVT). The effect of PVA on portal perfusion and primary graft dysfunction (PGD) has not been assessed.

AIM

To examine the outcomes of patients who required PVA in correlation with their LT procedure.

METHODS

All patients receiving PVA and LT at the Fundacion Santa Fe de Bogota between 2011 and 2022 were analyzed. To account for the time-sensitive effects of graft perfusion, patients were classified into two groups: prereperfusion (pre-PVA), if the arterioportal anastomosis was performed before graft revascularization, and postreperfusion (post-PVA), if PVA was performed afterward. The pre-PVA rationale contemplated poor portal hemodynamics, severe vascular steal, or PVT. Post-PVA was considered if graft hypoperfusion became evident. Conservative interventions were attempted before PVA.

RESULTS
A total of 25 cases were identified: 15 before and 10 after graft reperfusion. Pre-PVA patients were more affected by diabetes, decompensated cirrhosis, impaired portal vein (PV) hemodynamics, and PVT. PGD was less common after pre-PVA (20.0% *vs* 60.0%) (P = 0.041). Those who developed PGD had a smaller increase in PV velocity (25.00 cm/s *vs* 73.42 cm/s) (P = 0.036) and flow (1.31 L/min *vs* 3.34 L/min) (P = 0.136) after arterialization. Nine patients required PVA closure (median time: 62 d). Pre-PVA and non-PGD cases had better survival rates than their counterparts (56.09 months *vs* 22.77 months and 54.15 months *vs* 31.91 months, respectively).

CONCLUSION
This is the largest report presenting PVA in LT. Results suggest that pre-PVA provides better graft perfusion than post-PVA. Graft hyperperfusion could play a protective role against PGD.

Key Words: Liver transplantation; Portal vein arterialization; Arteriovenous anastomoses; Portal hypertension; Portal vein thrombosis; Spontaneous portosystemic shunts; Vascular steal phenomenon; Primary graft dysfunction; Early allograft dysfunction

Core Tip: Guaranteeing adequate graft perfusion is essential to obtain optimal outcomes after liver transplantation (LT). This retrospective single-center study analyzed 25 cases of portal vein arterialization (PVA) for portal flow optimization in LT. To account for the time-sensitive effect, cases were classified into two groups: prereperfusion (pre-PVA) if the arterioportal anastomosis was performed before graft revascularization and postreperfusion (post-PVA) if PVA was performed afterward. We found that pre-PVA yields better results than post-PVA and that hyperperfusion could play a protective role against graft dysfunction. Currently, this is the largest case series studying PVA during LT.

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INTRODUCTION

Portal vein arterialization (PVA) is a scarcely reported procedure in hepatobiliary and liver transplantation (LT) surgeries. It is considered a salvage intervention in critical scenarios where portal or arterial circulation has been compromised. PVA can artificially provide portal circulation with an arterial input to maximize blood flow and oxygen delivery to hepatic cells[1,2]. During both LT and hepatobiliary surgeries, it has been described as an alternative to guarantee biliary perfusion and prevent acute hepatic failure when the hepatic artery is injured, thrombosed or needs to be resected to obtain negative tumor margins[1,2]. In LT, it has been proposed as a bridge therapy for retransplantation when graft loss is unavoidable[1].

Other authors have used PVA to manage complex portal vein thrombosis (PVT) during LT when alternative methods for portal vein (PV) reconstruction are unsuccessful or unfeasible (*e.g.*, anastomosing the donor's PV to spontaneous portosystemic shunts (SPSS), renoportal anastomosis, and portocaval transposition)[3].

Previous reports have not assessed the potential role of PVA in portal flow optimization. Adequate perioperative graft perfusion is critical to reduce the risk of graft dysfunction in LT recipients[4,5]. Primary graft dysfunction (PGD), also known as early allograft dysfunction, is one of the most concerning complications after LT. PGD develops within the first days after graft reperfusion, negatively affecting graft and patient survival[4,6]. It is considered a consequence of graft intolerance in the process of procurement, transportation, and reimplantation[5]. When other interventions are unsuccessful, severe graft injury is established, ultimately leading to primary nonfunctioning (PNF), an emergency in which graft loss is unavoidable and retransplantation is the only life-saving intervention[5-7].

Here, we present our experience using PVA in LT as an alternative to optimizing graft perfusion, particularly when other interventions have failed to provide adequate portal blood flow in fragile recipients or risky graft conditions[1,3,8-12].

MATERIALS AND METHODS

Study population

LT surgeries performed at the Fundacion Santa Fe de Bogota between January 2011 and December 2022 were retrospectively reviewed. Patients who received a PVA were considered eligible. Split and auxiliary transplants were excluded. All patients received grafts from donors deceased after brain death.

Prereperfusion vs postreperfusion PVA

To assess the impact of delivering high-oxygen and high-pressure blood flow before or after graft reperfusion, we classified patients into two groups. Prereperfusion PVA (pre-PVA) was defined as an arterioportal anastomosis before graft revascularization, whereas postreperfusion PVA (post-PVA) was performed after routine portal flow was reestablished, either during the initial procedure or during a second surgical intervention.

Each case was reviewed separately. Patients considered for pre-PVA included those with very low pretransplant portal velocity (PVEL) or flow (PFLOW), those with severe vascular steal phenomenon secondary to SPSS, or those with PVT. Before considering arterialization, portal flow was optimized by surgically ligating accessible SPSS or attempting portal thrombectomy/thromboendovenectomy, if applicable. If the portal flow was considered to remain insufficient, the surgeon proceeded with pre-PVA.

Post-PVA was considered after restoring portal flow if signs of graft hypoperfusion were evident (*e.g.*, mottling, pale appearance, and uneven graft perfusion) or if PVEL or PFLOW remained suboptimal following more conservative interventions, such as SPSS ligation.

Surgical technique

Arterialization was performed either by repositioning the distal end of the recipient's visceral artery (*e.g.*, accessory mesenteric artery or splenic artery) or by anastomosing an allogenic iliac artery graft directly to the aorta. No synthetic vascular grafts were used. For pre-PVA, the arterial vessel was first attached to the recipient's PV, and then, a termino-lateral anastomosis with the graft's PV was created (Figure 1A-E). The same technique was used for post-PVA.

Variables and definitions

Recipient characteristics included liver disease etiology and severity assessed using the Child–Pugh (CP) and model for end stage liver disease (MELD) scores. Hepatic encephalopathy (HE) and ascites were graded using the West Heaven and International Ascites Club Scales, respectively. SPSS were identified using CT or MR imaging. Doppler ultrasound was used to estimate PVEL and PFLOW at the hepatic hilum. PVT was graded on the basis of the intraoperative findings as described by Yerdel *et al*[13]. Available donor characteristics were recorded. Surgical variables, including surgical times and blood products, were also collected.

Transplant-specific 30-d complications and all PVA-related complications were collected. The primary outcome of the study was the development of PGD. It was defined as an AST > 2000 IU/L within the second and seventh day post-LT, and prothrombin time > 16 s (INR > 1.5) or bilirubin > 10 mg/dL on the seventh day post-LT[4,6].

The US OPTN 9.1 policy for organ allocation and the Colombian national organ transplantation policy define PNF as an AST > 3000 UI/L and at least one of the following: arterial pH ≤ 7.30, venous pH ≤ 7.25, or lactate ≥ 4.0 mmol/L[14,15].

Statistical analysis

Categorical variables were presented as absolute values (%) and compared using Pearson's chi-square or Fisher's exact tests. Continuous variables were assessed for normality using the Shapiro–Wilk test, described as the mean (min–max; SD) or median (95%CI; IQR), and compared using Student's *T* or Mann–Whitney's *U* tests. Kaplan–Meier's method was used for survival analyses, and comparison between groups was performed using the logarithmic range test. Statistical significance was set at *P*-value < 0,05. IBM-SPSS v20® software was used for statistical analysis.

RESULTS

A total of 409 patients underwent LT during the study period. Twenty-five of them received PVA. The mean follow-up period was 76.6 (12.23–150.57) months for arterialized recipients. Fifteen patients required pre-PVA, and 10 required post-PVA.

Recipient characteristics

The basic demographic and pretransplant clinical characteristics are summarized in Table 1. Autoimmune diseases were the main cause of liver disease, followed by alcoholic cirrhosis and NASH. No significant etiological differences were recorded between Pre-PVA and Post-PVA groups. All patients with previous PNF included in the study met the criteria for pre-PVA at their second transplant. PNF was explained by refractory graft hypoperfusion.

Pre-PVA patients had a less favorable CP classification (B or C) (100.0% *vs* 70.0%, *P* = 0.024) but not the MELD score (≥ 20) (26.7% *vs* 50.0%, *P* = 0.234). Liver disease complications were homogeneously distributed in both groups. Diabetes mellitus was common in those who required pre-PVA (46.7% *vs* 0.0%) (*P* = 0.011). A total of 16 of 25 patients had PVT at the time of surgery; 3 were identified intraoperatively. PVT was also more frequent in pre-PVA patients (*P* = 0.009) (Table 2). Grade II and III PVT predominated in the cohort, whereas only one patient presented with grade IV PVT. The

Table 1 Recipient characteristics according to the timing of portal vein arterialization

Basic characteristics	Pre-reperfusion PVA	%	Post-reperfusion PVA	%	Overall	%	*P* value
n	15	60.0	10	40.0	25	100.0	
Sex (male)	8	53.3	5	50.0	13	52.0	0.870
Age (yr)	54.06 [27.0-71.0; 12.1][1]		53.20 [10.0-78.0; 20.3][1]		53.72 [10.0-78.0; 15.5][1]		0.895
Body composition							0.708
Underweight	1	6.7	1	10.0	2	8.0	
Normal	6	40.0	6	60.0	12	48.0	
Overweight	6	40.0	2	20.0	8	32.0	
Obesity	2	13.3	1	10.0	3	12.0	
Liver disease							
Etiology							0.459
Congenital biliary atresia	0	0.0	1	10.0	1	4.0	
Non-alcoholic steatohepatitis	3	20.0	2	20.0	5	20.0	
Alcoholic	3	20.0	2	20.0	5	20.0	
Autoimmunity[2]	4	26.7	3	30.0	7	28.0	
Hepatitis C	2	13.3	0	0.0	2	8.0	
Hepatocellular carcinoma	0	0.0	1	10.0	1	4.0	
Hemochromatosis	1	6.7	1	10.0	2	8.0	
Cryptogenic	1	6.7	0	0.0	1	4.0	
Secondary biliary cirrhosis	1	6.7	0	0.0	1	4.0	
Prior primary non-functioning	3	20.0	0	0.0	3	12.0	0.132
CHILD Pugh Score B/C	15	100.0	7	70.0	22	88.0	0.024
MELD Score ≥ 20 points	4	26.7	5	50.0	9	36.0	0.234
Primary hepatic neoplasia	1	6.7	5	50.0	6	24.0	0.013
Hepatic encephalopathy	7	46.7	6	60.0	13	52.0	0.513
Ascites	13	86.7	6	60.0	19	76.0	0.126
Hypertensive gastropathy	7	46.7	6	60.0	13	52.0	0.513
Upper gastrointestinal bleeding	8	53.3	2	20.0	10	40.0	0.096
Hepatorenal syndrome	2	13.3	1	10.0	3	12.0	0.802
Comorbidities							
Type 2 diabetes mellitus	7	46.67	0	0.0	7	28.0	0.011
Hyperlipidemia	1	6.7	3	30.0	4	16.0	0.119
Arterial hypertension	4	26.7	2	20.0	6	24.0	0.702
Cardiac failure	1	6.7	1	10.0	2	8.0	0.840
Hemodynamic support	2	13.3	1	10.0	3	12.0	0.840
Chronic renal insufficiency	1	6.7	0	0.0	1	4.0	0.535
Acute kidney injury	3	20.0	1	10.0	4	16.0	0.535
Malnourishment	3	20.0	5	50.0	8	32.0	0.124
Decreased bone mineral density	7	46.7	5	50.0	12	48.0	0.427
Pulmonary disease/impairment	9	60.0	0	0.0	9	36.0	0.095
Hypothyroidism	4	26.7	1	10.0	5	20.0	0.381

[1]Continuous variable with normal distribution [mean (min-max; SD)]. It was compared using Student's *T* test.
[2]Autoimmune causes of liver disease include primary biliary cirrhosis, autoimmune hepatitis and overlap syndrome. PVA: Portal vein arterialization; MELD: Model for end-stage liver disease.

Table 2 Preoperative portosystemic circulation and portal doppler ultrasound parameters according to timing of portal vein arterialization

	Pre-reperfusion PVA	%	Post-reperfusion PVA	%	Overall	%	*P* value
n	15	60.0	10	40.0	25	100.0	
Collateral portal circulation	13	87.0	7	70.0	20	80.0	0.358
Splenomegaly	12	80.0	6	60.0	18	72.0	0.378
Perigastric/periesophagic varices	7	47.0	5	50.0	12	48.0	1.000
Umbilical vein recanalization	6	40.0	2	20.0	8	32.0	0.402
Paracaval portosystemic shunt	1	7.0	0	0.0	1	4.0	1.000
Epiploic shunts	2	13.0	1	10.0	3	12.0	1.000
Mesenteric varices	3	20.0	0	0.0	3	12.0	0.250
Splenorenal shunts	3	20.0	3	30.0	6	24.0	0.653
Portal vein thrombosis[2]	13	86.6	3	30.0	16	64.0	0.009
Grade I	3	20.0	0	0.0	3	12.0	
Grade II	5	33.3	3	30.0	8	32.0	
Grade III	4	26.7	0	0.0	4	15.0	
Grade IV	1	7.7	0	0.0	1	4.0	
Preoperative doppler ultrasound							
Portal vein velocity (cm/s)[1]	11.60 [8.30-18.86; 10.8]		16.00 [13.10-23.20; 7.6]		14.00 [11.7-19.0; 10.5]		0.048
Portal vein flow (L/min)[1]	0.59 [0.40-0.70; 0.23]		0.68 [0.40-0.94; 0.80]		0.59 [0.47-0.73; 0.56]		0.367

[1]These variables do not have normal distribution [median (p5-95; IQR)]. They were compared using Mann-Whitney's *U* test.
[2]Portal vein thrombosis was classified according to Yerdel's classification. PVA: Portal vein arterialization.

latter received pre-PVA (Table 2). NASH (25.0% *vs* 11.1%) and alcoholic cirrhosis (31.3% *vs* 0.0%) were frequent in recipients presenting with PVT (P = 0.041). Decompensated liver disease (CP B/C) was common in those with PVT (100.0% *vs* 66.7%) (P = 0.037) (Supplementary Table 1). All recipients with diabetes had PVT, and 43.8% of those with PVT had diabetes (P = 0.027) (Supplementary Table 1). All patients who required retransplantation had PVT before the first transplant. No recipient characteristic was associated with the development of PGD.

Table 2 shows how portosystemic circulation was established and its repercussions on preoperative portal hemodynamics. Although the distribution of these collaterals was relatively homogeneous among groups, a more intense vascular steal phenomenon was evidenced in pre-PVA patients, as demonstrated by the decreased mean PVEL (11.60 cm/s *vs* 16.00 cm/s) (P = 0.048) and PFLOW (0.59 L/min *vs* 0.68 L/min) (P = 0.367).

Donor characteristics

Limited data on donor characteristics could be collected. The mean donor age was 34.00 years (16.0–56.0; 14.5), and most patients were males (64.00%). Here, 80.00% had a normal BMI. The most common cause of brain death was traumatic brain injury (64.00%). No donor characteristic was related to PGD, but PNF was less frequent in grafts from male donors (40.00% *vs* 70.00%) (P = 0.034).

Transplant surgery

Intraoperative LT variables were presented according to PVA timing (Table 3), SPSS ligation, preoperative PVT, and PGD development (Supplementary Table 2). The pre-PVA group had longer median transplant surgical times (8.60 h *vs* 5.60 h) (P = 0.004). Other surgical variables were similar in the two groups. Of the 20 cases presenting with severe portosystemic circulation, 10 (50.0%) had accessible SPSS and all of them were surgically ligated. A tendency to longer WIT was found in those who had PVT or SPSS ligation, although these differences were not statistically significant (P = 0.777 and P = 0.276, respectively). A total of 9 of 16 (53,6%) patients with PVT underwent mechanical thrombectomy/thromboendovenectomy before PVA. PVT and the need for SPSS ligation did not affect other intraoperative variables. No surgical variable

Table 3 Surgical variables according to the timing of portal vein arterialization

Intraoperative events	Pre-reperfusion PVA	%	Post-reperfusion PVA	%	Overall	%	*P* value
n	15	60.0	10	40.0	25	100.0	
Surgical time (h)	8.60 [7.7-10.90; 3.9][2]		5.6 [4.2-8.82; 2.8][2]		7.2 [6.8-9.5; 4.30][2]		0.004
Arterialization technique							0.130
Supraceliac graft	7	47.0	1	10.0	8	32.0	
Infrarenal graft	5	33.0	7	70.0	12	48.0	
ARHA	1	7.0	1	10.0	2	8.0	
Splenic artery	0	0.0	1	10.0	1	4.0	
AMA	2	13.0	0	0.0	2	8.0	
Thrombectomy[3]	6	40.0	3	30.0	9	36.0	0.691
CIT (h)	9.87 [4.0-13.8; 2.4][2]		8.81 [4.9-13.7; 2.7][2]		9.4 [4.0-13.8; 1.5][2]		0.322
CIT > 10 h	6	40.0	3	30.0	9	36.0	0.691
WIT (min)	43.33 [22.0-8.0; 13.8][2]		40.50 [24.0-65.0; 12.6][2]		42.2 [22.0-78.0; 12.8][2]		0.6
WIT > 45 (min)	5		3	30.0	8	32.0	1
PRBCs (Units)	12.00 [6.7-18.0; 13.0][1]		4.50 [1.8-12.8; 1][1]		10.0 [6.4-14.2; 12.0][1]		0.160
Plasma (Units)	18.00 [12.2-3.1;15.0][1]		12.00 [8.9-16.5; 8.3][1]		12.0 [12.2-22.1; 13.0][1]		0.414
Cryoprecipitates (Units)	22.00 [14.0-3.6;1][1]		20.00 [7.0-21.4; 20.3][1]		20.0 [13.5-3.0; 17.5][1]		0.103
Platelets (Units)	12.00 [4.6-4.1; 24.0][1]		9.0 [0.0-30.7; 17.0][1]		12.0 [7.6-3.1; 27.0][1]		0.311
PVA after LT	0	0.0	4	40.0	4	16.0	0.170

[1]Continuous variables without normal distribution [median (p5-95; IQR)]. They were compared using Mann-Whitney's *U* test.
[2]Continuous variables with normal distribution [mean (min-max; SD)], they were compared using Student's *T* test.
[3]Whether mechanical thrombectomy or thromboendovenectomy. ARHA: Accessory right hepatic artery; AMA: Accessory mesenteric artery; CIT: Cold ischemia time; WIT: Warm ischemia time; PVA: Portal vein arterialization; LT: Liver transplant; PRBC: Packed red blood cells.

was associated with progression to PGD. No hepatic outflow issues were identified.

Postoperative course

Table 4 and Supplementary Table 3 depict the postoperative variables and complications according to PVA timing and preoperative PVT and SPSS ligation, respectively. They were homogeneously distributed in all categories, except for HE and AKI, which were more common in those who underwent SPSS ligation (70.0% *vs* 20.0%) (P = 0.037) and (60.0% *vs* 20.0%) (P = 0.041), respectively.

The overall PGD incidence was 36.0% (9 cases). It was less common in the pre-PVA group (20.0% *vs* 60.0%) (P = 0.041). Six patients in the post-PVA group developed PGD, and four of them progressed to PNF. In contrast, three patients in the pre-PVA group developed PGD, but only one reached PNF. Three of five PNF cases underwent retransplantation.

Patients with PVT had less PGD (18.8% *vs* 66.7%) (P = 0.031) and PNF (6.3% *vs* 44.4%) (P = 0.040), but those whose SPSS were ligated developed PGD more often (60.0% *vs* 20.0%) (P = 0.041).

Nine patients required PVA closure (eight endovascularly and one surgically) secondary to: ascites (two cases), gastroesophageal varices (four cases), upper gastrointestinal bleeding (UGIB) (two cases), hypertensive gastropathy (one case), and right-heart overload (two cases). No patient developed HAT after surgery. The median time for PVA closure after LT was 62 d (28.37–236.52).

PV hemodynamics

Low pre-LT median PVEL (11.60 cm/s *vs* 16.00 cm/s) (P = 0.048) was associated with pre-PVA. PFLOW (0.59 L/min *vs* 0.68 L/min) (P = 0.367) was also decreased, although the difference was not statistically significant (Table 2).

A comparison between preoperative and postoperative PVEL/PFLOW according to the presence of PVT, SPSS, and PGD is found in Table 5. PVT was associated with slower preoperative PVEL (11.80 *vs* 17.00 cm/s) (P = 0.037) and PFLOW (0.55 L/min *vs* 0.87 L/min) (P = 0.187), whereas SPSS mainly caused decreased preoperative PFLOW (0.51 L/min *vs* 0.90 L/min) (P = 0.002). PVA led to a median increase of 52.70 cm/s in PVEL (P < 0.001) and 3.21 L/min in PFLOW (P < 0.001). Notably, those who developed PGD had a smaller increase in PVEL after arterialization (25.00 cm/s

Table 4 30-d Postoperative outcomes according portal vein arterialization timing

Postoperative events	Pre-reperfusion PVA	%	Post-reperfusion PVA	%	Overall	%	*P* value
n	15	60.0	10	40.0	25	100.0	
ICU LOS (d)[1]	3.00 [0.0-15.1; 4.0]		3.50 [1.6-4.7; 4.2]		3.00 [1.0-10.6; 4.0]		0.935
LOS (d)[1]	10.00 [0.0-48.0; 17.0]		10.50 [5.5-17.8; 11.7]		10.00 [3.8-33.0; 13.5]		0.849
Hemoperitoneum	1	6.7	1	10.0	2	8.0	1.000
Bowel resection	3	20.0	0	0.0	3	12.0	0.250
Upper gastrointestinal bleeding	3	20.0	3	30.0	6	24.0	0.653
Infection	7	46.7	7	70.0	14	56.0	0.414
Ascites	3	20.0	3	30.0	6	24.0	0.653
Pleural effusion	3	20.0	2	20.0	5	20.0	1.000
Pulmonary complications	6	40.0	2	20.0	8	32.0	0.402
Encephalopathy	4	26.7	6	60.0	10	40.0	0.122
Postoperative atrial fibrillation	1	6.7	1	10.0	2	8.0	1.000
Congestive cardiac failure	1	6.7	1	10.0	2	8.0	1.000
Acute kidney injury	7	46.7	6	60.0	13	52.0	0.688
Hemodialysis requirement	3	20.0	3	30.0	6	24.0	0.653
Reintervention	4	26.7	3	30.0	7	28.0	1.000
Postoperative PVA closure	6	40.0	3	30.0	9	36.0	0.691
PGD	3	20.0	6	60.0	9	36.0	0.041
PNF	1	6.7	4	40.0	5	20.0	0.121
Retransplantation	1	6.7	2	20.0	3	12.0	0.543
30-d mortality	4	26.7	5	50.0	9	36.0	0.397

[1]Continuous variables without normal distribution (median [p5-95; IQR]); they were compared using Mann-Whitney's *U* test. ICU: Intensive care unit; PVA: Portal vein arterialization, LOS: length of stay, PGD: Primary graft dysfunction; PNF: Primary non-functioning.

vs 73.42 cm/s) (P = 0.036) and PFLOW (1.31 L/min *vs* 3.34 L/min) (P = 0.136) compared with those who did not develop PGD.

Survival

Pre-PVA patients tended to have better mean survival compared with those with post-PVA (56.09 months *vs* 22.77 months) (P = 0.256). As expected, recipients who developed PGD had worse survival than those who did not (31.91 months *vs* 54.15 months) (P = 0.108).

Nine patients died within the first month of transplantation (Table 5). Seven deaths were related to PGD. Of these, five occurred in the post-PVA group and two in the pre-PVA group. The other two early deaths occurred in the pre-PVA group but were unrelated to PGD. One was attributed to complications after an intraoperative cardiac arrest, and the other to renal vein thrombosis during a liver–kidney transplant. Notably, 30-d mortality was increased in those with PVT (P = 0.031), as shown in Supplementary Table 3. No patient died secondary to PVA-related complications.

Late deaths were secondary to a lymphoproliferative disease at 6 and 12 months in 2 cases, mesenteric venous thrombosis after 7 months, COVID-19 at 12 months, sepsis after 3 years, and chronic allograft rejection after 5 years caused death in the other case.

DISCUSSION

PVA is a controversial procedure that has been described as a last-resort intervention in various scenarios in the setting of LT. Although limited by its retrospective nature, this study is currently the largest cohort presenting PVA during LT. This novel approach was proposed for patients at a higher risk of graft dysfunction.

Table 5 Comparison of preoperative and postoperative doppler portal ultrasound according to portal vein thrombosis, ligation of spontaneous portosystemic shunts and primary graft dysfunction

Doppler ultrasound parameter	Variable	Preoperative	Postoperative	Delta (post-preoperative)
Portal vein velocity (cm/s)	Overall	14.00 [11.7-19.0; 10.45]	71.00 [58.4-102.8; 68]	52.70 [41.24-89.23; 73.50]
	No PVT	17.00 [13.25-25.98; 12.5]	88.00 [60.68-116.50; 45]	36.80 [13.89-80.699; 79.10]
	PVT	11.80 [8.58-17.50; 8.48]	48.00 [43.09-109.25; 55.91]	60.35 [41.21-109.44; 81.40]
	P value[1]	0.037	0.169	0.276
	No SPSS	14.00 [7.31-23.40; 12.8]	84.50 [61.62-121.41; 78.4]	75.20 [46.13-109.15; 77.00]
	SPSS	13.50 [11.02-19.82; 9.95]	67.00 [37.51-106.15; 19.16]	25.50 [5.32-87.93; 64.60]
	P value[1]	0.338	0.115	0.080
	No PGD	11.80 [8.52-18.63; 8.98]	85.82 [64.73-127.48; 80.55]	73.42 [48.78-115.95; 86.00]
	PGD	15.00 [12.53-24.20; 8.6]	46.00 [31.05-75.25; 49.25]	25.00 [9.78-59.78; 65.50]
	P value[1]	0.890	0.570	0.037
Portal vein flow (L/min)	Overall	0.59 [0.47-0.73; 0.56]	3.6 [2.69-4.99; 4.55]	3.21 [2.09-4.40; 4.24]
	No PVT	0.87 [0.41-1.02; 0.82]	2.68 [3.29-6.04; 3.05]	1.52 [0.65-4.17; 3.22]
	PVT	0.55 [0.40-0.67; 0.47]	2.05 [1.68-5.07; 4.4]	3.35 [2.10-5.31; 4.76]
	P value[1]	0.187	0.065	0.419
	No SPSS	0.9 [0.73-1.34; 0.32]	2.68 [2.41-5.40; 4.17]	1.77 [1.64-4.63; 3.88]
	SPSS	0.51 [0.38-0.66; 0.5]	3.97 [1.58-5.30; 8.65]	3.26 [1.19-5.59; 5.50]
	P value[1]	0.002	0.723	0.849
	No PGD	0.75 [0.50-0.82; 0.36]	3.95 [2.96-6.07; 4.73]	3.34 [2.29-5.42; 4.54]
	PGD	0.30 [0.24-0.74; 0.51]	2.20 [0.93-4.33; 3.1]	1.31 [0.41-3.88; 3.09]
	P value[1]	0.677	0.169	0.136

[1]*P* value corresponds to the significance level of the comparison of either subgroups whether preoperatively, postoperatively or their difference. These variables do not have a normal distribution [median (p5-95; IQR)]. They were compared using Mann-Whitney's *U* test. PVT: Portal vein thrombosis; SPSS: Spontaneous portosystemic shunt; PGD: Primary graft dysfunction.

Physiopathologically, PGD is driven by ischemia–reperfusion injury (IRI). IRI begins at procurement when hepatic circulation ceases, creating a hypoxic environment that triggers cell damage and death[16]. This is further exacerbated during reperfusion when reactive oxygen and nitrogen species are produced, and in combination with a hostile inflammatory environment, it impairs graft adaptation to its new host[17,18]. Although some degree of IRI is admissible during any transplantation procedure, severe and sustained ischemia favors the development of PGD[17]. Several donor, graft, and recipient factors predispose to the development of PGD, and despite the tremendous efforts made by the transplantation teams, they cannot be fully addressed and PGD occurs[5,7,19].

Multiple diagnostic criteria have been proposed for PGD. They vary according to surrogated biochemical or functional abnormalities that assess the severity of hepatocellular damage and the loss of liver synthetic and clearance capacities[5]. During the last decade, dynamic PGD scores have been validated to predict the risk of 3-month graft loss[7,19,20]. In our setting, a practical definition was used to allow efficient decision-making[4,6].

The overall incidence of PGD in arterialized patients was 36.0%. Despite including only high-risk patients in this cohort, our results fit within the expected 5.2%–36.3% incidence of PGD reported by other groups[4]. No recipient characteristic was related to the development of PGD. Whether liver disease severity is a risk factor for this complication remains controversial as LT is expected to resolve PHT and vascular steal over time. Although some authors suggest that MELD ≥ 20 might be predictive of PGD[21], our data do not support this correlation[22,23]. Although preoperative severity scores were not used as a criterion for PVA, those who received pre-PVA were more often decompensated according to the CP score but not to the MELD score.

Pre-PVA recipients had less PGD than post-PVA recipients (20.0% *vs* 60.0%; $P = 0.041$). Five patients progressed to PNF: One patient in the pre-PVA and four in the post-PVA group. Although we used post-PVA as a last resource to prevent PGD, our results suggest that it was not as effective as pre-PVA. This could be partially explained by the fact that before graft reperfusion, ischemia has already depleted the graft's energy stock, and even if some oxygen is delivered through portal circulation, it takes several minutes for these molecules to become readily available[24]. Providing an insufficient blood supply to the graft would prolong warm ischemia. In this setting, post-PVA may cause a massive entry

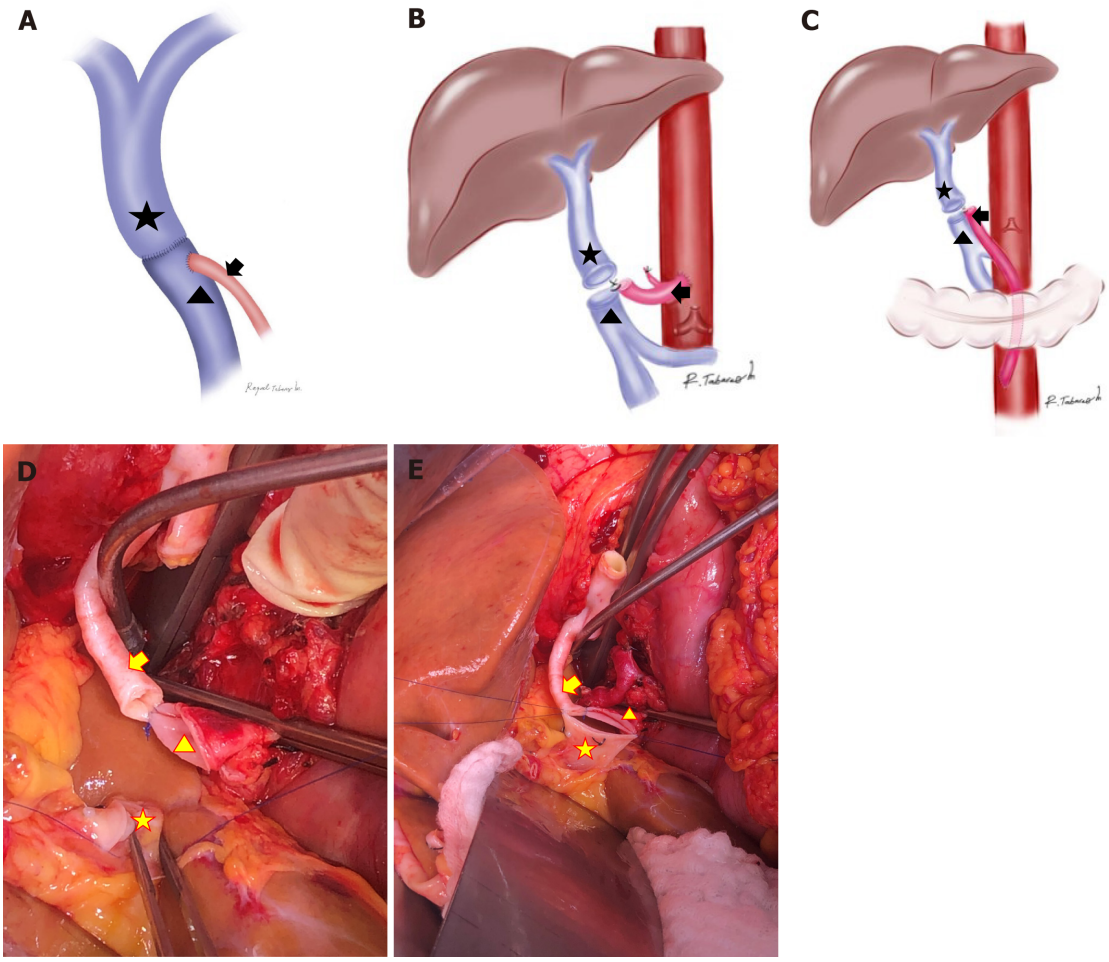

Figure 1 Portal vein arterialization reconstruction techniques. A: Arterioportal illustration depicting the distal terminolateral anastomoses used to anastomose the portal vein (PV) and the arterial allograft during portal vein arterialization (PVA); B: Supraceliac PVA: the proximal end of the arterial allograft could be anastomosed to the abdominal aorta, superior to the celiac trunk; C: Infrarenal PVA: the proximal end of the arterial allograft could also be anastomosed to the abdominal aorta, inferior to the renal arteries. During this reconstruction, the arterial allograft is passed through the mesocolon; D: Photography demonstrating how the recipient PV (star) is attached to the donor iliac artery graft (arrow) previously anastomosed to the supraceliac aorta; E: Photograph depicting how both donor (arrowhead) and recipient PV (star) are approached terminoterminally, whereas the distal end of the donor iliac artery graft (arrow) arises laterally from the supraceliac aorta.

of oxygen to persistently ischemic mitochondria, resulting in an outburst of reactive oxygen and nitrogen species[25]. This reaction causes direct hepatocyte damage and intense danger-associated molecular pattern production and enhances the inherent sterile inflammatory response caused by the transplantation process[26].

Our hypothesis is further supported by a rat LT model in which arterialization at the moment of graft reperfusion resulted in an adequate flow of highly oxygenated blood that rapidly restored the energy stocks depleted during ischemia [27]. This may result in less reperfusion injury and inflammation, similar to the principles of normothermic perfusion machines[28]. In conclusion, timing is critical: If PVA is considered for optimizing portal flow, it should be performed before graft reperfusion; Post-PVA may not revert the IRI of a hypoperfused graft and perhaps may even aggravate it[29].

When compared with post-PVA, preoperative PVEL and PFLOW were significantly lower in pre-PVA patients. SPSS and PVT were associated with this reduction. Interestingly, patients who developed PGD reached acceptable PVEL and PFLOW after transplantation, challenging the idea that suboptimal portal hemodynamics are necessary for PGD development. Although combining LT with PVA demonstrated a significant increase in both PVEL and PFLOW compared with preoperative values in both groups, patients who reached higher values were less likely to develop PVA. This suggests that hyperperfusion may play a protective role against PGD.

Notably, patients with PVT also demonstrated a reduction in PGD (18.8% *vs* 66.7%; $P = 0.031$), whereas those who received SPSS ligation developed PGD more often (60.0% *vs* 20.0%; $P = 0.041$). This can be explained by the predominant inclusion of patients with PVT and unmanageable SPSS in the pre-PVA group. As previously described[30], we found that diabetes mellitus was common in patients with PVT and those who received pre-PVA. Because patients with diabetes are predisposed to have PVT or impaired portal hemodynamics, this condition may reinforce the decision to arterialize the PV.

Unfortunately, literature on PVA is scarce. It is limited to case reports or small case series with heterogeneous characteristics. Therefore, it is impossible to contrast our findings and create clinical recommendations because this is the first time that the effects of PVA on graft perfusion have been described. A recent systematic review reported 57 PVA per-

formed during different hepatobiliary surgeries, and it was indicated when the hepatic artery was either compromised by a tumor (32), accidentally ligated (11), or injured (4) or when its reconstruction was not feasible (10)[2]. In LT, Bhangui and colleagues arterialized the PV at the French Paul Brousse Hospital[1]. They described seven transplant recipients whose PV was arterialized for HAT management after the initial surgery. They performed PVA between 2 d and 29 months after the LT[1]. PVA has also been attempted during LT if recipients have PVT, particularly when regular thrombectomy or eversion thromboendovenectomy was not feasible, failed to resolve the obstruction, or did not lead to an adequate portal flow[1,8-11]. Reports generally described PVA during primary LT. However, Ott and colleagues described it in the setting of retransplantation[11].

A major concern for arterializing the PV in LT recipients relies on the theoretical risk of inducing PHT. Portal circulation is a low-pressure low-oxygen system without valves or flow regulatory mechanisms[3,12]. PVA is a nonphysiologic reconstruction in which the PV is provided with a high-pressure high-oxygen blood supply. This concept explains why PVA could be used for the management of HAT in hepatobiliary or LT surgeries as the goal is to prevent biliary ischemia through PV hyperperfusion[2,31]. In this scenario, PVA maintains biliary tree oxygenation until collateral arterial circulation is established. When the naïve organ remains in place, extrahepatic and intrahepatic collaterals appear at 4–6 wk[32,33], and in LT recipients, extrahepatic collaterals are lost and collateral circulation arises only from intrahepatic circulation[2].

Significant complications in our cohort included infection, AKI, HE, ventilatory impairment, and ascites. UGIB, bowel ischemia/obstruction, congestive cardiac failure, paroxysmic atrial fibrillation, and intrabdominal bleeding were less common. PVA timing did not affect complication distribution. Interestingly, AKI was more frequent when splenorenal shunts were ligated, although it was not associated with this procedure in previous publications[34,35]. These complications were similar to those reported in previous studies where PVA was used for complex PVT management or HAT: AKI[8,36], ascites[1,10,37], UGIB[37], right-sided heart failure[10], intra-abdominal bleeding, encephalopathy, and PVA thrombosis[1]. Intrahepatic abscess[29] and cholangitis[1] have been described, but they are more likely to be related to HAT than to PVA. Some studies have reported aneurysmatic dilation of the PV[26,38], biliary stenosis[39], hepatomegaly [10,37], or acute hepatic failure[11], but none of these were reported in our cohort.

Some authors recommend that PVA should be closed at the onset of elevated portal pressures or even prophylactically when successful liver perfusion is achieved[2]. Because arterioportal shunts can be easily closed endovascularly, we consider PVA a safe procedure as it can be left in place until signs of PHT or volume overload become evident. Moreover, in some cases, PVA does not cause any complications, so it can be placed indefinitely without obvious side effects. At our center, only 9 of 25 patients required closure of the PVA. This was performed using minimally invasive techniques, except for one case that was ligated prophylactically in another unrelated intervention. PVA was closed secondary to PHT in seven cases and to right-heart overload in two cases. PHT presented as gastroesophageal varices in four cases (two resulting in UGIB), refractory ascites in two cases, and one case of hypertensive gastropathy. Other authors also reported PVA closure by interventional radiology or surgical ligation[10,37,38]. Careful patient selection with adequate cardiac pretransplant assessment is mandatory if PVA is considered before LT.

The long-term consequences of PVA have not been studied. A murine model did not find significant histological disruption: only mild nonspecific inflammation and occasional hepatocyte fat droplets were found in arterialized rat livers. A normal Ki-67 index indicated usual mitotic rates. However, periportal and perisinusoidal collagen deposition has been found at 4 wk after PVA[40]. By contrast, other studies found that PVA was associated with increased apoptosis, portal obliterans vasculopathy, and upregulated procollagen I RNA after 3 months[12,29]. Nevertheless, fibrosis was not found on biopsy after 3 years in a human recipient who required PVA at the time of LT[10].

Studies have found that PGD increases the 6-month mortality rate and 6-month graft loss rate by 10-fold (RR = 10.7, 95%CI: 3.6–31.9) ($P < 0.001$) and 7-fold (RR = 7.4, 95%CI: 3.4–16.3) ($P < 0.0001$), respectively[6]. In our case, those who did not develop PGD had better mean survival at 5 years than those who did (54.15 months *vs* 31.91 months). These survival rates match those found when comparing the pre-PVA and post-PVA groups (56.09 months *vs* 22.77 months). We hypothesize that if PGD decreases survival and planned PVA can prevent it, pre-PVA may improve survival in patients at risk.

The first 6 months were critical for mortality. Those who survived this period remained alive thereafter. Most importantly, the main cause of death in the post-PVA group was PGD, whereas most deaths in the pre-PVA group were not caused by PGD. No mortality was associated with PVA complications. Notably, PVT was a crucial determinant of 30-d mortality, a finding previously described by Englesbe *et al*[41], who found that PVT had a 1.32 hazard ratio for post-transplant mortality ($P = 0.02$). In conclusion, if early mortality is prevented, long-term survival can be achieved. We emphasize that as no other studies have prevented PGD using this technique, no direct comparison can be conducted. However, if the survival rates of those who required LT-related PVA are compared, we found that 3- or 10-year survival can be achieved[9-11,42,43]. In these reports, the earliest mortality was reported by Zhang *et al*[8] after a pulmonary infection 2 months after LT. Transplanted patients who received PVA for HAT in Bhangui's series achieved a 1-year survival of 71.0%[1].

Regarding our PVA technique, our team used an interposition donor iliac artery graft in 20 cases and ancillary splanchnic arterial branches in 5 patients. Grafted vessels were preferred to reduce the risk of bleeding or ischemia in the territories supplied by other recipient's arteries[31], as reported by other authors[10,36-38]. Our approach is in contrast with other reports. For example, Bhangui *et al*[1] used only ancillary vessels or a prosthetic graft. Similarly, other authors have used branches of the celiac trunk or the superior mesenteric artery[8,9,37,39], as well as direct arterioportal anastomosis using the recipient's common hepatic artery[10]. The calibration of the anastomosed artery to prevent portal hypertension secondary to arterialization has also been reported but was not attempted at our institution[10,44]. Twenty-one of our patients received PVA at the time of LT. The remaining four were arterialized at a redo laparotomy. This finding explains why pre-PVA prolonged surgical lengths compared with post-PVA.

CONCLUSION

PVA continues to be a viable alternative approach for obtaining adequate graft perfusion during LT. Our investigation revealed that arterialization preceding graft reperfusion (pre-PVA) may confer superior advantages compared to doing so after revascularization. Although some researchers have cited concerns regarding portal hypertension as a significant drawback to this technique, our findings suggest that graft hyperperfusion may effectively mitigate graft dysfunction. Regrettably, our observations did not associate with an optimal survival rate in the pre-PVA cohort. Nonetheless, it is noteworthy that mortality within this group was attributed to external factors unrelated to graft dysfunction or PVA-related complications, underscoring the potential suitability of this technique pending resolution of these external factors.

Our study was limited by its retrospective design, which limited access to specific data, such as donor-related variables. In addition, incomplete data further hindered our capacity to perform a comprehensive comparison between arterialized and nonarterialized LT recipients. Despite the inherent statistical limitations of our modest sample size, it is crucial to highlight that this cohort currently represents the largest series investigating the utilization of PVA in LT. Consequently, it offers invaluable insights into the intricate dynamics surrounding PVA application in LT. Future studies must investigate the suitability and efficacy of this intervention in patients at risk before definitive recommendations can be made.

FOOTNOTES

Author contributions: Vera-Torres A is the Transplant Surgeon and director of the Transplantation program at Fundacion Santa Fe de Bogota, he proposed and performed the technique for these liver transplant recipients; Cortes-Mejia NA, Vera-Torres A, and Bejarano-Ramirez DF designed the research study; Cortes-Mejia NA and Trivino-Alvarez DR performed the primary literature review; Cortes-Mejia NA performed data extraction; Bejarano-Ramirez DF and Cortes-Mejia NA performed the statistical analysis; Vera-Torres A, Cortes-Mejia NA and Guerra-Londono JJ wrote the manuscript; Vera-Torres A, and Guerra-Londono JJ were responsible for revising the manuscript for important intellectual content; and all authors read and approved the final version. Tabares-Mesa R is a general surgeon, and she drew the pictures illustrating the surgical intervention analyzed during this manuscript.

Institutional review board statement: Data collection, analysis, and publication were approved by the Fundacion Santa Fe de Bogota Corporative Ethics Committee for Research (CCEI) (act CCEI-15197-2023) on March 28, 2023. The authors acted according to the Helsinki and Istanbul Declarations of ethical principles.

Informed consent statement: Because of its retrospective nature, the requirement for written consent was waived by the CCEI.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Data sharing statement: For further supplementary, multimedia, statistical code, and dataset, please contact the corresponding author at email address rural.trasplantes@fsfb.org.co.

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ORIGINAL ARTICLE

Observational Study

Translation and cross-cultural adaptation of the Kidney Transplant Questionnaire 25 to Greek

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Abstract

BACKGROUND

Kidney transplantation leads to continuous improvement in the survival rates of kidney transplant recipients (KTRs) and has been established as the treatment of choice for patients with end-stage kidney disease. Health-related quality of life (HRQoL) has become an important outcome measure. It is highly important to develop reliable methods to evaluate HRQoL with disease-specific questionnaires.

AIM

To translate the disease-specific instrument Kidney Transplant Questionnaire 25 (KTQ-25) to the Greek language and perform a cross-cultural adaptation.

METHODS

The translation and adaptation of the original English version of the KTQ-25 to the Greek language were performed based on the International Quality of Life

Assessment.

RESULTS

Eighty-four KTRs (59 males; mean age 53.5 ± 10.7 years; mean estimated glomerular filtration rate 47.7 ± 15.1 mL/min/1.73 m^2; mean transplant vintage 100.5 ± 83.2 months) completed the Greek version of the KTQ-25 and the 36-item Short-Form Health Survey, and the results were used to evaluate the reliability of the Greek KTQ-25. The Cronbach alpha coefficients for all the KTQ-25 dimensions were satisfactory (physical symptoms = 0.639, fatigue = 0.856, uncertainty/fear = 0.661, appearance = 0.593, emotions = 0.718, total score = 0.708). The statistically significant correlation coefficients among the KTQ-25 dimensions ranged from 0.226 to 0.644. The correlation coefficients of the KTQ-25 dimensions with the SF-36 physical component summary (PCS) ranged from 0.196 to 0.550; the correlation coefficients of the KTQ-25 with the SF-36 mental component summary (MCS) ranged from 0.260 to 0.655; and the correlation coefficients of the KTQ-25 with the total scores with the SF-36 PCS and MCS were 0.455 and 0.613, respectively.

CONCLUSION

According to the findings, the Greek version of the KTQ-25 is valid and reliable for administration among kidney transplant patients in Greece.

Key Words: Kidney Transplant Questionnaire 25; Kidney transplantation; Kidney transplant recipients; Health-related quality of life; Quality of life

Core Tip: The Kidney Transplant Questionnaire 25 (KTQ-25) is a disease-specific instrument that is used to evaluate the health-related quality of life of patients who suffer from end-stage kidney disease and who have undergone kidney transplantation. Prior to this study, there was no disease-specific instrument for these patients in our country. We translated the KTQ-25 into Greek according to the International Quality of Life Assessment. The translated version of the KTQ-25 was administered to a Greek cohort of kidney transplant recipients. Scores of the five dimensions of the KTQ-25 were calculated, and statistical tests were performed to estimate the reliability and validity of the translated scale.

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INTRODUCTION

There is an increasing amount of interest in the evaluation of health-related quality of life (HRQoL), especially among patients suffering from chronic diseases. The importance of evaluating HRQoL should not be underestimated because this process it plays an essential role in determining the efficacy of medical interventions, improving the process of making clinical decisions, and evaluating the quality of health care[1]. Moreover, the assessment of patients' perceptions of their health status is especially important for the evaluation of chronic disease outcomes. These perceptions are important for health care professionals to understand disease complications among patients and the effects of treatment on their health status. Based on this information, treatment adjustment should be considered to improve the management and progression of patients[2,3].

Kidney transplant recipients (KTRs) are a special category of patients suffering from chronic disease. Kidney transplantation is widely available and remains the gold standard treatment for patients with end-stage kidney disease receiving renal replacement therapy, hemodialysis, or peritoneal dialysis[4]. Compared with dialysis, kidney transplantation ensures improved patient outcomes, including cardiovascular and total survival as well as QoL[5]. The ability to evaluate HRQoL among KTRs is critical not only for optimizing the care of an individual patient but also for assessing the effectiveness of various treatment strategies and guiding future improvements in health care among specific populations. The estimation of HRQoL among KTRs requires the use of an instrument that is able to achieve both comprehensive and disease-specific assessments, considering that patients are maintained on chronic immunosuppressive therapy after kidney transplantation[6,7].

Most experts in the field of HRQoL evaluation recommend the use of two kinds of questionnaires when the target group concerns patients with chronic diseases. One disease-specific instrument was designed especially for the disease of interest, and one generic instrument was used[8,9]. The generic questionnaire enables comparisons of the studied patient group with the general population and with other patient groups; the disease-specific questionnaire is more accurate for estimating longitudinally changes in HRQoL, especially changes related to specific therapeutic interventions[2,8,10].

In Greece, there are no translated and adjusted disease-specific questionnaires for the estimation of HRQoL among KTRs. Thus, this study aimed to translate the "Kidney Transplant Questionnaire 25 (KTQ-25)" to Greek and to subsequently assess its reliability and validity in this patient population[11]. A Greek version of such a questionnaire is highly necessary considering the growing number of KTRs in Greece. Furthermore, a national transplant project has been initiated with the aim of increasing organ donation and the number of kidney transplantations over the next few years.

MATERIALS AND METHODS

Study population and data collection

This was an observational, prospective, single-center study conducted at the Kidney Transplant Unit of the University Hospital of Ioannina. The study population included 84 KTRs who were recruited during their routine follow-up visit at the outpatient clinic of the Kidney Transplantation Unit of our hospital. All patients signed an informed consent form after being informed in detail about the study. The inclusion criteria were adults (age ≥ 18 years), a well-functioning kidney graft for ≥ 12 months, stable clinical condition during the last month, and good knowledge of the Greek language. The exclusion criteria were active malignancy, chronic severe liver or infectious disease, recent (< 1 month) hospitalization for bacterial or viral infection, acute rejection, cardiovascular event and bone fraction, and scheduled switch to dialysis due to failing graft in the next 3 months. The study protocol was approved by the Ethics Committee of the University Hospital of Ioannina.

At enrollment, social-demographic and anthropometric data along with medical history details were collected from the patients' medical files. Complete hematological and biochemical laboratory parameters and morning urine analysis tests were performed at study entry. The KTQ-25 was administered *via* in-person interviews to all KTRs by the same health care professional (registered nurse) to enhance the participants' understanding of the questions and to minimize missing data. All interviews were conducted in a relaxed and quiet environment to avoid any distractions. The general health-related instrument utilized was the existing Greek version of the SF-36 Health Survey (SF-36)[12]. Each patient completed both questionnaires on the same date and during the interview.

Questionnaires

The original KTQ-25 was developed in 1993 by Laupacis *et al*[11]. It consists of 25 items grouped in the following 5 dimensions: (1) Physical symptoms (6 items); (2) Fatigue (4 items); (3) Uncertainty/fear (5 items); (4) Appearance (4 items); and (5) Emotions (6 items). The first dimension (physical symptoms) is patient-specific. Each item is scored on a 7-point Likert scale. Higher scores for each item represent better health status and/or fewer health problems associated with the transplant. For the analysis, all scores in each domain were added and divided by the number of items in that dimension.

The SF-36 Health Survey is a generic HRQoL instrument that includes 36 items categorized into 8 dimensions: Physical functioning (10 items), role functioning-physical (4 items), bodily pain (2 items), general health (6 items), vitality (4 items), social functioning (2 items), role functioning-emotional (3 items) and mental health (5 items). Two subscales of the SF-36, *i.e.*, the physical component summary (PCS) and the mental component summary (MCS), estimate the physical and mental conditions of patients, respectively. Previous studies have described the use of the SF-36 among patients with end stage renal disease and KTRs[13,14].

Translation methodology

The authors of the KTQ-25 were contacted to obtain the full English version of the KTQ-25 and to obtain permission for the translation. The Greek version of the KTQ-25 was developed according to the cross-cultural adaptation guidelines of the International Quality of Life Assessment translation methodology[15]. The process of developing the Greek KTQ-25 was as follows: Initially, two native Greek speakers with a good level of English language knowledge independently translated the original English version to Greek. Then, a group of health care experts, including a nephrologist, a psychologist, and renal care nurses, revised the two separate translations and developed one common final provisional translation (forward translation). Subsequently, the provisional translation was translated to its original English language by two native English speaker experts (backward translation). Subsequently, the two questionnaires were checked for differences by the expert group, and corrections were made where deemed necessary. The provisional Greek-translated questionnaire was first tested on a pilot basis in a group of 10 KTRs. At the end of the interview, the KTRs were asked about their opinions about the KTQ-25, and all reported that they had no problems completing it or difficulties understanding its content. Consequently, the expert group decided that the translated Greek version of the KTQ-25 was suitable for a larger sample of patients.

Statistical analysis

The KTQ-25 scores are expressed as the means and standard deviations. The reliability of the KTQ-25 was assessed by estimating Cronbach's alpha coefficient. The construct validity was examined by calculating the Pearson correlation coefficients between the KTQ-25 dimensions, and the concept validity was based on the Pearson correlation coefficients between the scores of the KTQ-25 dimensions and the scores of the two component summaries of the SF-36 (PCS and MCS). Items with a correlation coefficient of 0.4 or more with their own hypothesized scale were accepted[16]. All the collected variables were entered into a database, and a statistical analysis was carried out with the SPSS v26.0 statistical package. Significance was set at 0.05 in all cases.

RESULTS

Overall characteristics of patients

A total of 84 KTRs were included in the study, and the majority of participants were male (59, 70.2%). The mean age was 53.5 ± 10.7 years, and the mean transplant duration was 100.5 ± 83.2 months. Regarding kidney graft donor type, 59.5% of KTRs (n = 50) received a deceased donor graft, 39.3% of KTRs (n = 33) received a living donor graft, and one KTR was transplanted twice. The mean time on the deceased donor transplant list was 53.5 ± 39.7 months. At study initiation, the mean estimated glomerular filtration rate was 47.7 ± 15.1 mL/min/1.73 m^2 and the mean serum creatinine level was 1.6 ± 0.5 mg/dL.

KTQ-25

The mean time required to complete the KTQ-25 was approximately 13 min, and none of the patients reported any problems understanding and/or completing the questionnaire. The highest score on the KTQ-25 was found for the appearance dimension (6.31 ± 0.94), while the lowest score was found for the physical symptoms dimension (3.98 ± 1.60). The mean scores of the other dimensions were 5.30 ± 1.36 for fatigue, 5.16 ± 1.33 for uncertainty/fear, and 5.03 ± 1.07 for emotions, whereas the total score of the KTQ-25 was 5.20 ± 0.87 (Table 1).

The Pearson correlation coefficients for the KTQ-25 dimensions, which were used to evaluate construct validity, are presented in Table 2. The statistically significant correlation coefficients ranged between a minimum of 0.226 for the "Uncertainty/Fear" and "Physical Symptoms" dimensions and a maximum of 0.644 for the "Emotion" and "Uncertainty/Fear" dimensions.

The results of the concept validity test, measured by the correlation coefficients between the KTQ-25 dimensions and the component summaries of the SF-36 Health Survey dimensions, are presented in Table 3. The coefficients for the dimensions of the SF-36 were positive in all cases. The correlation coefficients between the KTQ-25 dimensions and the MCS score ranged from 0.260 for the "physical symptom" dimension to 0.655 for the "emotion" dimension. Concerning the PCS score, the coefficients ranged between 0.196 for the "appearance" dimension and 0.550 for the "fatigue" dimension.

Reliability was measured by Cronbach's alpha coefficient, which was found to be greater than 0.7 for two dimensions (fatigue and emotion) and less than 0.7 for the other three dimensions (physical symptoms, uncertainty/fear, and appearance). The reliability of the total KTQ-25 score was found to be 0.708, ensuring the required acceptable level. A correlation coefficient of $r > 0.70$ is considered to indicate an acceptable level of reliability. However, there are references in the literature that even values smaller than 0.7 may be acceptable, especially if the sample, as in our case, is relatively small, while other researchers argue that for the initial stages of a study, a Cronbach alpha coefficient between 0.5 and 0.6 is sufficient[17,18]. The calculated values of Cronbach's coefficient α for each dimension of the Greek version of the KTQ-25 are listed in Table 4.

DISCUSSION

The Greek version of the KTQ-25 is the first disease-specific instrument for the evaluation of the HRQoL in KTRs that has been translated into the Greek language and validated in a cohort of stable kidney transplanted adults. According to our study results, the Greek version of the KTQ-25 is valid and reliable for administration in Greek KTRs.

The sample size of other studies evaluating the psychometric properties of specific disease instruments, as in our study, can never reach the sample number that is used for the validation of generic instruments due to the shortage of available patients with a certain disease. The validation study of the original version of the KTQ-25 included only 26 KTRs, whereas the Spanish validation study included only 31 participants[2,11]. Notably, a total of 84 KTRs agreed to participate in the present study, a sample size far exceeding those of previously published studies.

We considered that it would be optimal to apply the questionnaires by the method of in-person interviews (conducted by the same person) to minimize the number of items that would left incomplete. As the mean duration required to complete the questionnaire was approximately 13 min, this short time required renders the KTQ-25 a suitable tool for everyday clinical use. Moreover, the KTQ-25 could be utilized as a self-completed questionnaire after providing brief instructions to the patients. In the latter scenario, the time required to complete the questionnaire might be even less.

Most of the correlation coefficients found between the five dimensions of the KTQ-25 were statistically significant, and these were in all cases positive and usually moderately strong, ensuring satisfactory construct validity. Furthermore, all the correlation coefficients found between the dimensions of the KTQ-25 and the two summary components, the PCS and the MCS, of the SF-36 were positive, proving that both instruments evaluated the same concept and ensured the appropriate concept validity of the translated KTQ-25.

The internal consistency reliability of the KTQ-25 and its five dimensions was satisfactory, as Cronbach's α coefficient for the overall KTQ-25 was 0.708, which was marginally greater than the acceptable limit of 0.7 but not for all of its individual dimensions. The minimum Cronbach α coefficient was 0.593 for the appearance dimension, and the maximum was 0.856 for the fatigue dimension. Cronbach's α coefficient for the original version of the KTQ-25 was 0.76 for physical symptoms, 0.94 for fatigue, 0.63 for uncertainty/fear, 0.61 for appearance, and 0.80 for emotions[8,11]. Similarly, in the Spanish version by Rebollo *et al*[2] and the study by Chisholm-Burns *et al*[19], the lowest Cronbach α coefficients were observed in the appearance dimension (0.69 and 0.62, respectively), and the highest coefficients were observed in the fatigue dimension (0.93 and 0.90, respectively). According to the available literature, if a scale shows a low degree of internal consistency, the clarity of the propositions may need to be reconsidered, or this may be due to the small degree of

Table 1 Kidney Transplant Questionnaire 25 scores (*n* = 84)

KTQ-25 dimensions	Mean	SD
Physical symptoms	3.98	1.60
Fatigue	5.30	1.36
Uncertainty/fear	5.16	1.33
Appearance	6.31	0.94
Emotion	5.03	1.07
Total score	5.20	0.87

KTQ-25: Kidney Transplant Questionnaire 25.

Table 2 Correlation coefficients among Kidney Transplant Questionnaire 25 dimensions

		Physical symptoms	Fatigue	Uncertainty/fear	Appearance	Emotion
Physical symptoms	Pearson correlation		0.354[b]	0.226[a]	0.187	0.395[c]
Fatigue	Pearson correlation			0.487[c]	0.182	0.584[c]
Uncertainty/fear	Pearson correlation				0.073	0.644[c]
Appearance	Pearson correlation					0.193

[a]$P < 0.05$.
[b]$P < 0.01$.
[c]$P < 0.001$.

Table 3 Correlation coefficients among Kidney Transplant Questionnaire 25 dimensions and SF-36 (*n* = 84)

KTQ-25 dimensions	PCS	MCS
Physical symptoms	0.143	0.260[a]
Fatigue	0.550[a]	0.528[a]
Uncertainty/fear	0.304[a]	0.605[a]
Appearance	0.196[a]	0.023
Emotion	0.278	0.655[a]
Total Score	0.455	0.613[a]

[a]$P < 0.05$.
KTQ-25: Kidney Transplant Questionnaire 25; MCS: Mental component summary; PCS: Physical component summary.

propositions per dimension[17,18].

CONCLUSION

The findings of our study show that the validity and reliability of the Greek version of the KTQ-25 are satisfactory. A useful disease-specific instrument for the evaluation of the HRQoL of KTRs is now available in the Greek language. In the future, multicenter studies with larger sample sizes are required to estimate the validity and reliability of the KTQ-25 and to establish the Greek version of the KTQ-25 structure through confirmatory factor analysis. Ideally, future studies should assess the clinical value of using the KTQ-25 to assess HRQoL in everyday practice, thus providing guidance for therapeutic approaches. Furthermore, future studies should examine the significance of the Greek version of the KTQ-25 as a potential predictor of adverse outcomes.

Table 4 Cronbach's alpha coefficient (*n* = 84)

KTQ-25 dimensions	Cronbach's alpha	Items
Physical symptoms	0.639	6
Fatigue	0.856	5
Uncertainty/fear	0.661	4
Appearance	0.593	4
Emotion	0.718	6
Total Score	0.708	25

KTQ-25: Kidney Transplant Questionnaire 25.

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FOOTNOTES

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ORIGINAL ARTICLE

Basic Study

Hyperacute experimental model of rat lung transplantation using a coronary shunt cannula

Munehisa Takata, Yusuke Tanaka, Daisuke Saito, Shuhei Yoshida, Isao Matsumoto

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Abstract

BACKGROUND

Lung transplantation is a well-established treatment of end-stage lung disease. A rodent model is an inexpensive way to collect biological data from a living model after lung transplantation. However, mastering the surgical technique takes time owing to the small organ size.

AIM

To conduct rat lung transplantation using a shunt cannula (SC) or modified cannula (MC) and assess their efficacy.

METHODS

Rat lung transplantation was performed in 11 animals in the SC group and 12 in the MC group. We devised a method of rat lung transplantation using a coronary SC for coronary artery bypass surgery as an anastomosis of pulmonary arteriovenous vessels and bronchioles. The same surgeon performed all surgical procedures in the donor and recipient rats without using a magnifying glass. The success rate of lung transplantation, operating time, and PaO2 values were compared after 2-h reperfusion after transplantation.

RESULTS

Ten and 12 lungs were successfully transplanted in the SC and MC groups, respectively. In the SC group, one animal had cardiac arrest within 1 h after reperfusion owing to bleeding during pulmonary vein anastomosis. The operating time for the removal of the heart-lung block from the donor and preparation of the left lung graft was 26.8 ± 2.3 and 25.7 ± 1.3 min in the SC and MC groups, respectively (P = 0.21). The time required for left lung transplantation in the recipients was 37.5 ± 2.8 min and 35.9 ± 1.4 min in the SC and MC groups, respectively (P = 0.12). PaO2 values at 2 h after reperfusion were 456.2 ± 25.5 and

461.2 ± 21.5 mmHg in the SC and MC groups, respectively (P = 0.63), without difference between the groups.

CONCLUSION
A hyperacute rat lung transplantation model using a coronary SC was created using a simple technique. The MC was inexpensive, easy to prepare, and simple to operate.

Key Words: Lung transplantation; Rat; Shunt cannula; Modified cannula; Reperfusion

Core Tip: We developed a rat lung transplantation technique using a coronary shunt cannula (SC) for the pulmonary arteriovenous system and bronchial tube anastomosis. This method is simple and can be performed by a surgeon. This study evaluated the usefulness of this method by using a modified cannula (MC), which we developed by modifying the SC and improving its shortcomings. The MC is inexpensive and easy to prepare and operate. Presently, a hyperacute lung transplantation model is feasible, and future improvements, such as a smaller cannula and reduced foreign body reaction, will be made to create a chronic rat lung transplantation model.

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INTRODUCTION

Lung transplantation is a well-established treatment of end-stage lung disease. Many immune and non-immune mechanisms in lung transplantation are highly complex, and post-transplant complications such as infections and primary and chronic lung allograft dysfunction must be reduced to improve survival. Therefore, there is a need for immunological and pathophysiological analyses using animal lung transplantation models.

The rat lung transplantation model was first reported in 1971[1], followed by the Mizuta Cuff model[2] in 1989. Since then, various improvements in surgical techniques, cuffs, and instruments have been reported[3-7]. The advantage of using a rodent model is that it permits inexpensive collection of biological data from a living model after lung transplantation. Although trained surgeons can perform the transplantation procedure, mastering the surgical technique takes time due to the small size of the organs. The risks associated with this technique include damage to the vulnerable pulmonary artery (PA) and pulmonary vein (PV) vessel walls during anastomosis, as well as stenosis of the anastomotic site.

We developed an anastomotic technique using a coronary shunt cannula (SC) for cardiac coronary artery bypass surgery as an alternative to the previously reported cuff method[2-6]. This method enables anastomosis by inserting and ligating a cannula into the lumen of the PA, PV, and bronchus (Br), which is simpler and more reliable than conventional methods.

This study aimed to determine problems with rat lung transplantation using the SC, develop an improved cannula, and investigate its utility.

MATERIALS AND METHODS

Instruments

A cannula was used for anastomosis of the PA, PV, and Br during rat lung transplantation. The SC (CLEARVIEW®; Medtronic, Minneapolis, United States) used for coronary artery bypass surgery had a luminal structure with tips on both ends to prevent injury during insertion and removal from the coronary artery.

In this experiment, we divided the subjects into two groups: One using CLEARVIEW® (SC group) and the other using a cannula developed in our laboratory (modified cannula group: MC group) (Figure 1). The SC group and the MC group consisted of 11 and 12 animals, respectively, to be used as lung transplantation models. The CLEARVIEW® cannula used has a lumen diameter of 1.2 mm. The issues with the CLEARVIEW® cannula included a narrow lumen diameter of 0.8 mm at both tip ends and an excessive length of 20 mm, which posed challenges for anastomosis of the PA, PV, and Br in rats. To create a more physiologically-reliable lung transplantation model for maintaining constant blood flow in the pulmonary arteriovenous vein, we developed an MC with a constant lumen diameter. A polyamide catheter with a lumen diameter of 1.2 mm throughout its entire length (coronary artery perfusion catheter; Forte Grow Medical Corporation, Tochigi, Japan) was used as the MC. Although shorter catheters could be more physiologic and desirable for lung transplantation, the polyamide catheter was cut into a length of 10 mm in this study. Cyanoacrylate resin (Aron

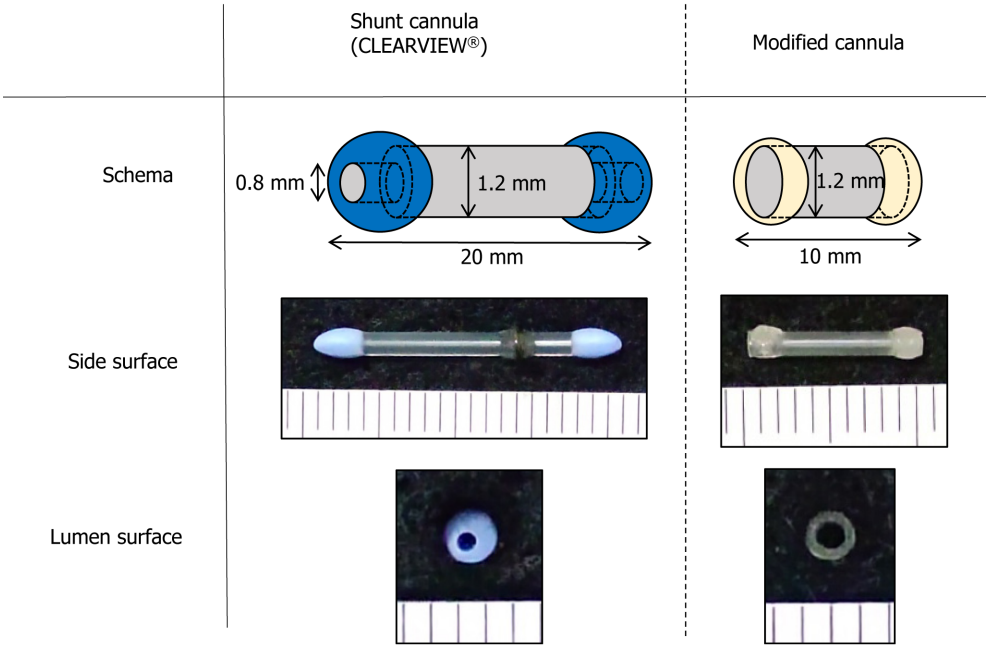

Figure 1 Shunt cannula and modified cannula. The shunt cannula (Clearview®) is 20 mm long with a lumen diameter of 0.8 mm at the entrance and 1.2 mm at the middle. The modified cannula was 10 mm long with a lumen diameter of 1.2 mm over its entire length.

Alpha A; Daiichi Sankyo Company, Limited, Tokyo, Japan) was adhered to both ends to form a tip smaller than the CLEARVIEW® cannula and used for the experiment.

Animals

Male Wister rats (8–10 wk old, 240–300 g; Japan SLC, Inc., Hamamatsu, Japan) were purchased and used as donors and recipients. All experiments were conducted in the Kanazawa University Animal Testing Laboratory. Experimental animals were used following the Guidelines for the Care and Use of Laboratory Animals of Kanazawa University (approval no. AP-163743) and the Guide for the Care and Use of Laboratory Animals (8th edition) published by the National Research Council in 2011.

Surgical procedure

The same surgeon performed all surgical procedures in the donors and recipients, without using magnifying glasses. Regarding induction of anesthesia, 4%–5% isoflurane (Wako Pure Chemical Industries, Osaka, Japan) was administered with a maintenance dose of 1.5%–3%. The rats were intubated using an 18-gauge intravenous catheter through a transverse cervical incision. After intubation, the rats were ventilated using a ventilator (settings: Tidal volume, 10 mL/kg; respiratory rate, 60/min); fraction of inspired oxygen, 0.21).

Donor procedure

The animals were supinely positioned, a median abdominal incision was made, and 250 units of heparin were injected through the inferior vena cava. A median sternotomy was made to expose the thoracic cavity. The right ventricular wall was punctured, and a 24-gauge intravenous catheter was inserted into the PA. The superior and inferior venae cavae were incised and drained while 20 mL of saline solution was injected over a period of approximately 1 min. The trachea was clamped, and the cardiopulmonary block was removed with preservation fluid after completion of perfusion.

Graft preparation

The cardiopulmonary block was placed on a Petri dish cooled to 4 °C, and the work proceeded in the cooled state. The left PA/PV/Br was detached, and a cannula was inserted into each of the vessel and bronchial walls with only a partial incision (Figure 2A). The left lung graft was ligated with a 4-0 silk suture at the center of the tip of the cannula, including the vessel and bronchial walls (Figure 2B), and separated from the cardiopulmonary block. The left lung graft was stored at 4 °C for 24 h before transplantation.

Recipient procedure

The recipient was placed in the right lateral recumbent position, and the left-side chest was opened at the intercostal space where the heartbeat was felt. Two ribs were dissected dorsally caudal to the open chest wound, and the dissected ribs were pulled caudally to secure the view. The recipient's pulmonary hilum was elevated, and the PA, Br, and PV were dissected and secured. Subsequently, 250 units of heparin were injected through the PV. The central side of all three recipient structures was clamped with a microclip. When the PA/PV/Br anastomosis was performed, an incision was made in a part of the vessel wall and bronchial walls, while the left lung of the recipient was retained without resection.

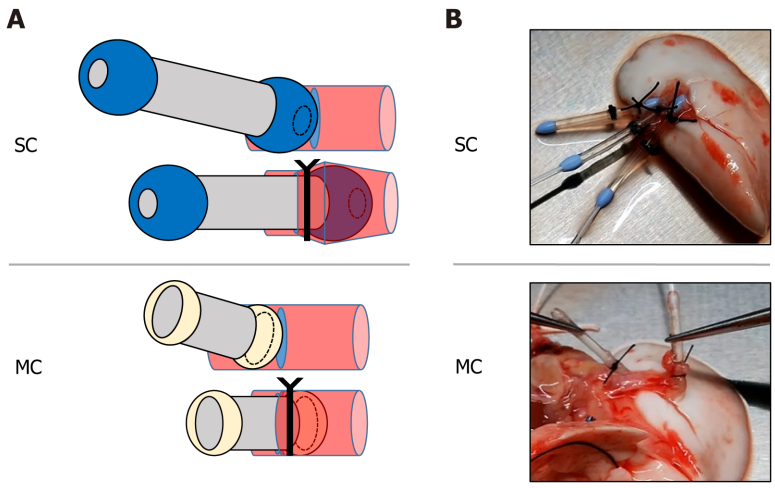

Figure 2 Graft preparation. A: Schema of cannula insertion. The tip makes it easy to insert the cannula into the lumen and prevents the cannula from falling out during ligature fixation. Regarding the modified cannula, the tip is smaller than that of the shunt cannula, resulting in easier insertion and simpler technique of ligation and fixation is simpler; B: Left lung graft after cannula insertion. MC: Modified cannula; SC: Shunt cannula.

The cannula tip was inserted into the left lung graft, and the anastomosis was completed by ligating the cannula following the same procedure used when the graft was created (Figure 3A). The microclip was removed, reperfusion was started, and pulmonary expansion and blood flow in the grafted lung were checked (Figure 3B). The left lung graft was removed after 2 h of continuous reperfusion at FiO2: 1.0, with general anesthesia maintained after transplantation.

Assessment

The success rates of the lung transplantation, operating time, and PaO2 values were compared between the two groups. The criteria for successful lung transplantation were: (1) Maintenance of recipient's circulation; (2) visual confirmation of blood flow in the cannula of the graft lung; and (3) maintenance of graft lung coloration after 2 h of reperfusion. The recipient's circulation was determined by visual inspection of pulse and heart rates. Graft lung coloration was classified into three grades (Grades 1–3) and defined as follows: Grade 1, insufficient blood flow in the grafted lung (white tone area) being > 10% of the total surface area; Grade 2, insufficient blood flow in the grafted lung (white tone area) being < 10% of the total surface area; and Grade 3, favorable blood flow throughout the graft. Successful grafting was defined as a graft with a color grading of 2–3. Blood was collected at the PV of the graft lung to measure PaO2 (i-STAT analyzer; Abbott Point of Care, Chicago, United States).

Statistical analysis

Data were analyzed using STATMATE (ATMS Co., Ltd., Tokyo, Japan), expressed as mean ± SD, and compared with an unpaired *t*-test. Values of $P < 0.05$ were considered statistically significant.

RESULTS

After creating 11 lung transplantation model animals in the SC group and 12 in the MC group, all animals underwent reperfusion. One animal in the SC group had cardiac arrest 1 h after reperfusion due to hemorrhage caused by vessel wall injury during PV anastomosis. Two hours after reperfusion, we visually confirmed the maintenance of recipient hemodynamics and blood flow in the graft pulmonary cannula in 10 animals in the SC group and 12 in the MC group.

The operating time for the removal of the heart-lung block from the donor and graft lung creation was 26.8 ± 2.3 min in the SC group and 25.7 ± 1.3 min in the MC group ($P = 0.21$, Table 1). The duration for left lung transplantation into the recipient was 37.5 ± 2.8 min in the SC group and 35.9 ± 1.4 min ($P = 0.12$, Table 1) in the MC group. Although no significant difference was found between the SC and MC groups, animals in the MC group experienced a slightly shorter operating time, smoother surgical technique, and less stressful procedure for the surgeons compared with those in the SC group.

The graft lung coloration (Grade 1/2/3) after reperfusion was 0/2/8 (SC group) and 0/2/10 (MC group), and all grafts were reported to be successful, except in one animal in the SC group that had cardiac arrest (Table 2).

The PaO2 values after 2 h of reperfusion were 456.2 ± 25.5 mmHg in the SC group and 461.2 ± 21.5 mmHg in the MC group ($P = 0.63$, Table 3), showing no significant difference between the groups.

Table 1 Rat lung transplantation procedure operating time

	SC group (*n* = 10)	MC group (*n* = 12)	*P* value
Donor procedure-Graft preparation (min)	26.8 ± 2.3	25.7 ± 1.3	0.21
Recipient procedure (min)	37.5 ± 2.8	35.9 ± 1.4	0.12

Table 2 Graft lung coloration after reperfusion

	SC group (*n* = 10)	MC group (*n* = 12)
Grade 1/2/3	0/2/8	0/2/10

Table 3 PaO_2 values after 2 h of reperfusion

	SC group (*n* = 10)	MC group (*n* = 12)	*P* value
PaO_2 (mmHg)	456.2 ± 25.5	461.2 ± 21.5	0.63

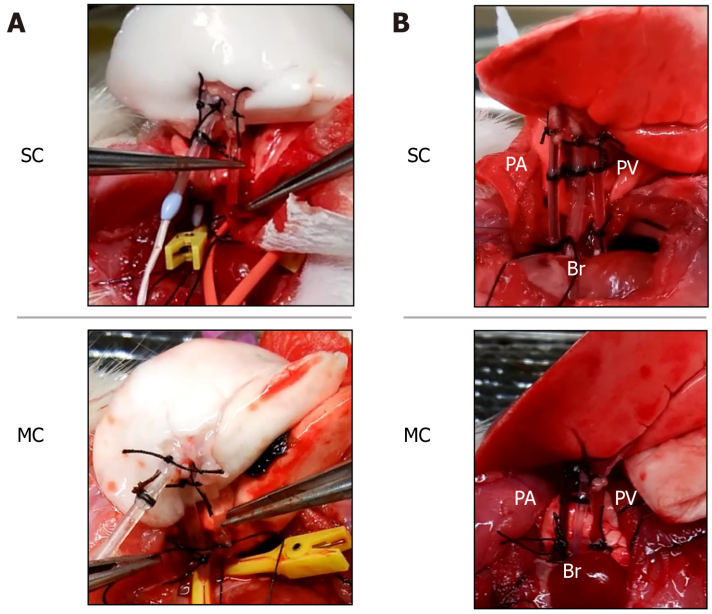

Figure 3 Recipient operation. A: Pulmonary vein anastomosis using a cannula; B: After lung graft revascularization, venous blood perfusion is visible in the pulmonary artery, and arterial blood perfusion is visible in the pulmonary artery. In the modified cannula group, the grafted lung is located closer to the pulmonary hilum compared with the shunt cannul group. PA: Pulmonary artery; PV: Pulmonary vein; Br: Bronchus; MC: Modified cannula; SC: Shunt cannula.

DISCUSSION

The SC technique used in this study was easy to learn and had a high success rate. In the SC group, the commercially available SC used had an inconsistent lumen diameter that could impair blood flow and was too long for use for rat lung transplantation. In the MC group, our lab-developed cannula that bypasses these limitations was used for rat lung transplantation.

The results showed no significant differences in operating time, graft success rate, or partial pressure of oxygen in the blood between the two groups, and both procedures were very easy. However, compared with those in the SC group, the procedures were easier, there were no surgical failures, and there was less stress for the surgeon in the MC group. This can be attributed to the smaller tip, enabling smoother insertion into the lumen of the blood vessel, and the overall diameter, allowing the grafted lung to be deployed in a position close to the pulmonary hilar region (anatomically correct position).

In rat lung transplantation, anastomosis of the fragile PA/PV is the most difficult[4,5]. Anastomosis using a cuff cut process from an intravenous catheter is simpler than direct anastomosis, and improvements in the cuff shape[5], anastomosis technique[3], anastomosis using the donor's descending aorta[4], and stabilizer for graft preparation[6] have been reported. However, the technique takes time to master.

In the method involving the use of a catheter in the hyperacute lung transplantation model, challenges associated with using a straight catheter include difficulties in securing the graft vasculature and catheter. Prolonged lung ventilation can also lead to misalignment at the anastomotic site. In this experiment, we used an SC for the following reasons: (1) The rounded tips could prevent damage to the PA and PV during insertion, (2) it was easy for a surgeon to secure the lumen and insert the cannula, and (3) the central side of the tip was ligated with the tissue to facilitate the procedure and prevent dislocation during revascularization and continuous lung ventilation. In addition, due to the transparent cannula body, visualizing blood flow during reperfusion was possible, which could be used as a criterion for successful transplantation. The MC is shorter in length, has a wider lumen, and is more maneuverable than existing products. Because the MC is inexpensive and easy to make, we believe that it can be used on a commercial basis in the future.

The limitations of this method include the following: (1) The cannula is long, preventing containment of the grafted lung in the body after anastomosis and prohibiting closure of the chest; and (2) the lumen of the cannula is not covered with biological tissue as in the cuff method. Therefore, considering our modified SC, this method could only provide convenience for performing hyperacute lung transplantation at this time. Therefore, evaluating the chronic phase is currently difficult using this method. Further improvement in surgical materials and protocols is needed to facilitate long-term survival of animals after transplantation.

The cannula size can be reduced by shortening the length and eliminating one of the tips, specifically on the donor side. This miniaturization allows the cannula lumen to be covered by the vessel wall, similar to the cuff method, thus reducing foreign body reactions and mechanical hemolysis. If the chest can be closed after transplantation, acute and chronic survival models can be created. However, further studies are needed to develop a chronic-phase rat lung transplantation model.

CONCLUSION

A rat lung transplantation model using a coronary artery SC could be created with a simple technique and may be a useful model for evaluating grafted lungs in the hyperacute phase after transplantation. The model using MC, which was modified in our laboratory, could be produced with easier surgical procedures and lower cost compared with those of the SC, as well as showing potential for commercialization.

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FOOTNOTES

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