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Experimental and Clinical Transplantation

OFFICIAL JOURNAL OF THE MIDDLE EAST SOCIETY FOR ORGAN TRANSPLANTATION

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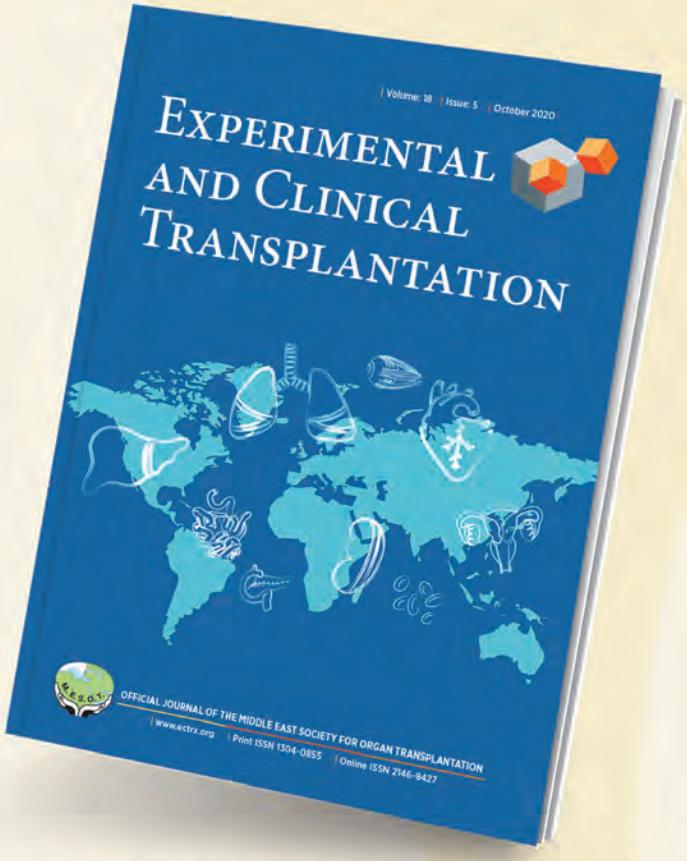

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Experimental and Clinical Transplantation (ECT) is the official journal of the Middle East Society for Organ Transplantation (MESOT). The Society was originally founded in Turkey in 1987, and was subsequently incorporated at Bern, Switzerland, in 1988 as a non-profit, international, scientific organization comprising 20 countries of the Middle East, North Africa, Mid-Asia, and neighboring nations.

The aim of the journal is to provide a medium forum for where clinical scientists, basic scientists, ethicists, and public health professionals to communicate ideas and advances in the field of experimental and clinical organ and tissue transplantation, and to discuss related social and ethical issues. The topics will be of interest to transplant surgeons, clinicians in all major disciplines and subspecialties, basic science researchers, and other professionals involved with sociological aspects of experimental and clinical transplantation.

Experimental and Clinical Transplantation is a peer-reviewed international publication that accepts manuscripts of full-length original articles, case reports, letters to the editor, and invited reviews. It is published in English bimonthly (February, April, June, August, October, and December).

Our editorial team is committed to producing a journal of extremely high standards. The journal is fully indexed in EBSCO, Excerpta Medica, Index Medicus, Journal Citation Reports/ Science Edition, MEDLINE, Science Citation Index Expanded™, and Turkey Citation Index. Full-text articles are available on the Internet via PubMed or at the Journal's Web site, at **http://www.ectrx.org**. ECT is also available as hard-copy bound volumes by subscription, printed on acid-free paper.

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- Malignancies
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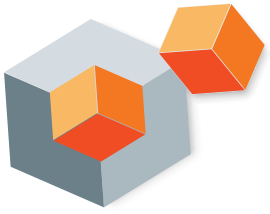

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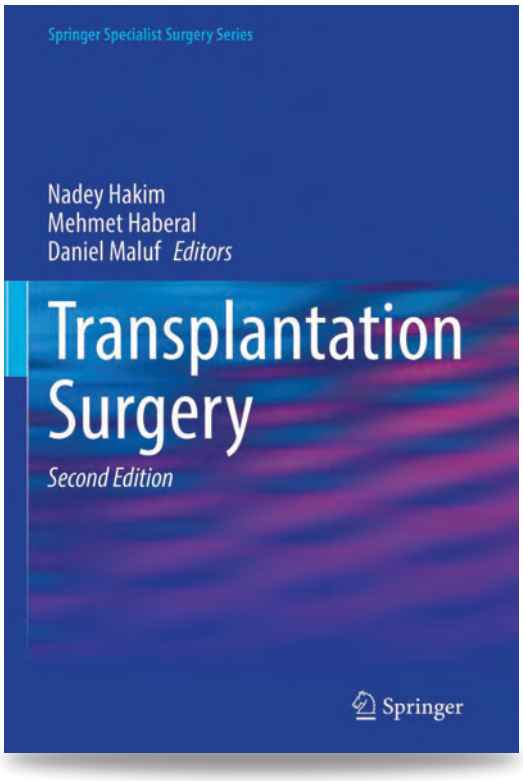

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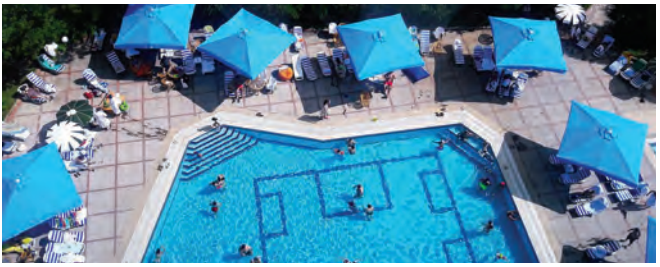

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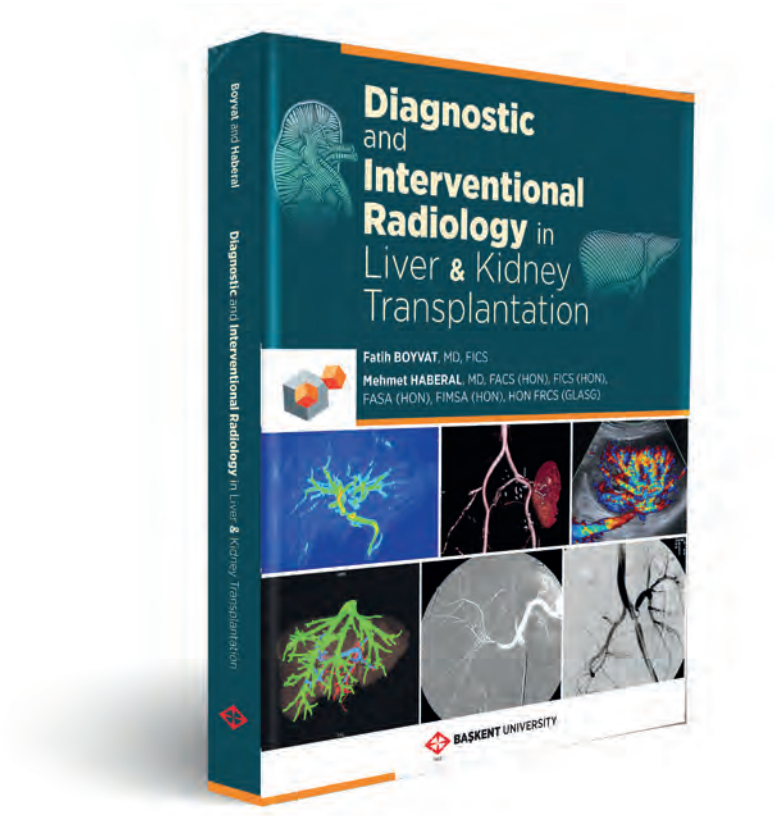

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Fatih BOYVAT, MD, FICS

Mehmet HABERAL, MD, FACS (HON), FICS (HON), FASA (HON), FIMSA (HON), HON FRCS (GLASG)

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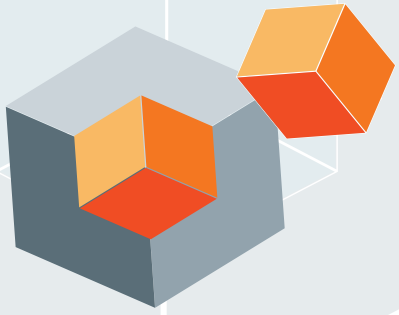

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Anti-Interleukin 6 Therapeutics for Chronic Antibody-Mediated Rejection in Kidney Transplant Recipients

Rajeev Sharma

Abstract

Chronic antibody-mediated rejection is the predominant cause for late renal allograft loss for which there is, as yet, no treatment approved by the US Food and Drug Administration, although there are clinical trials in progress to evaluate novel treatment strategies. The current standard of care treatment is based on expert consensus, rather than scientific evidence, and includes glucocorticoids, plasma exchange, and intravenous immunoglobulin, with or without rituximab or bortezomib. The low success rate with presently established management protocols represents a conspicuous exigency in the field of kidney transplantation. This review focuses on the biologic basis for interleukin 6 inhibitors, specifically tocilizumab and clazakizumab, and the safety and efficacy profiles of these agents for treatment of chronic antibody-mediated rejection in kidney transplant recipients.

Key words: *Clazakizumab, IL-6, Tocilizumab*

Introduction

Chronic (active and inactive) antibody-mediated rejection (CAMR) is the predominant cause for late renal allograft loss. As yet, no treatment for CAMR has received approval from the US Food and Drug Administration (FDA); however, clinical trials are in progress to evaluate novel treatment strategies. Most cases of CAMR are attributed to allograft damage caused by donor-specific antibodies (DSA) that were either present before transplant or developed after transplant. Donor-specific antibodies form after transplant as a result of immunosuppression reduction, either physician directed or as a result of patient nonadherence.[1]

The Banff Classification forms the basis of diagnosing and reporting antibody-mediated rejection (AMR) and has undergone several updates based on improvements in our understanding of this disease, since it was first introduced in 1997. The most recent changes to the Banff Classification system were applied in 2019.[2,3] These ongoing revisions reflect the progressive evolution of our understanding of this complex clinical condition, and many questions remain unanswered. The low rate of success of the presently accepted management protocols underscores the fact that our understanding of AMR is still evolving.

Antibody-mediated rejection, once considered an isolated incident occurring after transplant is now recognized to be a progressive condition that waxes and wanes over time and may ultimately lead to chronic allograft damage and allograft loss.[4] The current standard of care treatment for AMR is based on expert consensus,[5] rather than scientific evidence, and includes glucocorticoids, plasma exchange, and intravenous immunoglobulin (IVIG). Several therapeutic agents have been tested in randomized clinical trials, including anti-CD20 monoclonal antibody (mAb), rituximab, and the proteasome inhibitor, bortezomib, but these studies have failed to show a significant clinical benefit.[6,7] A few randomized trials have tested the efficacy of the anti-C5 mAb, eculizumab, which inhibits terminal complement activation, but no clinical benefit has been demonstrated.[8] A small pilot study has demonstrated the benefit of classical complement pathway blockade in late AMR with C1-esterase inhibitor.[9]

To address the urgent need for an effective treatment for AMR that could prolong renal allograft survival, the FDA has conducted open workshops

From the Michael and Marian Ilitch Department of Surgery, Wayne Health, Detroit, Michigan, USA

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with participation of industry, academia, and patient representatives to meet the challenges of clinical design for AMR-related clinical trials.[10] This review focuses on the biologic basis for anti-interleukin 6 (anti-IL-6) therapeutic agents, specifically tocilizumab and clazakizumab, and the safety and efficacy of these agents for treatment of CAMR in kidney transplant recipients.

Biologic Basis for Interleukin 6 Blockade in Chronic Antibody-Mediated Rejection in Kidney Transplant

Interleukin 6 is a pleiotropic inflammatory cytokine that can affect virtually all physiological systems, including bone marrow, hepatocytes, mesangial cells, and epithelial cells in the kidney, bone, and neurons. Abnormal production of IL-6 can result in chronic inflammation, immune stimulation, and neovascularization[11] and is associated with various autoimmune diseases, such as rheumatoid arthritis (RA), Castleman disease, and cancers.[12,13]

Originally described as the B-cell stimulating factor 2 or hepatocyte growth factor,[14] the IL-6 receptor (IL-6R) system consists of an 80-kDa IL-6R and a 130-kDa signal transducer (gp130). The 80-kDa receptor exists in a transmembrane form (mIL-6R) and a soluble form (sIL-6R). The mIL-6R has a short intracytoplasmic region and, upon stimulation by binding of the IL-6 molecule, triggers an association with gp130. The sIL-6R can form a stimulatory complex with IL-6 and thereby associate with gp130 to trigger cellular events in a process known as trans-signaling. The gp130 signal transducer has a transmembrane domain that facilitates signal transduction across the membrane.[15] The IL-6 molecule binds to mIL-6R (also known as CD126) or sIL-6R, and the IL-6/mIL-6R or IL-6/sIL-6R complex then binds to the gp130 IL-6 transducer (CD130), which results in gp130 dimerization, phosphorylation, and subsequent activation of receptor-associated kinases (Janus kinases Jak1 and Jak2 and tyrosine kinase 2),[16] followed by induction of tyrosine phosphorylation and recruitment of the signal transducer and activator of transcription 3 (STAT3), which dimerizes and translocates to the nucleus and leads to gene expression.[15] The IL-6 signaling systems are regulated by negative feedback of the suppressors of cytokine signaling (SOCS) and the protein inhibitors of activated STAT. The IL-6/IL-6R interaction activates STAT3, which targets SOCS1. The SOCS1 molecule then binds to the Jak tyrosine kinase and acts as a negative regulator of gp130 signal transduction.[15]

Interleukin 6 stimulates B-cell differentiation and secretion of antibodies and prevents apoptosis of activated B cells,[17-19] activates and induces proliferation of T cells, and, in the presence of interleukin 2, induces differentiation of mature and immature T cells into cytotoxic T cells.[20,21] Interleukin 6 promotes the development and maturation of B cells to plasma cells, which in turn produce DSA that target the allograft. These DSA damage the allograft via complement-mediated and non-complement-mediated pathways and induce graft endothelial cells to produce inflammatory (eg, P selectin, vascular cell adhesion molecule 1) and prothrombotic (eg, von Willebrand factor) molecules. Interleukin 6 also shapes the T-cell immune response to promote long-lived proinflammatory helper T cells (eg, follicular helper T cells as well as Th17, Th1, and Th2 cells) and inhibit immune regulatory T cells that promote allograft tolerance.[11] Classical IL-6/IL-6R signaling in hepatocytes induces the expression of acute-phase proteins that include C-reactive protein (CRP), serum amyloid A, fibrinogen, and hepcidin (contributes to anemia of chronic disease). Interleukin 6 inhibits other hepatic proteins including albumin, transferrin, and cytochrome P450 and also stimulates dermal and synovial fibroblasts, osteoclast differentiation, renal mesangial cell proliferation, megakaryocytes, and angiogenesis.[11]

Early clinical trials with anti-IL-6 murine mAb have demonstrated the safety of anti-IL-6 therapy, identified CRP as a surrogate marker, and shown that dosing must account for the high degree of variation in daily production of IL-6 with different disease states to achieve therapeutic inhibition.[22] With murine anti-IL-6 mAb therapy, it was observed that the half-life of IL-6 increased from a few minutes in untreated patients to several days in treated patients.[23] It was also observed that, at the end of anti-IL-6 mAb treatment, the ratio of the concentrations of free anti-IL-6 mAb to IL-6/anti-IL-6 mAb complexes decreased, allowing the sIL-6R or mIL-6R to disrupt the IL-6/anti-IL-6 mAb complexes. The resultant large amount of IL-6 released in circulation can trigger cell activation, resulting in quick recovery of CRP production, fever, and cancer cell progression at the end of anti-IL-6 treatment in some patients.[24]

Anti-IL-6R mAb therapy blocks the action of IL-6 without increasing the half-life of IL-6, as seen with anti-IL-6 cytokine mAb strategies.[15,23] Anti-IL-6R mAb therapy also blocks the action of the sIL-6R, which mediates several actions of IL-6, including osteoclast formation, synovial fibroblast proliferation, and cartilage degradation.[15] Hence, anti-IL-6 cytokine mAb therapy only partially blocks IL-6, allowing innate immune response to develop.[25] In the context of antibody-mediated rejection, IL-6 blockade by anti-IL-6 mAb or anti-IL-6R mAb can cause significant reductions of alloantibodies, antibody production by splenic and bone marrow plasma cells, direct inhibition of plasma cell anti-HLA antibody production, and induction of T regulatory cells with inhibition of T follicular helper cells.[11,26,27]

Tocilizumab

Tocilizumab is a humanized monoclonal antibody directed against IL-6R and is approved for the treatment of RA and idiopathic juvenile arthritis.[28,29] A number of clinical trials[30-32] have shown efficacy and a favorable safety profile of tocilizumab to treat active RA (Table 1).

Safety

Smolen and colleagues have reported comprehensive safety data of IL-6 blockade with tocilizumab in patients with RA as a part of the OPTION study in which 419 patients received tocilizumab[28] and experienced transient, mild, self-limited cutaneous adverse events such as localized skin rash or dermatitis, with or without pruritus, along with a transient rise in hepatic transaminases without any signs of hepatitis, as well as an increase in plasma concentration of high-density and low-density lipoprotein and total cholesterol was noted requiring treatment but was not associated with an increase in adverse cardiovascular events. Hypersensitivity reaction, transient neutropenia, and thrombocytopenia were also observed. Infectious events included pneumonia, *Pneumocystis* pneumonia, interstitial lung disease, cellulitis, and upper respiratory tract infection. A cerebrovascular accident occurred in 1 patient with cellulitis, and idiopathic pulmonary fibrosis was also reported. More serious adverse events included

Table 1. Efficacy and Safety Data for Tocilizumab

Study	No. of Patients	Efficacy	Safety
Choi et al. (2017)[27]	36 Patients received TCZ for CAMR.	4 Patients had graft loss. Allograft survival at 6 years was 80%. Significant reduction in iDSA and microvascular inflammation.	5 CMV viremia, 2 BK viremia, 1 trichodysplasia spinulosa, 7 bacterial infections, 1 stroke, 1 NSTEMI after ninth dose, 1 transient visual disturbance, 6 hypogammaglobulinemia.
Lavacca et al. (2020)[36]	15 Patients received TCZ as first-line therapy for CAMR.	Significant decrease in iDSA. Significant reduction in microvascular inflammation. Absence of progression in chronicity scores. Resolution of C4d deposition.	4 Bacterial urinary tract infections, 1 bacterial lower respiratory tract infection, 1 idiopathic encephalitis, 2 interstitial lung disease (1 related to adenovirus, 1 related to TCZ). Hypogammaglobulinemia requiring IVIG. Increase in LFTs and pancreatic enzymes.
Massat et al. (2020)[38]	9 Patients received TCZ: 6 with CAMR, 4 with mixed AMR/T-cell rejection.	No difference in graft survival or renal function in TCZ group compared with historical controls treated with standard of care. Dramatic reduction in tubulitis and microvascular inflammation scores. Reduction in iDSA.	1 Pulmonary aspergillosis, 1 *Microsporidia* infection, 1 pyelonephritis, 1 cutaneous abscess, 2 CMV viremia.
Pottebaum et al. (2020)[37]	7 Patients received TCZ: . 6 with acute AMR, 1 with CAMR	Significant reduction in iDSA in 4 of 6 patients. Reduction in microvascular inflammation, transplant glomerulopathy, and proteinuria in 1 patient with CAMR.	1 CMV esophagitis, 1 hypersensitivity reaction.
Sharma et al. (2021)[39]	1 Patient received TCZ for CAMR.	Stabilization of serum creatinine.	Increase in hepatic transaminases. Required TCZ discontinuation.
Sethi et al. (2021)[35]	83 Patients received TCZ for treatment of CAMR or desensitization.	Efficacy was not reported.	Urinary tract infection, 2 episodes of *Pneumocystis* pneumonia, *Clostridium difficile* colitis, bacterial gastroenteritis, blood infections (primary or secondary bloodstream infections), skin/soft tissue infections, viral infections (mild cases of varicella-zoster virus, BK virus, CMV), fungal infections, 1 case of infectious colitis with colonic stricture that resulted in perforation during gastrointestinal procedure.

Abbreviations: AMR, antibody-mediated rejection; CAMR, chronic AMR; CMV, cytomegalovirus; DSA, donor-specific antibodies; iDSA, immunodominant DSA; IVIG, intravenous immunoglobulin; LFT, liver function test; NSTEMI, non-ST elevation myocardial infarction; TCZ, tocilizumab

gastrointestinal perforation and peridiverticular abscess.[28] In patients with RA who were treated with tocilizumab, there was a higher incidence of gastrointestinal perforation,[28,33] which was likely related to chronic glucocorticoid and nonsteroidal anti-inflammatory drug use in this population.[34]

Sethi and colleagues recently presented robust data on infectious risks of tocilizumab in kidney transplant patients.[35] A total of 57 infectious episodes were observed in 83 kidney transplant recipients treated with tocilizumab for desensitization or treatment of AMR, of which 31 episodes (54%) required hospitalization. There were no infection-related deaths, and there was a lower rate of infections associated with tocilizumab versus a contempo raneous group of 65 kidney transplant recipients who received IVIG and rituximab for similar indications. Urinary tract infections and pneumonia (2 episodes of *Pneumocystis* pneumonia) were the most common infections, whereas gastrointestinal complications (*Clostridium difficile* colitis, bacterial gastroenteritis), blood infections (primary or secondary bloodstream infections), skin/soft tissue infections, viral infections (mild cases of varicella-zoster, cytomegalovirus, and BK virus), and fungal infections were less common. In 1 patient with infectious colitis, a colonic stricture resulted in a perforation during a gastrointestinal procedure.[35]

In a previous publication from the same group of researchers, Choi and colleagues reported that, of the subset of 36 patients who received tocilizumab for CAMR, there were 7 patients with bacterial infections that resolved with treatment without the need to discontinue tocilizumab. Hypogammaglobulinemia was also noted and managed with IVIG. Three patients developed cardiovascular complications. One of the 3 patients experienced a stroke while on tocilizumab, but therapy was not discontinued, and this patient recovered with no residual deficits. The second of the 3 patients developed non-ST elevation myocardial infarction (NSTEMI), possibly related to hyperkalemia, after the ninth dose of tocilizumab. The third patient experienced NSTEMI at 2 years after therapy completion, but this was not related to tocilizumab. One case of trichodysplasia spinulosa (a benign skin condition related to polyomavirus) was also reported, but this patient recovered 1 month after the completion of tocilizumab therapy.[27]

Lavacca and colleagues used tocilizumab as a first-line therapy for 15 patients with CAMR and reported 4 patients with bacterial urinary tract infection and 1 patient with bacterial lower respiratory tract infection. These complications resolved with medical therapy without tocilizumab discontinuation. One patient developed idiopathic encephalitis and required temporary discontinuation of tocilizumab until recovery. Two patients developed interstitial lung disease, one related to adenovirus requiring temporary discontinuation of tocilizumab, and the other related to tocilizumab requiring therapy cessation. They also found a higher incidence of hypogammaglobulinemia requiring IVIG. A rise in liver function tests (LFTs), specifically hepatic transaminases, and pancreatic enzymes was also noted.[36]

Other adverse events associated with tocilizumab treatment of AMR in kidney transplant patients have been reported, including 1 patient with cytomegalovirus esophagitis for whom tocilizumab was discontinued but was successfully treated with valganciclovir.[37] Fungal infections, including 1 patient with pulmonary aspergillosis and 1 patient with *Microsporidia* infection, have been reported by Massat and colleagues in 9 kidney transplant patients with AMR who were treated with tocilizumab.[38] Discontinuation of tocilizumab in response to hypersensitivity has also been reported.[37] Sharma and colleagues observed a transient rise in hepatic transaminases in a patient after the fifth dose of tocilizumab, but liver function test results recovered to normal levels after cessation of tocilizumab.[39]

Efficacy

The largest reported experience with tocilizumab therapy in kidney transplant recipients included 36 patients with CAMR refractory to standard of care therapy (including steroids and IVIG plus rituximab) from a single center who received tocilizumab therapy for 6 to 25 months. There was a significant reduction in immunodominant DSA (iDSA), along with a reduction in microcirculation inflammation (glomerulitis plus peritubular capillaritis scores). Graft loss was noted in 4 patients, for whom tocilizumab was discontinued for medical reasons in 1 patient and for insurance reasons in the other 3 patients. The results of this study showed an overall graft survival probability of 80% at 6 years after CAMR diagnosis; in addition, in patients with transplant glomerulopathy, a 77% graft survival

probability was reported at 6 years after CAMR diagnosis.[27] These results from Choi and colleagues are in stark contrast to results published by Redfield and colleagues (in 2016), who had reported a 55% rate of 2-year graft survival for CAMR patients treated with standard of care treatment, and a 20% rate of 2-year graft survival for CAMR patients without any treatment.[40]

Lavacca and colleagues used tocilizumab as a first-line therapy for 15 patients with CAMR with severe transplant glomerulopathy and severe microvascular inflammation. Allograft loss was reported for a single patient, at 25.3 months after discontinuation of tocilizumab. There was a significant decrease in iDSA, along with a significant reduction in microvascular inflammation, and an absence of progression in chronicity scores or C4d deposition.[36] Pottebaum and colleagues treated 7 patients with tocilizumab. Of these 7 patients, only 1 had CAMR, and this patient completed 6 months of tocilizumab therapy and demonstrated stable serum creatinine, marked reduction of iDSA, reduction of microvascular inflammation, and stabilization of transplant glomerulopathy and proteinuria.[37] In the study by Sharma and colleagues, their patient with refractory CAMR (without DSA) was removed from tocilizumab therapy after the fifth dose due to rise in serum transaminases, but the creatinine returned to baseline and remained stable at 1 year follow-up.[39]

In contrast to the previously mentioned studies, Massat and colleagues found no difference in graft survival or renal function in patients with AMR refractory to standard of care who were treated with tocilizumab versus patients in historical control groups who were treated with standard of care. This study included 9 patients, 6 of whom had CAMR and 4 had mixed AMR/T-cell rejection. Despite their stated conclusion, they did find a dramatic reduction in tubulitis and microvascular inflammation scores along with a reduction in iDSA as reported in other studies.[38]

Clazakizumab

Clazakizumab is a genetically engineered humanized immunoglobulin G1 (IgG1) monoclonal antibody that binds to human IL-6.[41] Multiple assays for signaling and cellular functions in response to IL-6 alone (to measure classical signaling) and a combination of IL-6 and sIL-6R (to measure trans-signaling) have shown clazakizumab to be a potent and full antagonist of IL-6-induced signaling as measured by phosphorylation of STAT3, as well as cellular functions such as cell proliferation, differentiation, activation, B-cell production of immunoglobulins, and hepatocyte production of acute phase proteins (CRP and fibrinogen). In addition, clazakizumab is a competitive antagonist of IL-6-induced cell proliferation. A large ongoing phase 3 multicenter international trial is underway to study the effect of clazakizumab treatment in kidney transplant patients with CAMR (IMAGINE: Clazakizumab for the Treatment of Chronic Active Antibody Mediated Rejection in Kidney Transplant Recipients; ClinicalTrials.gov Identifier: NCT03744910).

Safety

Safety data on IL-6 cytokine blockade have been reported from a phase 3 trial of sirukumab in patients with RA in which 1114 patients received the drug (SIRROUND-D: A Study of CNTO 136 [Sirukumab], Administered Subcutaneously, in Patients With Active Rheumatoid Arthritis Despite Disease-Modifying Antirheumatic Drug [DMARD] Therapy; ClinicalTrials.gov identifier NCT01604343). The most common adverse events were elevated liver enzymes, upper respiratory tract infection, bronchitis, nasopharyngitis, injection site erythema and pruritus, leukopenia, neutropenia, headache, and hypertension. The incidence of serious adverse events was 20.8%, which included 1 patient with a gastric perforation and 1 patient with perforated appendicitis.[42]

In the transplant literature, there is a single published report of a phase 2 study of anti-IL-6 blockade with clazakizumab in 20 kidney transplant patients with CAMR (Table 2). There was a 25% incidence of serious infectious events, including pneumonia, pyelonephritis, ovarian abscess, and coxsackievirus-associated meningitis. One patient developed recurrent pleural effusion requiring pleurodesis and, subsequently, permanent thoracic cavity drainage; 2 patients with diverticulosis developed diverticulitis, 1 of whom developed a colon perforation that required surgery, and the other patient with diverticulitis required percutaneous abscess drainage and antibiotics. Clazakizumab was also associated with mild injection site reactions, increases in lipid levels, and mild abnormalities of liver enzymes or blood cell count.[43]

Table 2. Efficacy and Safety Data for Clazakizumab

Study	No. of Patients	Efficacy	Safety
Doberer et al. (2021)[43]	20 patients with CAMR received clazakizumab.	Decrease in mean DSA. Significantly slower decline in eGFR. Significant reduction in molecular AMR and all rejection score at week 51. 38.9% of patients had a negative AMR score, 22.2% had resolution of AMR activity, and 27.8% demonstrated C4d disappearance. No significant change in microcirculation inflammation, and transplant glomerulopathy. Significant increase noted in interstitial fibrosis, and tubular atrophy.	25% Incidence of serious infectious events (pneumonia, pyelonephritis, ovarian abscess, coxsackievirus-associated meningitis); 1 patient with recurrent pleural effusion required pleurodesis, then permanent thorax cavity drainage; 2 patients developed diverticulitis (1 of these 2 patients developed colon perforation and required surgery; the 2nd patient required percutaneous abscess drainage and antibiotic therapy); mild injection site reactions; increases in lipid levels; mild abnormalities of liver enzymes and mild neutropenia.

Abbreviations: AMR, antibody-mediated rejection; CAMR, chronic AMR; DSA, donor-specific antibodies; eGFR, glomerular filtration rate; iDSA, immunodominant DSA

Efficacy

There was a decrease in mean DSA within 12 weeks of clazakizumab treatment, with a further decrease in DSA after prolonged treatment. A significantly slower decline in the estimated glomerular filtration rate was observed in the patients who received clazakizumab. There was also a significant reduction in molecular AMR and all rejection scores after prolonged treatment at 51 weeks; 38.9% patients had a negative AMR score, 22.2% had resolution of AMR activity, and 27.8% demonstrated C4d disappearance. However, there was no significant change in microcirculation inflammation, and transplant glomerulopathy remained essentially unchanged. A significant increase was noted in interstitial fibrosis and tubular atrophy.[43]

Drug Interactions

The manufacturer's prescribing information for tocilizumab contains a recommendation that, upon therapy initiation or discontinuation, therapeutic monitoring of effect (eg, warfarin) or drug concentration (eg, calcineurin inhibitors) should be performed and the individual dose of the cytochrome P450 enzyme substrate drugs should be adjusted as needed (Actemra [tocilizumab] injection, for intravenous or subcutaneous use; Prescribing information, Genentech, August 2017). Furthermore, caution is advised when coadministering with CYP 3A4 substrate drugs (eg, oral contraceptives, β-hydroxy β-methylglutaryl-coenzyme A reductase inhibitors) where a decrease in effectiveness is undesirable .

Conclusions

Sufficient safety data have been compiled for IL-6 inhibitors from reports on treatment in patients with RA; however, kidney transplant data is small, and caution is warranted when evaluating these scant data. In a phase 2 study, clazakizumab was associated with serious adverse events such as gastrointestinal perforation, diverticulitis, and peridiverticular abscess; therefore, in patients with diverticulosis, clazakizumab should be avoided entirely or used with caution. Given the high incidence of infectious adverse events, it is prudent to consider a reduction in the dose of mycophenolate mofetil by 50% during tocilizumab or clazakizumab therapy and to initiate prophylaxis for *Pneumocystis* pneumonia and cytomegalovirus as well; however, a paucity of reports precludes any conclusive recommendations.

Tocilizumab therapy has been shown to consistently and significantly reduce iDSA, C4d, and microvascular inflammation scores and stabilize transplant glomerulopathy, whereas clazakizumab has been shown to significantly slow the rate of decline in estimated glomerular filtration rate without any significant change in microvascular inflammation and transplant glomerulopathy, although there was an increase in interstitial fibrosis and tubular atrophy with clazakizumab. These effects could be related to the differences in the mechanisms of action of the 2 drugs, specifically, partial IL-6 blockade by anti-IL-6 cytokine mAb, clazakizumab.

Larger studies are needed to make sense of these observed effects, because there is only limited experience with these 2 drugs in the transplant setting. In conclusion, IL-6 blockade is a powerful tool to prolong renal allograft survival; however, given the high rate of allograft failure with standard of care treatment in CAMR, as well as the absence of an FDA-approved treatment, if IL-6 blockade is selected as rescue therapy for patients with CAMR when standard of care treatment has failed, then it must be used cautiously.

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Global Practices and Policies of Organ Transplantation and Organ Trafficking

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Abstract

Objectives: **Organ trafficking has emerged worldwide as an important medical and ethical concern. In this study, we reviewed the literature presented on this matter to evaluate the global practices, ethical standards, and legal aspects of organ transplantation.**
Materials and Methods: **We adopted a qualitative study design to perform this study, which included conduct of a literature review. The main focus was organ transplantation.**
Results: **Our review suggested a dire need to adopt ethical principles and implement equitable distribution of organs around the globe as per the respective need.**
Conclusions: **Further studies are needed to evaluate the role and status of organ recipients to create a much more organized environment for safe and effective implantation of evidence-based principles of clinical transplantation globally.**

Key words: *Ethical concerns, Human trafficking Transplant commercialism, Transplant tourism*

Introduction

Organ transplantation is considered to be one of the most important advancements in the medical field.[1] Over the span of about 100 years, solid-organ transplant has advanced from an experimental theory to a clinically effective procedure with ever-increasing efficacy and standards of care. With the success of the procedure of retrieving a functioning organ from one human body and transplanting it to the affected individual's body, the chances of prolonging life and improving quality of life have significantly improved. Organ transplantation not only reflects advances in clinical technology and close cooperation between various specialities of medical sciences but also highlights the magnitude of human compassion spreading throughout the globe to help and save lives. Regardless of the achievements and positive outcomes of this life-saving therapy, there have also been gains in negative aspects in society in the process of organ transplantation. These factors include aspects in culture, legality, and political affluence along with factors concerning procurement, organ preservation, donor allocation, immunological implications, and efficient management of infections.[1-4]

Although standard and cost-effective transplant procedures are available to save patients with organ failure, successes in their implementation have been victim to ever-increasing gaps between the number of potential recipients waiting for organs and the number of available donors.[1] Presently, the number of patients waiting to receive an organ transplant has reached up to 100 000 globally.[1] Unfortunately, these numbers are higher than the number of available donors and organs. These gaps between recipients on wait lists and the number of donors have subsequently influenced states to adopt different strategies to encourage organ donation from potential sources. The most encouraging tactics have involved inspiring healthy people to donate organs after death. Despite various efforts, the increasing demand for organs has resulted in serious problems worldwide, including nonconsensual retrieval and organ trafficking.[1,2] The issue of organ trafficking has increased globally, resulting in the World Health Organization identifying the need to protect vulnerable people

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from transplant tourism and selling of tissues and organs. In 2004, the World Health Organization highlighted the significance of tackling the issue of international trafficking in organs and human tissues.[2,5]

Over the years, trafficking of human organs around the globe has commercialized into an underground business running on large sums of finances moving worldwide.[6] The concept mainly involves recipients who have an adequate amount of money to spend and express a strong demand for an organ, leading to the exploitation of vulnerable groups. A vulnerable person may either sell an organ in exchange for money consensually or may get trapped into the trafficking network and lose an organ without any active consent to operate. The flow of commercial networking is mainly concentrated in underdeveloped countries that encourage patient tourism to procure the organs.[7] Although cases of illicit and unethical removal and trafficking of tissues and organs from human bodies have been reported, the matter was still disregarded in the 2006 annual meeting of active-member states of the United Nations. The matter was not given priority due to limited data and lack of a possibility to estimate the magnitude of human organ trafficking.[6,7] However, in 2007, the World Health Organization addressed commercial trafficking in the Second Global Consultation on Human Transplantation,[2] presenting that commercial sales of organs retrieved from living donors had been increasing worldwide. This global conduct mainly includes kidney transplants, which account for 5% to 10% of operations per year.[8] The subject has been addressed extensively at the International Summit on Transplant Tourism and Organ Trafficking Convened by The Transplantation Society and International Society of Nephrology in Istanbul, Turkey, April 30 through May 2, 2008. The related definitions as quoted by the Summit are shown in Table 1.[2,9]

Over the years, commercial transplantation has evolved into a clinical crime network. The modality includes diverse issues, from trafficking of vulnerable humans to medical complications that may arise with lack of postoperative care in such cases. Lack of consent and lack of knowledge with the added probability of higher morbidity and mortality rates are important concerns. In every aspect, the practice of commercial organ transplantation is deemed unacceptable in terms of medical ethics.[10]

Problem Statement

Despite the familiarity with its serious violations of human rights and laws, the business of human trafficking for organ removal is common in countries with vulnerable populations.[6] To highlight the violation of human rights and to protect the people at risk of human or organ trafficking, the United Nations has developed protocols directed toward human trading. It has been realized that most targets of these underground and illegal industries are women and children, who are often engaged in organ trafficking through deception. In fraud cases, many people realize too late that they have lost an organ during a course of time; others are kidnapped and then deserted after the organ retraction. Along with these practices, many are left to suffer or even die because of lack of postoperative care.[10-12]

It should also be realized that legal and protective systems have also recognized vulnerable people as victims who may have sold their organ in exchange for money due to poverty or other situation. It is considered as exploitation of position or situation of a human that again comes under laws against human rights.[10-12] Although laws have been asserted to protect humans from victimization in organ trafficking, it is considered important to filter out the reasons behind these criminal activities. The most notable factor in

Table 1. Definition of Terms From the International Summit on Transplant Tourism and Organ Trafficking[2,9]

Term	Definition
Organ Trafficking	"Organ trafficking is the recruitment, transport, transfer, harbouring or receipt of living or deceased persons or their organs using the threat, force or other forms of coercion, of abduction, of fraud, of deception, of the abuse of power or a position of vulnerability, or of the giving to, or the receiving by, a third party of payments or benefits to achieve the transfer of control over the potential donor, for exploitation by the removal of organs for transplantation."[2,9]
Transplant Commercialism	"Transplant commercialism is a policy or practice in which an organ is treated as a commodity, including by being bought or sold or used material gain."[2]
Travel for Transplantation	"Travel for transplantation is the movement of organs, donors, recipients, or transplant professionals across jurisdictional borders for transplantation purposes."[2]
Transplant Tourism	"Travel for transplantation becomes transplant tourism if it involves organ trafficking and/or transplant commercialism or if the resources (organs, professionals, and transplant centres) devoted to providing transplants to patients from outside a country undermine the country's ability to provide transplant services for its own population."[2]

this regard is that organ trafficking started as an underground industry that is being run with hefty financial backup. The main driving force of organ trade is recipient driven, where recipients may possess the capability of spending earnest amounts for an organ.[10]

Significance of the Study

Organ trading remains a major concern, and its roots have strengthened within an underground market. Although organ trafficking is considered a form of human trafficking, it has failed to be recognized and given importance in legal contexts due to a lack of perspective and evidence. Today, the number of chronic disorders is increasing worldwide, with an expanding life expectancy. The rising number of cardiovascular diseases has led to more with organ dysfunction, which may further progress to organ failure. As stated earlier, the rising figures and demands for organs is far higher than the available number of donors. The lack of donated organs, the rise of demand for organ transplants, and the increase in available resources and finances of recipients are potential influencers of organ trafficking. The underground market has been fuelling and running on these factors since the beginning.[6] The underlying core reason and the common theme are a criminal empire and selfish demand for organs, hinged on an unavailability of donated organs. Nonetheless, our primary focus is not the unavailability of donors. Rather, our focus is to understand the factors that have led to organ trade and how to address this serious issue of global concern.

Materials and Methods

Study objectives

Our objective was to evaluate the practices, ethical standards, and legal aspects of organ transplantation globally, and our literature search reviewed and analyzed published studies on global organ transplantation. We adopted a qualitative study design to perform this study, which included conducting a literature review.

Search strategy

For the literature search, we conducted an online search for appropriate materials. During the search, the primary key terms included the following: commercial transplant, organ transplant, organ trafficking, organ tourism, organ trade, and patient tourism. We conducted and collected literature search findings in our institute's database. Accordingly, we filtered data to optimize findings using the following characteristics: article types included scientific research papers and reports, text availability included full text of the article, publication dates included 10 years from 2008 to 2018, study subjects included humans, and publication language was English.

Organ Trafficking as a Global Problem

Despite its illegal and unethical practices, the underground market of organ trafficking has flourished globally. Exploitations have not only occurred within small-scale groups but have also included high-profile organizations and names in the trade. The market for illegal organs runs on large sums of money that have big profits for traders. This market has flourished more so in underdeveloped countries, where the population is poor and more vulnerable. There are rare instances where victims are put under anesthesia and wake to find their organs missing or are murdered for their organs. However, despite increased awareness throughout the globe regarding organ trafficking and organ donation, illegal practices alarmingly remain. The practice of organ trafficking is mainly attributed to the demand for healthy organs in the international market and the lack of affordable dialysis programs in resource-limited health care systems. Despite advancements and continuous research in immunology, grafting, and infection management that have improved allograft survival, these have diluted hindrances of precise biological matching.[13-16]

An ever-increasing gap in demand versus supply of donor organs in wealthy countries with poor regulatory systems has fuelled the unethical practice of money changing hands in exchange for donor organs.[11] Organ trafficking is driven by 3 factors: first, the values of those in society who consider that the selling of the transferable organs should be legalized with the consent and authoritative power of the seller or donor; second, the prevailing environment of neoclassical economics that refer to consider transferable organs as a commodity. According to their approach, consideration of an organ treated as a commodity can increase its

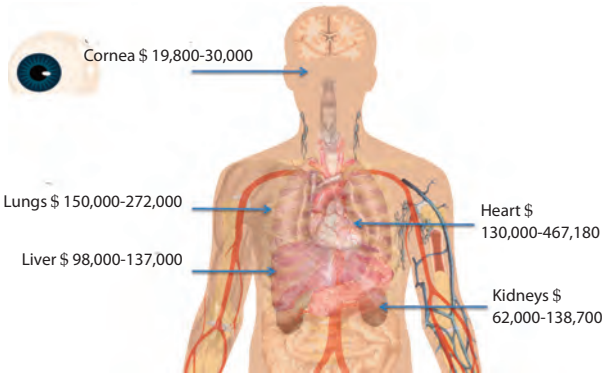
availability in the market, with the willingness to share the organ in exchange for payment. This has led to "organ for sale" becoming a new normal. Third, many unscrupulous surgeons and specialists in the field have colluded with young men under the burden of responsibility. These professionals have encouraged the market forces to retrieve organs from any possible means irrespective of its fairness in ethical or legal terms.[10-12,17]

Regardless of the position in the society and level of education attained by each group, the desperation to obtain a healthy organ is reflected in a compromise in ethics and substandard practices in the medical field.[18] It is known that the victims are mostly individuals from underdeveloped states, and such groups of people are often exploited. Exploitation not only involves deception but also involves the concept of economic desperation among the groups. Moreover, ignorance has also led to the contemptuous apathetic attitude of those at the helm of affairs toward a vulnerable and poor segment of society who are exploited because of obliviousness to their rights. That is why the trade of organs is seen as an abuse to the justice and rights of humans in a vulnerable situation.[18] Therefore, it is also considered important to reflect on the role of organ retractors and traders to get more familiar with the characteristics of organ trafficking. Thus, below we review sellers in the organ trade market.

Organ Trafficking: Hidden Form of Human Trafficking

Among different forms of human trafficking, organ trafficking is the most concealed form, which uses devious methods by exploiting loopholes. Unlike forced labor or prostitution, organ trafficking is difficult to trace and lacks robust laws and regulations to control or even identify culprits and traffickers. Usually, the victim is recognized after the loss of an essential organ, which cannot be retrieved back. The criminal footprints in this regard are destroyed easily, and the traffickers remain to earn high profits. The value of each organ that can be transplanted varies with the desperation of demand of the organ and the difficulty of supply in the market.[16] Organs that are transplanted include cornea, lungs, heart, liver, and kidney. Figure 1 shows differences in value of transplantable organs in 2007 and 2017.[13,19]

Figure 1. Monetary Value for Each Transplantable Organ, estimated in US Dollars[13,19]



According to a report presented by Global Financial Integrity, about 10% of the transplanted liver, lungs, and heart are obtained through organ trafficking globally. Apart from these, the most highly demanded and also the most illegally trafficked organ are kidneys, which comprise about 75% of the illegal organ market.[20] The World Health Organization estimated that 10 000 kidneys are trafficked illegally around the world for transplantations. This equals more than 1 kidney retrieved unethically from a human body every 1 hour. Furthermore, the report stated that organs are often retrieved from vulnerable populations. These populations are mainly from China, India, and Pakistan.[21] Although these 3 countries are infamous for organ procurement for "organ sale," other countries have been also involved, including Mexico, Costa Rica, Peru, Turkey, Egypt, Sri Lanka, Cambodia, Vietnam, Philippines, Singapore, and Indonesia.[16]

The involvement and integration of an international market led to the phrase "patient tourism," which involves the seeker or receiver of treatment to travel to obtain the best possible treatment, management, and care. For patients with organ failure and the need for transplant, organs are the main driving factor for travelling. In these aspects, the seeker sometimes travels to another country to obtain the organ or the trader takes the responsibility of delivering a healthy organ to the buyer. This is referred to as the "transplant tourism," where an individual may travel to retract an organ from the market.[2]

Transplant Tourism

According to the records, the first case of selling a human organ was reported in the 1980s.[22] Today, the

business of trading human organs for transplant has evolved into an established market. Initially, the practice involved street dealing with only a few people involved in obtaining organs through coercion. However, this dealing has evolved into a major trade and expanded its roots through both developed and underdeveloped countries. Most organ trades involve long-distance travel, as organs are resourced through vulnerable populations who are either deceived into the practice or paid poorly in exchange for the organ. Due to high awareness, practices of management and care, and the power over finances, it is not convenient to perform these activities in economically wealthy states. Therefore, these activities are conducted in underresourced areas. These underresourced targets mainly include Asia and Africa, including India, Pakistan, Egypt, and the Philippines, as well as some parts of Eastern Europe. Prisoners in China have been victims of the inhumane practice of using them as organ donors, raising suspicion of whether orders of execution involved the demand for their allografts.[23-25] Nonetheless, in searches for healthy organ, buyers frequently travel to these locations that somewhat encourage tourism, which equates to a major medical crime.[25]

Transplant tourism has gained interest as more and more people have been travelling for organ procurement. Individuals with strong financial capabilities tend to be more inclined toward transplant tourism. However, there have been instances of misuse of the system, in which a select few have had backup from their government or health insurance to fulfil the expenses of procuring an organ. Travelling for transplant tourism has been observed in wealthy states of the Gulf region, Europe, and Israel. Major transactions and procurement activities have been mainly performed in regions of Asia, Eastern Europe, Latin America, and South Africa, where buyers arrive for trading. The kidneys remain the most obtained and demanded organ; kidneys have been advertised on online platforms or through brokers in the market.[23,24]

It is important to locate areas of demand and control the eagerness and desperation to seek monetary profits and health benefits that involve selfishness and violation of human rights. Organ trafficking involves varying factors and many targeted organs. However, it has been realized through estimations and reports that the most demanded and valuable organ on the international market is the kidney.[26] Furthermore, recent research has shown that chronic renal diseases are significantly increasing among the people of the United Arab Emirates.[27,28] The region is well-known for economic strength and improvements in living standards over the past few decades. However, the evolution of urban culture has led to an increase in people with chronic disorders.[27,28]

Chronic renal disorders are also increasing globally. About 13.4% of the global population has chronic renal disorders, with the greatest number of patients at stages 3, 4, and 5 of chronic kidney disease. About 4.6% of men and 2.8% of women in the United Arab Emirates are affected with different stages of chronic kidney disease.[27] In line with these observations, a possible emerging need for kidney transplants has been identified due to the rising prevalence of chronic kidney disorders. Of note, the United Arab Emirates is known for financial strength; therefore, the combination of demand and availability of adequate finances can attract organ traffickers in the region to market illegal organ procurement.

International Organ Shortages

Some organs can be transplanted from a living person, whereas others can only be explanted after the death of a potential donor. Transplantable organs include the heart,[29] lungs,[30] the liver,[31] kidneys,[32] corneas,[33] and pancreas.[34] Contemporary research has even made advances in transplanting the uterus to treat and manage infertility.[35]

According to a report from the World Health Organization, there are 91 countries that practice kidney transplant.[36] In about 1 year, 100 000 operations are conducted globally that involve human solid-organ transplants. In 2007, the following transplants were recorded: 68 250 kidney, 19 850 liver, 5179 heart, 3245 lung, and 2797 pancreas transplants,[37] with a total of 139 024 organ transplants performed worldwide.[38] In the United States, 39 718 organ transplant procedures were conducted in 2019. However, over 112 000 people are on organ wait lists in the United States, and a new person is added every 10 minutes. On average, 20 people die every day waiting for an available organ in the United States alone.[39] Similarly, in 2009 in China, there were 86 500 renal transplant procedures, with 14 500 hepatic, 900 cardiac, and about 220 other types of transplant operations. Regardless of being under the category of a vulnerable population for organ trade,

around 164 clinical institutes in China are legally licensed to conduct organ transplants.[37]

Although the number of transplant procedures seems notable, it should be considered that these figures are not enough to fulfil the demand of the whole industry. Despite resources and organ donations, the number of available organs for transplant is not enough to achieve the level of global demand. In 2007, the Global Database on Donation and Transplantation reported about 21 489 people who had consented to donate organs after death and from whom the organs were procured after their death.[40] These numbers are not enough to cover the demands of millions of people who are waiting for a healthy organ. In 2010, the United States had 105 966 people waiting for an organ transplant.[39,41]

Likewise, the United Kingdom, another economically stable region, also has a lack of organ donations. In 2008, about 3500 organ transplant operations were conducted in the United Kingdom. However, there were about 9000 patients on wait lists. However, the United Kingdom medical legislation made changes to eliminate bias from the system. The change involved banning private treatment of patients for organ allocation. Private facilities had been raising concerns because wealthy patients could pay for services regardless of other patients waiting for the same organ transplant. This systematic ban to eliminate possible organ trading was implemented in 2009.[42]

In 2007, the European Commission stated that there were 40 000 people waiting for organ transplants. Because the number of donated organs remains low, about 10 patients on wait lists die each day in the European Union.[36] In China, about 14 000 transplants are conducted annually, whereas wait lists in China exceed 300 000 individuals.[43]

The gap between number of donors or donated organs and the number of people waiting for a transplant continues to increase. Moreover, the increasing number of ailments is adding to an ever-increasing gap. Although several institutions are working on ways to spread awareness and spread knowledge on organ donation, the number of donated organs remains low. It is important to understand why the number of donors continues to not increase and why the number of recipients continues to increase. Life expectancy has also increased over the years; therefore, donors are living a longer life, perhaps leading to declined numbers of available organs. To understand these aspects, it is important to review the international approach toward organ donation and its related aspects.

Organ Donation Policy in Different Parts of the World

Although donation and transplant rates for organs vary around the world, there seems to be a shortage of organs for transplant. To combat the immediate need of organ availability, various approaches have been attempted to increase the number of donors. Unfortunately, some approaches have been illegal and unethical. Recently, many international societies of political and social backgrounds have begun to express interest in organ donation. Almost all these organizations have preferred to exercise under practices directed by the World Health Organization. Among the leading bodies, The Transplantation Society has also been an active professional organization in the international pool. The main joint focus of this union is to develop and implement a legally and ethically acceptable plan to encourage states to exterminate the unethical activities and to control the illegal procurement of transplantable organs. Furthermore, their aim also includes encouraging people to participate in organ donation programs with active consent. Many other nations have also initiated ways to become self-sufficient in organ procurement as primary attainment.[44]

Organ transplant has high clinical importance. It is well known that transplant procedures are cost-effective and sometimes the only mode of action to treat patients with end-stage organ failure. Over the past decade, both professional and governmental organizations around the world have started to put their words and actions into the matter of organ transplants, including programs focused on maximizing organ procurement potential by encouraging deceased organ donation and decreasing the demand for transplant using ethical conduct, safe clinical methods, and equal opportunity to every seeker. To ensure the safety of human rights and lives at risk, both deceased and living organ donations have been considered. However, living donation has been the preferred mode globally. Deceased organ donation remains insufficient to fulfil organ demands. Living organ donation, although it does not exist in many parts of the world, is often seen as a healthy source for

transplantable kidneys and livers. However, living donation has the possibility of overt or subtle exploitation of donors; therefore, transplant programs should include strong safety policies.[44-46]

Some countries have adopted policies for organ donation and transplant per guidelines from the World Health Organization and strategies specified by The Transplantation Society and the International Society of Nephrology. Table 2 presents guidelines quoted from the World Health Organization on organ transplant.[44]

With policies defined by the World Health Organization and in collaboration with professional and internationally recognized societies, many countries have set ethically sound approaches for organ procurement. Regions actively taking part include the United Kingdom, the United States, Australia, and Spain.[44] The approaches of each region for procuring transplantable organs are further described below.

Organ procurement in the United Kingdom

Clinicians in the United Kingdom follow a nationally recognized structure as recommended by the Organ Donation Taskforce. The Organ Donation Taskforce functions in 3 steps: (1) delivering the vision of the organization regarding donation in the region, (2) familiarizing local clinical practices with working elements of the donation program, and (3) developing a program friendly environment to present better outcomes. The program's focus is to enhance the number of donors. The primary framework also refers to deceased donation, which considers action during end-of-life care.[46]

Organ procurement in the United States

The Organ Procurement and Transplantation Network (OPTN) was established by the National Organ Transplant Act of 1984. As per the framework of the organization, Medicare and Medicaid Services require hospitals to recognize a potential donor and connect them to their local organ procurement organization. The identification process is mainly conducted in emergency departments, where a potential organ donor is identified.[44,47]

Organ procurement in Australia

Despite the involvement of federal and state administration, Australia struggled to upgrade their organ procurement activities for about 2 decades.

Table 2. Guidelines From the World Health Organization on Organ Transplant

1.	"Cells, tissues, and organs may be removed from the bodies of deceased persons for the purpose of transplantation if any consent required by law is obtained, and there is no reason to believe that the deceased person objected to such removal."
2.	"Physicians determining that a potential donor has died should not be directly involved in the cell, tissue, or organ removal from the donor or subsequent transplantation procedures; nor should they be responsible for the care of an intended recipient of such cells, tissues, and organs."
3.	"Donation from deceased persons should be developed to their maximum therapeutic potential, but adult living persons may donate organs as permitted by domestic regulations. In general, living donors should be genetically, legally, or emotionally related to their recipients. Live donations are acceptable when the donor's informed and voluntary consent is obtained when professional care of donors is ensured and follow-up is well organized, and when selection criteria for donors are scrupulously applied and monitored. Live donors should be informed of the probable risks, benefits, and consequences of donation in a complete and understandable fashion; they should be legally competent and capable of weighing the information; and they should be acting willingly, free of any undue influence or coercion."
4.	"No cells, tissues, or organs should be removed from the body of a living minor for transplantation other than narrow exceptions allowed under national law…. What applies to minors also applies to any legally incompetent person."
5.	"Cells, tissues, and organs should only be donated freely, without any monetary payment or other rewards of monetary value. The prohibition on sale or purchase of cells, tissues, and organs does not preclude reimbursing reasonable and verifiable expenses incurred by the donor, including loss of income, or paying the costs of recovering, processing, preserving, and supplying human cells, tissues, or organs for transplantation."
6.	"Promotion of altruistic donation of human cells, tissues, or organs utilizing advertisement or public appeal may be undertaken in accordance with domestic regulation. Advertising the need for or availability of cells, tissues, or organs, to offer or seek payment to individuals for their cells, tissues, or organs, or, to the next of kin, where the individual is deceased, should be prohibited. Brokering that involves payment to such individuals or third parties should also be prohibited."
7.	"Physicians and other health professionals should not engage in transplantation procedures, and health insurers and other payers should not cover such procedures, if the cells, tissues, or organs concerned have been obtained through exploitation or coercion of, or payment to, the donor or the next of kin of a deceased donor."
8.	"All health-care facilities and professionals involved in the cell, tissue, or organ procurement and transplantation procedures should be prohibited from receiving any payment that exceeds the justifiable fee for the services rendered."
9.	"The allocation of organs, cells, and tissues should be guided by clinical criteria and ethical norms, not financial or other considerations. Allocation rules, defined by appropriately constituted committees, should be equitable, externally justified, and transparent."
10.	"High-quality, safe, and efficacious procedures are essential for donors and recipients alike. The long-term outcomes of the cell, tissue, and organ donation and transplantation should be assessed for the living donor and the recipient in order to document benefit and harm… This requires the implementation of quality systems including traceability and vigilance, with adverse events and reactions reported, both nationally and for the exported human product."
11.	"The organization and execution of donation and transplantation activities and their clinical results must be transparent and open to scrutiny while ensuring that the personal anonymity and privacy of donors and recipients are always protected."

The major influence in the enhancement of organ procurement in Australia developed with the volunteering of surgeons, clinicians, and doctors involved in transplant surgeries and intensive care units. Because of the lack of a structure, the organ donation rate had seen a decline in Australia. However, with voluntary activities in the country, people soon realized the significance and need for organ donation and transplant. This awareness has been largely stimulated through government-financed activities and also the inclusion of known public figures in the campaigns. Over the past few decades, a framework for organ procurement has evolved in Australia that runs on the services of dedicated transplant departments and procurement system. Currently, the Australian Organ and Tissue Authority manages donations in the region, with individual bodies of the state government conducting cross-matching and allocation of tissue types for transplant. Furthermore, Australia has also developed an organization named "DonateLife," which is solely dedicated to organ donation and related concerns. The organization has not only focused on spreading public awareness but has also managed to develop a systematic pool of medical professionals to provide seekers with the best services for transplant. Moreover, the program also has options for potential donors to obtain medical aid in the future. The allocation system in Australia has been established on a national level that includes donation after cardiac death and paired kidney exchange programs. Consequently, organ procurement has been greatly enhanced in Australia. The major contribution in this regard has been of the community, who actively participate in raising awareness, and the political backup to movements and organizations. Currently, the Australian government has taken over the system of organ donation and is now handling all matters at the state level. Therefore, previous voluntary programs also now fall under the category of governmental organizations and/or activities.[44,48]

Organ procurement in Spain

Spain has a defined model for organ transplant that is known as the Spanish Model of Donation and Transplantation. The model includes the Transplant Donor Coordinators, a group introduced by the National Transplant Organisation of Spain. Most of these coordinators are either doctors or nurses. This organ donation model has been successful with regard to the contribution of these active coordinators. The reference points of this model include the activity on the national level along with the practice in regions and hospitals. Coordinators working in hospitals tend to work on enhancing the number of organ donors within their centers. Previously, coordinators were mainly physicians; however, nurses are also now involved in the group.[49,50]

Another factor of success for the Spanish transplant model has been the active involvement of legal protocols. Furthermore, the organ donation program allows participants to opt-out at any moment, giving them space and comfort to look into the program and its benefits in the future. Similarly, despite a patient's active consent during life, after death, relatives are asked about the organ donation and consent before any medical procedure. Nonetheless, approaches of coordinators to the family of the deceased patient and health counseling on the matter have greatly influenced the number of organ donations in Spain. Notably, the number of donations from the local population is equal to the number of donations from immigrants in Spain. Overall, the outcome of the program and the efforts of the coordinators for encouraging donation have been strongly positive.[44,49,50]

Iranian model for organ donation

The Iranian model for kidney donation was established and implemented in 1988. The program works on a legal framework to encourage unrelated individuals to donate kidneys within the community. The program basically works under the Iran Kidney Foundation; the purpose of this foundation is to identify matches for organ recipients among the population pool of unrelated donors. The program is under the administration of local governments along with compensation for recipients as per the requirements.[30,51,52] With extensive legal and governmental assistance, it is expected that the list of patients waiting for organ transplant in Iran might decline in the initial 10 years of implementation of this model. The donation model gained popularity due to its attitude toward the restriction of organ trading in the region, prohibition of organ transplant surgeries within institutes, and limitation to generate profit out of the practice.[40] Despite its commitment to welfare of the local community and great expectations, the Iranian model did not turn out to

be a success in the region. Consequently, in 2011, the list of patients waiting for organ donation expanded to about 17 000 cases.[53]

The Iranian model has some loopholes in terms of ethics and legal protocol. The varying concerns related to the donation model in Iran included the charitable approach of the model, autonomy of the donor, encouragement to living donation, possible coercion among the donors, the involvement of active consent, provision of complete information to the donor, and authoritative nature of the medical intervention.[50,51] Apart from all these issues, the most debatable issue in this regard has been the financial compensation. The model has mentioned defining ways to provide compensation to the donors, bringing concerns about the nature of the donation. The deficient follow-up program, with inadequate medical incentives for donors, has created a wave of uncertainty within the donor community.[54]

Istanbul Declaration on Organ Trafficking and Transplant Tourism, 2008

By 2005, commercial organ trading was a prevalent crime. Only after a long period of commercialization did this subject become noted on international forums in 2005. As stated earlier, most victims of organ trading have been the vulnerable populations of economically weak states like Egypt, India, Pakistan, and the Philippines. Moreover, unethical organ sourcing has also been reported through prisoners executed in China and deceased people of Colombia. In May 2008, the Declaration of Istanbul on Organ Trafficking and Transplant Tourism was developed as a response to this crisis of commercial organ trading. The Declaration was formed by The Transplantation Society and the International Society of Nephrology. At the event, the Declaration of Istanbul Custodian Group was also developed to endorse and manage the principles of organ procurement and transplantation, as defined in the Declaration of Istanbul.

In response to the Declaration, many countries developed and implemented strict policies concerning organ transplants.[24] Developments achieved in each state are described below.

Development in Pakistan

In 2010, the commercial selling of organs was deemed illegal in Pakistan. This proclamation was made under the leadership of the Sind Institute of Urology and Transplantation, in the city of Karachi, with support from the Declaration of Istanbul Custodian Group. Since then, the rate of illegal organ procurement has declined greatly. In the meantime, members of the Declaration of Istanbul Custodian Group have recognized other various illegal and unethical programs running in the region and have subsequently banned them. The declaration has still asserted to keep a check on local activities to cut down on the probability of recurrence of any such practice.[55]

Development in India

From 1980 to the 1990s, India was the most preferred region for commercial procurement of organs. However, in 1994, the Transplantation of Human Organs Act encouraged the Indian Parliament to ban commercial organ trading.[56] In response to the regulation of laws, the rate of organ trading has declined in India. Despite these control measures, the approach of the trading industry changed in the region. Vulnerable sections of society were then coerced into situations with emotional motivations, as the laws did not prohibit unrelated donors to donate in compassion.[24,57] However, these loopholes were amended with the introduction of the Declaration of Istanbul in the region.[56] The amendments then focused on defining relationships when donating organs, ensuring protection of vulnerable populations from exploitation, and having foreign recipients obtain acceptance to organ procurement from the Authorisation Committee of India. Furthermore, many attempts have been made to encourage and motivate the local population to consent to deceased organ donation.[58]

Development in China

It has been reported that organs were obtained from executed prisoners in China for global trade. This concept of donation by execution is an unethical practice, affecting the human rights of prisoners and also rights of the local population in need of organ transplants.[59] The practice had been greatly discouraged by the Declaration of Istanbul Custodian Group and Amnesty International and Human Rights Watch.[59-61] The government of China realized the unacceptance of the international forum on the matter and the illegal nature of the commercial organ trading in the region.[43,59] The responsible officials in China

banned several organ donation programs in the state as per the policies of the Declaration of Istanbul, including the donation by execution.[61] Nonetheless, it has been realized that Chinese law is not yet open to ethical scrutiny as per the human rights and internationally accepted principles of medical ethics concerning organ transplantation in the region.[24]

Development in the Philippines

Due to extreme poverty in some parts of the Philippines, the region evolved as a major source of organ procurement for organ sale. However, in 2008 and in response to the Declaration of Istanbul, a ban was imposed on providing organs to foreign recipients. Subsequently, the Anti-Human Trafficking Law was implemented to control organ trafficking in the region.[24] Soon after the implementation of new laws in the Philippines, the rate of organ recipients from international grounds declined greatly within a year.[62]

Development in Egypt

In the Middle East, Egypt has been considered the most sought state for organ procurement.[25] The Declaration of Istanbul Custodian Group and the World Health Organization intervened in this matter in 2010. In response, Egypt introduced the Law on Human Organ Transplantation, which banned organ trafficking or trading of any sort.[24] Regardless of these laws, Egypt has remained involved in commercial organ trading and trafficking of donors. The reason behind the negligence in the matter has been the political deviations in the country. The state requires a well-organized structure concerning organ transplant that can be effective in the long run.[24]

Development in Colombia and Latin America

For a long time, Colombia and other regions in Latin America provided organs for transplantation to foreign recipients. The regional governments collaborated on this matter and developed laws that concentrated on providing organs to local recipients with priority.[6,24,28] The Latin American Society of Nephrology supported the Declaration of Istanbul and established regulations with the term Document of Aguascalientes in the region, as introduced by the committee.[63] Among all the nations, Brazil was the first state in the region to include the regulation of Declaration of Istanbul as national commandments for organ transplantation.[24]

Organ trafficking in Syria

The ongoing Syrian Civil War has displaced 6.2 million individuals inside the country and forced 5.6 million to vacate Syria, creating an international refugee crisis. These refugees are left homeless and desperate, making them vulnerable to human trafficking, much of which happens during the transit out of Syria. In some host countries, like Egypt, Turkey, Lebanon, Jordan, and Iraq, 60% of Syrian refugees live below the poverty line, making them more desperate for work. Many choose to leave the Middle East entirely and turn to smugglers to get them illegally to Europe. This migration caused a boost in organ trafficking, as desperate Syrians have been willing to sell their kidneys and other organs to survive.[64,65] The illegal business is increasing, causing the Levantine region to become the new prime location for organ trafficking, surpassing China and the Philippines.

Organ trafficking in Iraq

A review of the underlying causes of the increase in human organs trafficked in Iraq showed political and socioeconomic factors as contributors. Following the US invasion in 2003, up to 5 million Iraqis have been displaced inside Iraq, which is the largest number of displacements in the region since 1948. They face strong social stigmas, are highly discriminated, and are forced to live in inhumane, poor conditions. The externally displaced are often living in extreme poverty and subjected to multiple displacements. Many families have no shelter, no finances, and no access to health care, education, or security of any kind, making them vulnerable to human trafficking. Hence, organ trafficking became a lucrative business in Iraq due to the high levels of poverty and little to no intervention from the Iraqi government. The presence of ISIS (Islamic State of Iraq and Syria) in the area had exacerbated the crisis further. Hundreds of cadavers discovered in ISIS-controlled territories in Iraq have revealed that organs appeared to have been purposefully removed, most likely to obtain money from organ retrieval and trading of human organs to the international trafficking mafia, including from its own injured members, prisoners, and deceased individuals. Moreover, the growing number of Syrian refugees in Iraq has put additional strains on local infrastructure and essential services, which were already significantly weakened by the years of war and instability and made these refugees

vulnerable to organ trafficking. As per the Director General of the Syria Coroner's Office, from 2011 to November 2015, more than 25 000 surgical operations were performed in refugee camps of neighboring countries and ISIS-controlled areas of Syria and Iraq, with an estimated 15 000 Syrian organs removed and sold on the black market.[66,67]

Current Approach of the Declaration of Istanbul

The Declaration of Istanbul has been recognized and endorsed by about 115 global bodies dedicated to the matter of organ transplant. The union on such a vast scale has been escalated by conference participation, organized by the members of the Declaration of Istanbul. The condition to participate, to present their work, or even to join as a guest speaker in the conference has been to endorse the policies of the Declaration. Furthermore, it was also necessitated for most internationally recognized journals to identify the author's association with the Declaration of Istanbul before publishing the paper. Once endorsed, members must ensure that any conflicts in exercising the policy shall be communicated to the Patient Affairs Committee. This committee has been dedicated to evaluating practices in certain locations and only communicates with the high authorities of the country rather than with the groups within. As a result, authorities in many countries seem to be more responsible for their local activities to avoid any possible chance of unethical conduct regarding organ procurement and transplant.[61]

Another significant impact was the media unit of the Declaration of Istanbul Custodian Group. The members of the media unit have been working extensively to encourage change in national policies of several countries, which has turned out to be a successful approach. The main focus of the media unit has been to discourage commercial trading of organs among people and to bring changes in the policies of states. Regardless of the extensive networking and massive upgrade of the system, the shortage of transplantable organs remains a global concern.[61,68] In the following section, we discuss the varying factors of this subject as per the global approach.

Organ transplants and the global approach

The World Health Organization has developed an association between the rates of transplants around the world and the Human Development Index (HDI). Countries with a low to average HDI have shown a decline in the rate of transplants. However, countries with comparatively higher HDI have exhibited increases in rates of transplant. The rates of transplant are recorded in units of pmp (per million population).[69] In 2010, economically stable regions like Australia, Western Europe, and the United States showed transplant rates of about 30 pmp (range of 20-30 pmp across countries).[61,70]

Among the more wealthy regions, the United States has had the highest number of total organ transplant surgeries as well as the highest rates of transplant per million population. Nonetheless, a variation in transplant rate has been observed within some US populations, particularly among minority groups and underprivileged communities, including African American and White populations. Moreover, it was also noted that, comparatively, women are more deprived of required transplant procedures in the United States.[70] Likewise, it has been recorded that Aboriginal populations have a 46% lower rate of transplant in Canada followed by 34% of African and 31% of Asian populations.[71] In Australia, the Aboriginal population has about 45% less probability of receiving transplants, whereas in New Zealand, the Maori population and people from the Pacific Islands have 53% less chance of organ transplant.[68] The rate of transplants also varies with the capability of the population. For instance, people with health insurance in Mexico tend to have a higher rate of transplant (ie, 72 pmp) compared with those who may not have insurance (ranging up to only 7 pmp).[71]

The reason behind the low rate of transplant in economically weak countries is the factor of instability among the local population. These reasons can vary according to regional differences, including social factors, cultural outlook, and economic stability along with the clinical concerns for immunology, biological matching, genetic cross-matching, metabolic factors, pharmacological concerns, and incidence of comorbidity in the community. Similarly, transplant rates may also vary with the availability of skilled professionals and postoperative care and management in the region for both the donor and the recipient.[69,] To attain more success in organ transplant, authorities must develop a friendly framework for organ procurement and management of patients. Moreover, it is also necessary to cultivate a globally integrated transplant program to enhance the rate of

procurement and transplant of organs for all kinds in populations around the world.

Ethics and Equality in Organ Transplant

The allocation of a donated organ is a complicated process that requires coordination of various factors, including among donors and recipients. During organ procurement and allocation, it is crucial to ensure that human rights codes are applied.

Organ recipients

As a result of the increasing number of cardio-metabolic disorders and increasing life expectancy, the incidence of end-stage organ failure has risen globally. Although organ transplant is required as a response to organ failure, it often becomes complicated for authorities to identify and prioritize recipients for an available organ. Nonetheless, the number of donated organs keeps declining, while the number of recipients keeps on increasing. To deal with this situation, organ transplant protocols have been restructured in some countries such as Singapore, Israel, and Chile with innovative donor-recipient clauses. It is stated that people who are registered as organ donors in the national registry will be prioritized for organ transplant if they would be in a situation to require transplant procedures in the future. The clause has been estimated to encourage more donors in the pool with a notable benefit for the future.[72]

Living donors

Research has shown that kidney retrieval from a living donor is clinically safe. However, a slight chance of death has also been reported in such cases.[20] It is often expressed that procuring kidneys from living donors could greatly influence the global sufficiency of renal transplants. Concerning the significance of living organ donation, the Declaration of Istanbul has asserted in their policies to ensure the protection of rights of living donors. Living donation, however, has been a part of commercial organ trading and trafficking for quite a long time.[73] Therefore, it is necessary to provide safety in this regard to donors and avoid the element of exploitation in such cases. Subsequently, living donors must be recorded and followed in case of clinical complications or need for medical aid in the future related to the organ donation.[73]

Deceased donors

Deceased organ donation is the most frequent form of organ procurement in the United States. It has been stated that a deceased individual can save multiple lives by donation of essential organs to clinical authorities. Although the individual must sign up in life to be a donor, the immediate family of the deceased individual can also consent for organ donation. Contemporary protocols have focused on enhancing the number of registered deceased organ donors globally, as 1 deceased donor has the potential of saving many lives and declining the gap between organ availability and the number of patients waiting for transplant.[73]

Medical ethics and other issues

For organ allocation, it is important to justify the need of the recipient. With regard to life expectancy of the recipient, it has been expressed that patients less than age 50 years should be prioritized for transplant. However, the clause has been deemed unethical to some extent; in response, it has been asserted that the biological fitness of a patient for transplant should be considered rather than age.[73]

Another concern that has often been observed in international fields is the lack of biological compatibility due to much higher mismatching among unrelated donors and recipients. Human leukocyte antigen matching among donors and recipients may show differences of races or ethnicities between donors and recipients, which may lead to longer waiting time for transplants and lesser chances for minorities to receive an organ.[74] Furthermore, with regard to physical fitness, people with obesity are often underprioritized for transplant and have to wait longer. The factors ultimately increase their risk of death during support procedures like dialysis.[74]

Reports and observations for organ recipients tend to express a bias in terms of economic stability, age, race, sex, and even geographical location.[74] Along with legal organ procurement protocols, there is also a need to develop globally organized well-regulated bodies for ethical organ allocation.

Conclusions

The review of global practices and policies of organ transplant has suggested a dire need for more ethical principles and a way to equitably distribute organs

around the globe as per the respective need. Authorities play a crucial role in controlling the illegal and unethical forms of organ procurement. The main concern in this matter is that each affected region, in terms of organ trafficking, has its own legal system and varying ethical values. These variations within societies and communities play a part in the ethical and legal procurement and distribution of organs. Therefore, it is proposed that individual evaluations be conducted on the ground level in each region. Moreover, increased attention is needed in the legal procurement of organs. There should be a focus on the ethical allocation of organs to recipients and consensual organ procurement from potential organ donors.

Limitation of the Study

A review of the global literature involves vast searches of materials and reviews of the literature. However, evidence on the matter of organ trafficking or trading is rather limited. The main reason behind this limitation is the lack of global legal regulations. Likewise, due to certain laws and the influence of large finances, such medical crimes are often cleared easily or not easily traced, especially without the subtle (or implied) support of the highest in the land. Therefore, information provided from certain regions may have been restricted. Similarly, data may have also changed over time.

Recommendations for Further Approach

In support of the discussion of Clawson and associates,[75] it is recommended that studies should evaluate the role and status of organ recipients to create a much more organized environment for safe and effective implementation of evidence-based principles of clinical transplantation. Furthermore, future approaches should emphasize the challenges of unethical practices in organ donation.[13] A comprehensive study should be conducted on the challenges of organ donation so that professionals could recognize prevailing issues within each region and then counteract each problem accordingly. Previously evaluated records have already highlighted the health care systems that are most affected by the unethical practices of organ trade. The next step with respect to both research and practical approaches is with regard to organ facilitation.

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Outcomes of Nonstandard Donor Kidney Transplants in Recipients Aged 70 Years or More: A Single-Center Experience

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Abstract

Objectives: **There is a global increase in the prevalence of end-stage kidney disease among the elderly. As a result, more elderly recipients are being considered for kidney transplants. Because of the scarcity of donor organs, such patients are more likely to receive transplants from nonstandard donor kidneys. Here, we examined the outcomes of kidney transplants with a nonstandard donor allograft in recipients ≥70 years of age.**

Materials and Methods: **Records of patients who received transplants at a single UK center from April 1, 2015, through March 31, 2021, were retrospectively analyzed to identify those who were ≥70 years old at the time of surgery. Outcomes of those who received a kidney transplant from a nonstandard donor (group 1) were compared to those who received a kidney transplant from a standard criteria donor or living donor (group 2).**

Results: **During the study period, of 670 kidney transplant procedures, 67 recipients (10%) were ≥70 years of age at the time of surgery, with 54 (80.6%) identified in group 1 and 13 (19.4%) identified in group 2. Cold ischemia time (*P* = .001) and incidence of delayed graft function (*P* = .044) were significantly higher in group 1. Duration of graft survival at the end of follow-up was not different between the groups (log rank = 0.218), but the mean serum creatinine values at 2 years (*P* = .016) and 3 years (*P* = .048) years were significantly higher in group 1. Patients in group 1 had shorter survival time (log rank = 0.037).**

Conclusions: **Nonstandard donor kidneys should be used cautiously in elderly recipients as patient survival was shown to be comparatively poor compared with elderly recipients who received a kidney transplant from a standard criteria donor or a living donor.**

Key words: *Elderly recipient, Extended criteria donor, Renal transplant*

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Introduction

The prevalence of end-stage kidney disease (ESKD) in the elderly keeps on increasing.[1] Current guidelines recommend kidney transplant (KT) as the best mode of renal replacement therapy for most patients, irrespective of their age.[2] Advanced age is no longer considered as an absolute contraindication for KT, and the age cutoff used to define the "elderly recipient" has progressively increased.[3] According to data, the age of the recipient does not preclude the advantages of KT, such as better survival and quality of life.[4,5]

The widening disparity between the number of patients on wait lists and the availability of suitable donor organs has been a major limiting factor for the more widespread adoption of KT in patients with ESKD. The utilization of kidneys from nonstandard donors (NSD) has emerged as a solution for this problem. With regard to KT, extended criteria donors (ECDs) and donors after circulatory death (DCD) are categorized as NSDs. An ECD is defined as a brain dead organ donor (DBD) who is ≥60 years of age or a donor aged 51 to 59 years with at least 2 of the following risk factors: hypertension, cerebrovascular cause of death, or terminal creatinine >1.5 mg/dL.[6]

Patients who receive KTs from ECDs or DCDs have better outcomes than those who remain on dialysis. However, when compared with KT from a living donor (LD) or a KT from an SCD, recipients of these marginal allografts have increased risks of complications such as delayed graft function (DGF) and acute rejection.[5]

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Current national organ allocation policies tend to age match donor-recipient pairs, so elderly patients listed for deceased donor KTs are more likely to receive organ offers from ECDs or elderly DCDs.[7] Recipients with advanced age are more likely to have comorbidities, and their physiology may not tolerate the added toll of a serious posttransplant complication. Thus, the decision to transplant an elderly recipient with an NSD kidney may not be straightforward. In this retrospective study, we examined the outcomes of such NSD KTs performed at the Royal Liverpool University Hospital in recipients aged ≥70 years.

Materials and Methods

Electronic medical records of patients who received a KT at the Royal Liverpool University Hospital from April 1, 2015, through May 31, 2021, were retrospectively reviewed to identify recipients who were aged ≥70 years at the time of transplant. The standard induction immunosuppression regimen was 2 doses of intravenous basiliximab. Sensitized recipients, the presence of 2 mismatches at the HLA DR locus, and those who were transplanted with a DCD organ were preferentially given a single dose of subcutaneous alemtuzumab 30 mg at the induction. Maintenance immunosuppression was with tacrolimus and mycophenolate mofetil. After discharge from the hospital, patients were followed up at transplant or nephrology clinics as outpatients.

Outcomes after KT of those who received a kidney from an NSD donor (group 1) were compared against those who received a kidney from an SCD or LD (group 2). Living donors included related (parents to offspring and sibling to sibling) and nonrelated (spouse to spouse) donors. Delayed graft function was defined as the need for dialysis within the first week of transplant.

Statistical analyses

We analyzed data using SPSS statistical software. We used the Fisher exact test to determine the relationship between 2 variables and the independent sample *t* test to compare means across the groups. We used Kaplan-Meier survival curves to calculate and compare recipient and graft survival rates. $P < .05$ was statistically significant.

Results

Recipient and transplant characteristics

During the study period, 670 KTs were conducted at our center, and 67 recipients (10%) were aged ≥70 years at the time of transplant. Among those recipients ≥70 years of age, most received organs from DCDs (32/67, 47.8%), followed by DBDs (27/67, 40.3%) and LDs (8/67, 11.9%: 2 parent to offspring donations, 4 sibling to sibling donations, and 2 spouse to spouse donations). Group 1 included 54 recipients (80.6%) who had KTs from DCDs (n = 32) or extended criteria DBDs (n = 22), and group 2 included 13 recipients who had KTs from SCDs (n = 5) or LDs (n = 8).

The 2 groups had similar demographic characteristics, such as male-female distribution, mean age, and comorbid conditions. There were no significant differences in the degree of HLA mismatch or the agent used for induction immunosuppression. The mean cold ischemia time (CIT) was significantly longer for recipients in group 1 (860.3 vs 548.08 min; $P = .001$). These findings are summarized in Table 1.

Table 1. Recipient and Transplant Characteristics

	Group 1 (n = 54)	Group 2 (n = 13)	*P* Value
Source of the allograft, No.			
DBD SCD	0	5	
DBD ECD	22	0	
DCD	32	0	
LD	0	8	
Mean recipient age	72.94	72.08	.828
Sex, No.			
Male	41	12	.180
Female	13	1	
Comorbidity			
Diabetes	12	2	.454
Hypertension	48	11	.487
Peripheral vascular disease	2	2	.167
Mean donor age, years	64.26	49.08	.094
Mean CIT, min	860.3	548.08	.001
Induction agent, NO.			
Alemtuzumab	28	4	.145
Basiliximab	26	9	
Mean HLA mismatch	3/6	3.23/6	.051

Abbreviations: CIT, cold ischemia time; DBD, brain dead organ donor; DCD, donor after circulatory death; ECD, extended criteria donor; LD, living donor; SCD, standard criteria donor

Group 1 were kidney transplant recipients aged ≥70 years who received an organ from a nonstandard donor. Group 2 were kidney transplant recipients aged ≥70 years who received an organ from a standard criteria donor or a living donor.

Patient and graft survival

The median follow-up duration was 31 months (range, 1-73 months). At the end of follow-up, 19/54

recipients (35.18%) in group 1 and 1/13 recipients (7.69%) in group 2 had died. The commonest cause of death among patients in group 1 was infections (n = 8) followed by cardiovascular causes (n = 7) and malignancies (n = 4). The single patient death recorded in group 2 was due to myocardial infarction. The recipient survival rate was significantly less in group 1 (log rank = 0.037). Table 2 shows overall recipient survival rates at 1, 3, and 5 years posttransplant. Figure 1 depicts the Kaplan-Meier survival curves for recipients in each group.

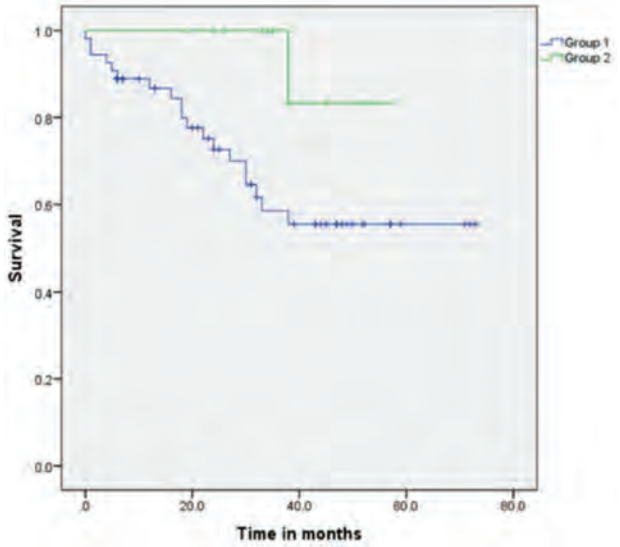
Death-censored graft survival rates in groups 1 and 2 at the end of follow-up were 88.88% (48/54) and 100% (13/13), respectively. There was no significant difference in graft survival between the groups (log rank = 0.218).

Table 2. Recipient Survival Rate

Time Posttransplant	Survival Rate	
	Group 1	Group 2
1 year	86%	100%
3 years	78%	100%
5 years	56%	82%

Group 1 were kidney transplant recipients aged ≥70 years who received an organ from a nonstandard donor. Group 2 were kidney transplant recipients aged ≥70 years who received an organ from a standard criteria donor or a living donor.

Figure 1. Kaplan-Meier Survival Curves for Recipients in Groups 1 and 2



Group 1 were kidney transplant recipients aged ≥70 years who received an organ from a nonstandard donor. Group 2 were kidney transplant recipients aged ≥70 years who received an organ from a standard criteria donor or a living donor.

Graft function

There was no statistically significant difference in the mean serum creatinine level across the 2 groups at 3 months, 6 months, and 1 year. However, at 2 years (P = .014) and 3 years (P = .048), a significantly higher mean serum creatinine value was noted in group 1.

Posttransplant complications

The incidence of DGF was significantly greater in group 1 versus group 2 (13/54 vs 0/13; P = .044). Twelve recipients in group 1 were treated for acute rejection, whereas 0 recipients in group 2 had this complication (P = .057). There was no statistically significant difference in the incidence of viral or bacterial infections between the 2 groups (Table 3).

Table 3. Posttransplant Complications

	Group 1 (n = 54)	Group 2 (n = 13)	*P* Value
Delayed graft function, No.	13 (24.07%)	0	.044
Acute rejection, No. (%)	12 (22.22%)	0	.057
Viral infection			
Total	17 (31.48%)	2 (15.38%)	.212
CMV	11 (20.37%)	1 (7.69%)	.265
EBV	4 (7.4%)	0	.413
BK virus	5 (9.25%)	2 (15.38%)	.410
Bacterial infection	16 (29.62%)	3 (23.07%)	.462

Abbreviations: CMV, cytomegalovirus; EBV, Epstein-Barr virus

Group 1 were kidney transplant recipients aged ≥70 years who received an organ from a nonstandard donor. Group 2 were kidney transplant recipients aged ≥70 years who received an organ from a standard criteria donor or a living donor.

Discussion

The burden of ESKD in the elderly population continues to increase.[1] Kidney transplant has been recommended as the optimum mode of renal replacement therapy for selected patients with advanced age. At present, no upper age cutoff has been recommended to exclude a patient with ESKD as a potential KT candidate.[2] Thus, the number of elderly recipients who are listed for KT has increased, and there is a reciprocal rise in the number of transplants performed in this age group.[8,9] Previous studies have reported encouraging outcomes in KT recipients over 70 years of age, and currently "fit" octogenarians are offered KT.[10,11]

To bridge the ever-widening gap between the supply and demand for transplantable organs, the utilization of kidneys from NSDs has increased.[5] The present national organ allocation policies preferentially offer kidneys retrieved from such NSDs to elderly recipients.[3,7] The rationale behind this practice is to achieve a better match between the life expectancy of the recipient and the donor organ, as kidneys from NSDs have a comparatively lower

average length of function.[7] Another proposed advantage of such allocation is the reduction of waiting time for elderly recipients; elderly recipients are at a higher risk of death if they remain on wait lists for prolonged durations.[3,12]

Previous studies have reported conflicting outcomes after NSD KTs in elderly recipients. Rao and colleagues noted a 25% reduction in the mortality risk in recipients ≥70 years of age when they were transplanted with ECD kidneys.[10] In another study, Savoye and colleagues reported that ESKD patients aged 60 years or more had better survival after receiving transplants from ECDs compared with remaining on the waiting list.[13] In contrast, Bonal and colleagues noted that ESKD patients from 65 to 70 years of age had no mortality benefit after transplant.[9] Another study from Peters-Sengers and colleagues reported that recipients aged ≥65 years who received a kidney from an elderly donor had a 5-year mortality rate comparable to those who remained on dialysis.[7]

Our findings suggested that recipients aged 70 years or above who were transplanted with LD or SCD kidneys do better in terms of survival than recipients in the same age group who have received an NSD kidney. The overall graft survival was not significantly different across the 2 groups, but graft function at 2 and 3 years posttransplant was inferior in those transplanted with an NSD kidney. When recipient- and transplant-related factors were compared between the 2 groups, apart from the difference in the source of the donor organs, recipients in group 1 (NSD recipients) had significantly longer CIT and greater incidence of DGF. We believe that these disparities may have contributed to the inferior recipient and graft outcomes seen in group 1. Thus, interventions aimed at limiting the CIT and DGF may improve the outcomes of NSD transplants in elderly recipients.

The value of limiting CIT has been recognized before by the Eurotransplant Senior Program, which allocates kidneys retrieved from deceased donors aged ≥65 to recipients aged ≥65 on a regional basis. This strategy limits the CIT compared with offering such marginal organs on a national level.[14]

Donor-related risk factors for DGF, such as advanced age, presence of hypertension, and DCD status, are more common in NSD kidneys.[16] Delayed graft function has been recognized as a predictor of adverse graft and recipient outcomes after KT.[15,16] Recent studies have indicated that machine perfusion of deceased donor kidneys significantly reduces the risk of DGF compared with traditional static cold storage.[17] Thus, machine perfusion of marginal allografts before implantation may lead to better outcomes in elderly recipients who receive such organs.

Gill and colleagues reported that older recipients with high cardiovascular risk have significantly reduced risk of perioperative mortality when they are preferentially transplanted with kidneys procured from LDs.[16] Thus, for elderly recipients with a high cardiovascular risk, LD transplants should be encouraged. Donor nephrectomy can be performed safely in carefully selected elderly LDs, and a LD transplant between an age-matched donor-recipient pair will be an acceptable option.[18,19] When there are no suitable LDs, consideration should be given to allocating better quality DBD organs to elderly patients with risk factors.

Conclusions

Our experience with transplanting recipients aged 70 years or more with NSD kidneys indicated that these recipients have a higher risk of mortality compared with those of similar age who received an SCD or a LD transplant. There are several limiting factors in our study. It was a retrospective, single-center study with a small sample size, and the comparison group included those who received kidneys from standard criteria DBD donors as well as LDs. However, we believe that our findings highlight that there is a need for a national study with larger patient numbers to examine the post-KT outcomes of elderly recipients who receive NSD kidneys. Furthermore, strategies should be considered that may improve the outcomes of such transplants in the elderly, such as limiting the CIT and machine perfusion of donor organs.

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Diagnosis and Treatment of Latent Tuberculosis Infection in Kidney and Liver Transplant Recipients in Iranian Candidates for Transplant

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Abstract

Objectives: **The rates of tuberculosis and its mortality are higher in solid-organ transplant recipients than in the general population. In this study, we compared the rate of active tuberculosis disease conversion in solid-organ transplant recipients based on pretransplant tuberculin skin test results and also its association with treatment.**

Materials and Methods: **This cross-sectional study included kidney/liver transplant recipients who had pretransplant tuberculin skin test indurations of ≥5 mm and who were seen from March 2009 to March 2019 at the Shiraz Nemazi Hospital Transplant Center (Shiraz, Iran). Data were analyzed using SPSS software, and *P* < .05 was considered significant.**

Results: **Of 6289 solid-organ transplant recipients seen at our center over the 10-year period, 334 recipients (mean age of 46.0 ± 13.8 years; 67.6% men) had tuberculin skin test indurations of ≥5 mm. Of these 334 recipients, 76.3% had kidney transplant, and the remainder had liver transplant. Of patients who received complete treatment for latent tuberculosis, the rate of conversion to active tuberculosis was lower than in those who did not adhere to medication (8.6% vs 43.7%; *P* < .001). In addition, the rate of active tuberculosis development was higher in patients who had pretransplant tuberculin skin tests results of ≥10 mm compared with those who had results of 5 to 9 mm (15.8% vs 3.4%; *P* < .001).**

Conclusions: **Latent tuberculosis diagnosis and treatment before solid-organ transplant can reduce active tuberculosis conversion and its associated morbidity and mortality. We recommend modifying the cutoff point considered for tuberculin skin test positivity for solid-organ transplant candidates in Iran to ≥10 mm, although further evaluations are needed.**

Key words: *Kidney transplantation, Latent tuberculosis infection, Liver transplantation,* Mycobacterium tuberculosis

Introduction

In solid-organ transplant (SOT) recipients, the incidence of *Mycobacterium tuberculosis* disease has been reported to range from 0.2% to 13.7%, which is 20 to 74 times higher than in the general population. Mortality associated with *M. tuberculosis* can be as high as 31% in the SOT population[1,2] as a result of immunosuppressive drugs, which inhibit T-cell (CD4-positive T cell) proliferation. Although there is an explicit time delay between *M. tuberculosis* infection and T-cell response, it has been proved that T cells play a key role in protection against the infection.[3-5]

Active tuberculosis (TB) in transplant recipients can arise from latent TB (LTBI) in the candidate recipient or donor, can occur from a de novo posttransplant infection, and can occur in a patient with TB after transplant.[6,7] Latent TB is defined by the World Health Organization as "a state of persistent immune response to stimulation by *Mycobacterium tuberculosis* antigens with no evidence of clinically manifest active TB."[8] The lifetime average rate of LTBI conversion to active TB disease is approximately 5% to 10%, which can be as high as 22% to 25% in SOT recipients, especially in those who do not receive treatment.[7-10]

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Pretransplant screening of recipients and, if possible, donors for TB infection is an important component of the transplant process.[2,7] Current methods for screening LTBI are tuberculin skin test (TST) and interferon-gamma release assay (IGRA), which are based on measuring immune responses to *M. tuberculosis* antigens.[11] However, there is no strong evidence in the superiority of IGRAs over TST for LTBI diagnosis, as IGRA positivity is more related to the radiological evidence of previous TB.[12]

The recommended cutoff points of positive TST in SOT recipients vary between guidelines (considering induration size of either ≥5 mm or ≥10 mm) on the basis of local TB endemicity.[2] Although the incidence of TB in Iran has decreased in recent years as a result of better control measures, the danger of infections still exists because of proximity to high-TB burden countries like Pakistan and Afghanistan.[13] In this study, we analyzed rates of active TB disease conversion in kidney and liver transplant recipients who had pretransplant TST induration results of ≥5 mm and the association of outcomes in these patients with medication adherence. Patients with TST induration results of 5 to 9 mm versus ≥10 mm were also compared.

Materials and Methods

Study design and population

This cross-sectional study included kidney and liver transplant recipients who had pretransplant TST indurations of ≥5 mm and who were seen from March 2009 to March 2019 at the Shiraz Nemazi Hospital Transplant Center, Shiraz University of Medical Sciences (Shiraz, Iran).

Data collection

Demographic data and laboratory results of kidney and liver transplant recipients were retrospectively obtained from medical records at the Transplantation Office and the Health Center (Shiraz University of Medical Sciences). Data collected included sex, age, transplant time, cause of end-stage renal disease or liver cirrhosis, comorbid diseases, pretransplant TST and chest radiograph results, duration of LTBI treatment, and any history of conversion to active TB disease. We also collected information on post-transplant immunosuppressant drugs, transplant rejection, posttransplant admission duration, and any history of drug use.

Inclusion and exclusion criteria

Inclusion criteria were as follows: all kidney or liver transplant recipients who had pretransplant TST indurations of ≥5 mm. Exclusion criteria were as follows: pretransplant active TB disease, well-founded suspicion of active TB disease, patients who refused to attend follow-ups, patients with incomplete medical record data, and patients who died. All patients received deceased donor transplant procedures.

Screening and treatment of latent tuberculosis

Tuberculin skin test was performed by intradermal injection of 0.1 mL purified protein derivative (PPD); check-ups for induration results were viewed after 48 to 72 hours (Mantoux method). All patients with TST indurations of ≥5 mm were considered to have a positive test. Patients were categorized into the following 2 groups on the basis of their TST induration size: 5 to 9 mm and ≥10 mm. Active TB disease was ruled out in all patients with the use of an acid-fast bacteria culture for any patient who had clinical and/or radiological data in favor of the disease.

For treatment of LTBI, isoniazid and pyridoxine were prescribed for 9 months. Patients were followed up for any symptom of active TB disease (including fever, weight loss, night sweats); if any appeared, the diagnosis was confirmed by laboratory tests and radiographs. A complete treatment for LTBI prophylaxis was defined as taking isoniazid 300 mg/day supplemented with pyridoxine regularly for 9 months.[6]

Ethical considerations

The study was performed in accordance with the Declaration of Helsinki and approved by the local ethics committee of Shiraz University of Medical Sciences. Patients provided consent for use of their anonymized data before registration in the medical record database.

Statistical analyses

The results of continuous variables are presented as means ± SD and those related to the quantitative or categorical data are presented as frequency and percentage. Chi-square tests were used to assess the relationship of qualitative data, and independent *t* tests were used to evaluate the correlation of a quantitative data. We used Statistical Package for Social Sciences version 23 (SPSS Inc) for statistical analysis. $P < .05$ was considered significant.

Results

Over the 10-year study period, there were 6289 SOT recipients seen at our center, of which 3334 patients had liver transplant, 2817 had kidney transplant, and 138 had kidney and pancreas transplant. Of these 6289 SOT recipients, 334 (5.3%) had TST indurations of ≥5 mm (5.3%) and were included in our study. Among these 334 kidney or liver transplant recipients with pretransplant diagnosis of LTBI, only 34 (10.1%) developed active TB.

Table 1 shows characteristics of patients included in our study. Mean age was 46.0 ± 13.8 years, and 226 recipients (67.6%) were men. The mean age of women was significantly lower compared with the mean age of men (42.2 ± 13.5 vs 47.8 ± 13.5 years; $P < .001$). Of total recipients included in the study, 76.3% had kidney transplant; the most common causes of end-stage renal disease were hypertension (71.8%) and diabetic nephropathy (28.6%). In the liver transplant recipients, the most common causes of cirrhosis were viral hepatitis (50.6%) and cryptogenic cirrhosis (17.7%).

The mean duration time of transplant of studied patients was 4.7 ± 3.3 years (most of the patients have been included in our study 2 years after transplant). Patients had a mean of 3.8 ± 1.5 posttransplant admissions (range, 0-8). Of 334 recipients included in the study, 58 (17.3%) had a transplant rejection episode. The primary maintenance immunosuppressants used included steroids (94.6%), calcineurin inhibitors (93.1%), and mycophenolate mofetil (91.6%).

Patients who developed active TB (n = 34) had a mean age of 49.8 ± 11.2 years. Of these patients, 24 (70.5%) were men and 10 (29.4%) had allograft rejection. In addition, 22 patients with active TB (64.7%) were kidney transplant recipients and 12 were liver transplant recipients (Table 2). That is, of 2955 kidney transplant recipients, 0.75% developed active TB.

Of 303 patients (90.7% of total studied population) who received complete treatment regimens for LTBI, only 26 patients (8.6%) developed active TB disease. However, in 16 patients (4.8% of total studied population) who did not adhere to their medication, 7 (43.7%) developed active TB. Thus, the rate of LTBI conversion to active TB was significantly higher in patients who had poor adherence to their anti-TB regimens ($P < .001$).

Our results also showed that the rate of active TB development was significantly higher in patients who had pretransplant TST induration results of ≥10 mm versus those with TST induration of 5 to 9 mm (15.8% vs 3.4%; $P < .001$) (Table 3).

Table 1. Patient and Transplant Characteristics

Characteristic	Result (N = 334)
Mean age ± SD (range), years	46.0 ± 13.8 (14-76)
No. of men (%)	226 (67.6)
Kidney transplant patients, No. (%)	255 (76.3)
Common cause of end-stage renal disease,* No. (%)	
Hypertensive nephropathy	183/255 (71.8)
Diabetic nephropathy	73/255 (28.6)
Obstructive nephropathy	28/255 (11.0)
Liver transplant patients, No. (%)	79 (23.6)
Common cause of liver cirrhosis, No. (%)	
Viral hepatitis	40/79 (50.6)
Cryptogenic cirrhosis	14/79 (17.7)
Malignant infiltration of the liver	13/79 (16.5)
Other	12/79 (15.2)
Allograft rejection, No. (%)	58 (17.3)
History of chronic drug use, No. (%)	300 (89.8)
Mean duration of transplant ± SD (range), year	4.7 ± 3.3 (<1-11)
Mean posttransplant number of admission ± SD (range)	3.8 ± 1.5 (0-8)
Mean serum creatinine level ± SD(range), mg/dL	1.6 ± 1.5 (1-1.8)
Common maintenance immunosuppressant, No. (%)	
Steroids (prednisolone)	316 (94.6)
CNI (cyclosporine or tacrolimus)	311 (93.1)
Mycophenolate mofetil	306 (91.6)
mTOR inhibitor (sirolimus)	35 (10.4)
Common comorbidity	
Hypertension	184 (55.0)
Cardiovascular disease	104 (31.1)
Diabetes	90 (27.0)

Abbreviations: CNI, calcineurin inhibitor; mTOR, mechanistic target of rapamycin

*A patient could have presented with more than 1 cause.

Table 2. Distribution of Active Tuberculosis Among 34 Transplant Recipients

Characteristic	Results
Mean age ± SD (range), year	49.8 ± 11.2 (30-72)
Total No. of men (%)	24 (70.5)
Kidney transplant patients	22 (64.7)
Mean age ± SD, year	46.1 ± 11.0
No. of men (%)	13 (59)
Liver transplant patients	12 (35.3)
Mean age ± SD, year	57.1 ± 7.9
No. of men (%)	11 (91.6)
Allograft rejection	10 (29.4)

Table 3. Distribution of Latent Tuberculosis Conversion to Active Tuberculosis Based on Patient Treatment and Tuberculin Skin Test Response

Variable	Total, No. (%)	TB Infection, No. (%)		*P* Value
		Active TB	Latent TB	
Total	334 (100.0)	34 (10.1)	300 (89.8)	<.001
TB prophylaxis				<.001
Complete	303 (90.7)	26/303 (8.6)	277/303 (91.4)	
Incomplete	16 (4.8)	7/16 (43.7)	9/16 (56.3)	
No prophylaxis or unknown	15 (4.5)	1/15 (6.7)	14/15 (93.3)	
TST response (induration size)				<.001
5-9 mm	145 (43.4)	5 (3.4)	140 (96.6)	
≥10 mm	183 (54.7)	29 (15.8)	154 (84.2)	
Unknown	6 (1.8)	0 (0)	6 (100.0)	

Abbreviations: TB, tuberculosis; TST, tuberculin skin test

Discussion

In this study, we evaluated the rate of active TB disease conversion in 334 SOT recipients who had been diagnosed and treated for pretransplant LTBI. We also classified patients into 2 groups according to their pretransplant TST induration size (5-9 vs ≥10 mm) in order to compare the incidence rate of active TB disease between the 2 groups; this comparison could help us to consider a reasonable threshold for positive TST in SOT candidates in Iran.

In patients with chronic renal failure, TB tests are recommended, with induration of at least 10 mm being considered as a positive reaction.[14] Although some guidelines from different countries recommend a positive TST threshold of ≥5 mm,[15-18] other countries that have high TB burden recommend a threshold of >10 mm for a positive test.[5,19] Thus, cutoff points considered for TST positivity in SOT recipients vary across guidelines as result of different epidemiological burdens of TB among countries.[10,15] Positivity of TST results has been shown to range from 12% to 26%, 10% to 62%, and 17%, respectively, in countries with low, intermediate, and high TB burden.[20] Iran is a high-risk country due to its proximity to Pakistan and Afghanistan, which have high TB burden.[13] Studies conducted by Moradi and colleagues[21] and Tabrizi and colleagues[22] in Iran showed a high incidence of TB among immigrants who came from Afghanistan, Pakistan, Bangladesh, and India.

Although the currently used cutoff point for TST in SOT recipients in Iran is ≥5 mm,[23] our results showed a significant higher LTBI progression to active disease among patients who exhibited induration size of ≥10 mm (15.8%) compared with those with TST results of 5 to 9 mm (3.4%). Although the main LTBI treatment options, including isoniazid and rifamycins, are associated with serious side effects like hepatotoxicity1 and the cutoff point of 5 mm for TST positivity may cause an increased number of patients with LTBI diagnosis (and consequently more patients would be at risk of medication side effects[24]), our recommendation is to modify the cutoff point to ≥10 mm in Iran.

We found that the rate of active disease conversion was higher among patients who failed to adhere to their treatment regimens compared with those who took their medications regularly (43.7% vs 8.6%). The beneficial effect of isoniazid therapy for LTBI has been evaluated and confirmed in a retrospective 9-year cohort study in which the results showed that the rate of active TB conversion among 155 patients who did not receive isoniazid was higher (2%) than the 0% active TB conversion among 177 patients who received isoniazid therapy.[25] In our study, the rate of active TB disease conversion in SOT recipients was 10.1%, which confirmed the results of a prospective study conducted by Torre-Cisneros and colleagues.[26] In that study, 19% of all SOT recipients who did not have pretransplant PPD tests showed positive results (induration of ≥5 mm), with 6.2% developing active TB. In a retrospective 10-year study on liver transplant patients from Benito and colleagues,[27] the results were surprisingly different, with pretransplant TST results positive in 24% of patients and 0% developing TB disease; however, among 76% of patients with negative TST, 1.8% experienced active TB conversion. Furthermore, the results from Benito and colleagues also showed that the rate of active disease conversion was greater among patients who received isoniazid. This could have happened because of the impact of previous TB infection as a major risk factor for progression of posttransplant active disease, as confirmed in a retrospective 10-year study from South Korea,[28] which showed that positive pretransplant TSTs and radiographic features of untreated TB were significantly associated with posttransplant TB disease. In a retrospective 13-year study on kidney and liver transplant recipients, 2.3% of patients developed posttransplant TB of whom 22.2% had pretransplant positive TSTs; 1 patient had positive IGRA and 10 patients had radiographic features of untreated TB. Therefore, LTBI was reported as a major risk factor for development of active TB.[29]

Limitations

The limitations of our study were the use of TST as the main diagnostic test; these results can be false positive (exposure to non-TB bacteria or BCG vaccination) and can be false negative (cutaneous anergy due to impairment of cell-mediated immunity).[30] In addition, the time elapsed between transplant and active TB disease conversion was not mentioned in the patients' records. We also did not identify anergic patients.

Conclusions

Diagnosis and treatment of LTBI before SOT can reduce active TB conversion and its associated

morbidity and mortality. Although TST is the current diagnostic test to identify LTBI in Iran, the consideration of a reasonable cutoff point for its positivity is essential. Although further evaluations must be done to draw a definite conclusion, our recommendation is to modify the cutoff point considered for TST positivity for SOT candidates in Iran to ≥10 mm.

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Progression of Portal Hypertension in Acute Cellular Rejection After Liver Transplantation

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Abstract

Objectives: **This study was designed to investigate the frequency of computed tomography features indicating progression of portal hypertension and their clinical relevance in patients who experienced acute cellular rejection after liver transplantation.**

Materials and Methods: **This retrospective study included 141 patients with pathologically diagnosed acute cellular rejection following liver transplant. Patients were divided into early and late rejection groups according to the time of diagnosis. Two radiologists analyzed the interval changes in spleen size and variceal engorgement on computed tomography images obtained at the times of surgery and biopsy. Aggravation of splenomegaly and variceal engorgement were considered computed tomography features associated with the progression of portal hypertension. Clinical outcomes, including responses to treatment and graft survival, were compared between patients with and without these features.**

Results: **The frequency of progression of portal hypertension was 31.9% and did not differ significantly in patients who experienced early (30.8% [28/91]) and late (34.0% [17/50]) rejection (*P* = .694). In the late rejection group, computed tomography features indicating progression of portal hypertension were significantly associated with poor response to treatment (*P* = .033). Graft survival in both the early and late rejection groups did not differ significantly in patients with and without progression of portal hypertension.**

Conclusions: **Computed tomography features suggesting the progression of portal hypertension were encountered in about one-third of patients who experienced acute cellular rejection after liver transplant. Progression of portal hypertension was significantly related to poor response to treatment in the late rejection group.**

Key words: *Graft rejection, Imaging, Vascular complications*

Introduction

Acute cellular rejection is a common event after liver transplant (LT), occurring in up to 40% of these patients.[1] Although improvements in immunosuppression regimens have reduced the incidence of acute cellular rejection, it is still reported in 10% to 30% of LT recipients.[2,3] Elevation of hepatic enzymes and/or bilirubin is considered suggestive of acute cellular rejection; however, these are not sufficiently sensitive or specific in differentiating acute cellular rejection from other causes of graft dysfunction.[4,5] Imaging methods, such as Doppler ultrasonography (US) and computed tomography (CT), can exclude other major vascular and biliary complications of LT and increase suspicion of acute cellular rejection.[6-10] In particular, several CT features, including globular swelling, nonanastomotic stenosis of the major draining vein, and heterogeneous enhancement of the graft, were reported to be significantly associated with acute cellular rejection.[10] Nevertheless, a definitive diagnosis of acute cellular rejection requires liver biopsy. Most acute cellular rejection episodes respond to bolus doses of steroid or escalation of immunosuppression and generally do not affect long-term graft or patient survival.[2,11] However, the risks of chronic rejection and graft loss can be increased in patients who experience repeated episodes of severe acute cellular rejection[12,13] and in those with late-onset acute cellular rejection.[14-16]

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Portal hypertension, an indicator of end-stage liver disease, usually resolves in patients who do not experience significant complications after transplant. Decreases in spleen size and varices are well-recognized phenomena after LT.[17-19] However, posttransplant portal hypertension can occasionally be present as a result of various causes, including vascular complications (such as portal vein stenosis or venous outflow obstruction) and parenchymal diseases (such as acute cellular rejection).[20,21] Among the radiologic findings of acute cellular rejection, decreased portal blood flow velocity on Doppler US may be caused by portal hypertension. Moreover, hepatofugal flow at the main portal vein, which can also be diagnosed by Doppler US, represents an extremely severe form of portal hypertension and may be indicative of a fatal condition.[22,23] To our knowledge, however, the frequency of CT features associated with the progression of portal hypertension in patients with acute cellular rejection after LT has not been determined, nor has the clinical relevance of these features, as evaluated by treatment response to immune suppression and graft survival. The present study was therefore designed to determine the frequency of CT features indicating progression of portal hypertension and their clinical relevance in patients who experience acute cellular rejection after LT.

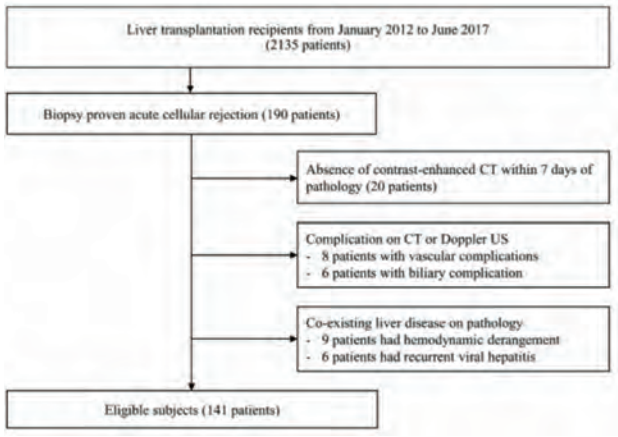
Materials and Methods

The study protocol was approved by the institutional review board of Asan Medical Center, which waived the requirement for informed consent because of the retrospective nature of this study.

Patients

Between January 2012 and June 2017, 2135 patients aged >18 years underwent deceased donor LT (n = 378, 17.7%) or living related donor LT (n = 1757, 82.3%) at our center for various liver diseases. Of living related donors, the relationships were first degree in 1359 (77.3%), family-in-law including spouse in 203 (11.6%), second degree in 101 (5.7%), and third degree in 94 patients (5.4%). All patients underwent CT scans before LT and regularly after LT for the surveillance of posttransplant complications. Of these patients, 190 were diagnosed with acute cellular rejection pathologically by transjugular or percutaneous liver biopsy. However, 49 were excluded: 20 because of absence of contrast-enhanced CT scans within 7 days before acute cellular rejection diagnosis; 14 because of coexisting major vascular (n = 8) or biliary (n = 6) complications on CT or Doppler US; and 15 because of coexisting liver diseases on pathologic examinations, including 9 patients with hemodynamic derangement and 6 with recurrent viral hepatitis. The remaining 141 patients, all of whom had undergone contrast-enhanced CT imaging within 7 days of pathologic acute cellular rejection diagnosis and did not have any coexisting posttransplant diseases, were included in our analyses (Figure 1). The 141 patients enrolled in this study included 97 men (68.8%) and 44 women (31.2%) with mean age of 51.8 ± 10.2 years (range, 20-73 years). The mean interval between LT and acute cellular rejection diagnosis was 212.7 ± 501.2 days (range, 4-3931 days). Patients were divided into 2 groups: early rejection (≤90 days after LT) and late rejection (>90 days after LT).

Figure 1. Patient Flow Diagram



Abbreviations: CT, computed tomography; US, ultrasonography

Computed tomography techniques

Computed tomography was performed using a 64- or 128-detector row CT scanner (Somatom Definition, Somatom Definition AS, and Somatom Definition Edge; Siemens Healthineers). Computed tomography images were obtained using the breath-hold technique at end-expiration at 120 kV and 200 to 220 mA, with automated dose modulation using the maximum allowable tube current. After unenhanced CT scans were acquired, intravenous contrast medium, consisting of 150 mL iopromide (Ultravist 370; Schering AG), was administered at a flow rate of 3 mL/s using a mechanical injector (Percupump II; E-Z-Em, Inc.). Arterial phase images were

acquired 15 seconds after the attenuation of the descending thoracic aorta reached 100 Hounsfield units. Portal venous-phase images were obtained 75 seconds after administration of contrast medium. Images were reconstructed with filtered back projection at slice thicknesses of 3 mm.

Image analysis

Computed tomography images were reviewed independently by 2 radiologists (KWK, with 20 years of experience in LT imaging, and JYC, with 1 year of experience in LT imaging). Both radiologists were blinded to pathologic information. Disagreements between the 2 readers were resolved by consensus evaluations.

Contrast-enhanced CT images at baseline and at the time of acute cellular rejection diagnosis were analyzed to determine the interval changes in spleen size and variceal engorgement. Baseline contrast-enhanced CT was defined as the first postoperative CT scan, obtained within 1 week after LT or, if unavailable, the preoperative CT scan. Interval changes in spleen size were categorized by S score, with NA defined as splenectomy or procedures potentially affecting spleen size, such as splenic artery/vein embolization/ligation or splenic devascularization; S0 as not enlarged originally or decreased over the interval; S1 as equivocally unchanged splenomegaly; and S2 as an increase over the interval. Interval changes in variceal engorgement were categorized by V score, with V0 defined as originally absent or disappeared following surgical ligation, radiological embolization, or spontaneously; V1 as slightly decreased with residual engorgement or equivocally unchanged; and V2 as interval aggravated. Progression of portal hypertension was considered in patients with scores of S2 or V2.

Histologic assessment of acute cellular rejection

Transjugular or percutaneous liver biopsy samples were obtained from patients with clinical suspicion of acute cellular rejection, such as elevated liver enzyme levels, no response to routine immunosuppressive treatment, or rebounding of liver enzyme level. Acute cellular rejection was histologically diagnosed using the Banff method.[24] The rejection activity index was calculated as the sum of the scores for the following criteria: (1) portal inflammation, (2) bile duct inflammation damage, and (3) venous endothelial inflammation, with the severity of involvement of each component scored on a scale of 0 to 3. Clinically relevant acute cellular rejection was diagnosed if the rejection activity index score was greater than 4.

Clinical outcomes

Clinical outcomes of patients with acute cellular rejection were investigated by reviewing their electronic medical records. Patients were grouped as good or poor responders depending on their response to immune suppression treatment. Patients were defined as good responders if they recovered without the need for additional liver biopsy or when follow-up biopsy showed a decreased rejection activity index. All other patients were considered poor responders, showing histological progression (no interval change/increase in rejection activity index or development of chronic rejection on follow-up biopsy) or graft failure (retransplant or graft-related death).

Statistical analyses

The demographic and clinical characteristics of patients who experienced early and late rejection were compared using *t* tests for continuous variables and the chi-square test or Fisher exact test for categorical variables. Interobserver agreement in CT scoring for interval changes in portal hypertension was assessed using Cohen's kappa coefficients with 95% confidence intervals. Kappa coefficients were interpreted by using the following convention: less than 0.20 indicated poor, 0.21 to 0.40 indicated fair, 0.41 to 0.60 indicated moderate, 0.61 to 0.80 indicated substantial, and 0.81 to 1.00 indicated nearly perfect. Subsequent analyses were performed using consensus review results. Differences in CT scores and clinical outcomes between the early and late acute cellular rejection groups were compared using Fisher exact tests. The relationships between the progression of portal hypertension (CT score of S2 or V2) and responses to treatment were compared in the early and late acute cellular rejection groups using Fisher exact tests. The relationship between the progression of portal hypertension and graft survival at 6 months, calculated from the date of acute cellular rejection diagnosis to the date of graft failure, was assessed by the Kaplan-Meier method and compared by the log-rank test. All statistical analyses were performed using SPSS Statistics for Windows (version 23.0; IBM Corp). Two-sided P values $< .05$ were considered statistically significant.

Results

The characteristics of the patients are shown in Table 1. Ninety-one patients (64.5%) were diagnosed with early rejection and 50 patients (35.5%) with late rejection. A total of 62 patients (44.0%) underwent surgical or radiological intervention, which can affect the portosplanchnic circulation. Thirty-seven patients (26.2%) underwent ligation/embolization of the portosystemic shunt, 20 (14.2%) underwent ligation/embolization of the splenic artery or splenic devascularization, and 15 (10.6%) underwent splenectomy, with 10 of these patients (7.1%) undergoing 2 or more of these procedures. There were no significant differences in age, sex, rejection activity index, type of graft, and incidence of intraoperative/perioperative procedures between the early and late rejection groups.

Table 1. Demographic and Clinical Characteristics of the Study Patients

Characteristics	Early ACR (n = 91)	Late ACR (n = 50)	*P* Value
Age, years	52.5 ± 9.9	50.4 ± 10.6	.233
Sex			.033
Male	57 (62.6%)	40 (80.0%)	
Female	34 (37.4%)	10 (20.0%)	
Histology			
Mean interval between transplant and ACR, days	25.4 ± 21.2	553.5 ± 730.2	<.001
Rejection activity index	6.0 ± 1.8	5.8 ± 1.6	.618
Type of graft			.712
DDLT	36 (39.6%)	17 (34.0%)	
Right LDLT	49 (53.8%)	27 (54.0%)	
Left LDLT	2 (2.2%)	2 (4.0%)	
Dual LDLT	4 (4.4%)	4 (8.0%)	
Intraoperative/perioperative management			.718
Ligation/embolization of portosystemic collaterals	21 (23.1%)	16 (32.0%)	
Ligation/embolization of splenic artery or splenic devascularization	12 (13.2%)	8 (16.0%)	
Splenectomy	7 (7.7%)	8 (16.0%)	

Abbreviations: ACR, acute cellular rejection; DDLT, deceased donor liver transplant; LDLT, living donor liver transplant
Results are shown as mean ± standard deviation or number (%).

Interobserver agreement between the 2 readers in CT scoring for interval change of portal hypertension at the time of acute cellular rejection diagnosis was substantial for both S score (κ = 0.72; 95% CI, 0.62-0.80) and V score (κ = 0.76; 95% CI, 0.67-0.86) (Table 2).

The CT scores for interval changes in portal hypertension and clinical outcomes in the early and late rejection groups are summarized in Table 3. Although the frequency of S2 did not differ significantly (*P* = .43) in the early rejection group (27.5% [25/91]) and late rejection group (24.0% [12/50]), the frequency of V2 was significantly higher (*P* = .047) in the late rejection group (18.0% [9/50]) than in the early rejection group (6.6% [6/91]). The frequency of progression of portal hypertension (S2 or V2), however, did not differ significantly (*P* = .694) between the early rejection group (30.8% [28/91]) and late rejection group (34.0% [17/50]).

Table 2. Interobserver Agreement on S Scores and V Scores

Reader 1			Reader 2			Kappa
S score	NA	S0	S1	S2	Total	
NA	20	2	2	0	24	.718
S0	0	36	12	2	50	
S1	0	3	24	4	31	
S2	0	2	4	30	36	
Total	20	43	42	36	141	
Reader 1			Reader 2			
V Score		V0	V1	V2	Total	
V0		66	12	0	78	.755
V1		3	43	2	48	
V2		0	3	12	15	
Total		69	58	14	141	

Abbreviations: NA, splenectomy or procedures potentially affecting spleen size, such as splenic artery/vein embolization/ligation or splenic devascularization; S0, not enlarged originally or decreased over the interval; S1, equivocally unchanged splenomegaly; S2, increase over the interval; V0, originally absent or disappeared following surgical ligation, radiological embolization, or spontaneously; V1, slightly decreased with residual engorgement or equivocally unchanged; V2, interval aggravated

Table 3. Computed Tomography Scores and Clinical Outcomes in Patients With Early and Late Acute Cellular Rejection

Characteristics	Early ACR (n = 91)	Late ACR (n = 50)	*P* Value
Portal hypertension score			
S score			.669
NA	13 (14.3%)	11 (22.0%)	
S0	34 (37.4%)	16 (32.0%)	
S1	19 (20.9%)	11 (22.0%)	
S2	25 (27.5%)	12 (24.0%)	
V score			.058
V0	49 (53.8%)	28 (56.0%)	
V1	36 (39.6%)	13 (26.0%)	
V2	6 (6.6%)	9 (18.0%)	
Progression of portal hypertension			.694
Overall	28 (30.8%)	17 (34.0%)	
S2 only	22 (78.6%)	8 (47.1%)	
V2 only	3 (10.7%)	5 (29.4%)	
Both S2 and V2	3 (10.7%)	4 (23.5%)	
Treatment response to immune suppression			.778
Good responder	55 (60.4%)	29 (58.0%)	
Poor responder	36 (39.6%)	21 (42.0%)	
Steroid-resistant ACR	15 (16.5%)	6 (12.0%)	
Chronic rejection	6 (6.6%)	13 (26.0%)	
Graft failure	21 (23.1%)	9 (18.0%)	
Retransplant	10 (11.0%)	4 (8.0%)	
Liver-related death	11 (12.1%)	5 (10.0%)	

Abbreviations: ACR, acute cellular rejection; NA, splenectomy or procedures potentially affecting spleen size, such as splenic artery/vein embolization/ligation or splenic devascularization; S0, not enlarged originally or decreased over the interval; S1, equivocally unchanged splenomegaly; S2, increase over the interval; V0, originally absent or disappeared following surgical ligation, radiological embolization, or spontaneously; V1, slightly decreased with residual engorgement or equivocally unchanged; V2, interval aggravated

Of the 141 patients with acute cellular rejection, 84 (59.6%) were good responders and 57 (40.4%) were poor responders to immune suppression therapy. The poor responders included 21 patients (14.5%) with steroid-resistant acute cellular rejection on follow-up biopsies, 19 patients (13.1%) who were pathologically diagnosed with chronic rejection, and 30 patients (21.3%) who underwent retransplant or died as a result of graft failure, including 13 with and 17 without steroid-resistant acute cellular rejection or chronic rejection. There was no significant difference in response to immune suppression therapy between the early and late rejection groups ($P = .778$).

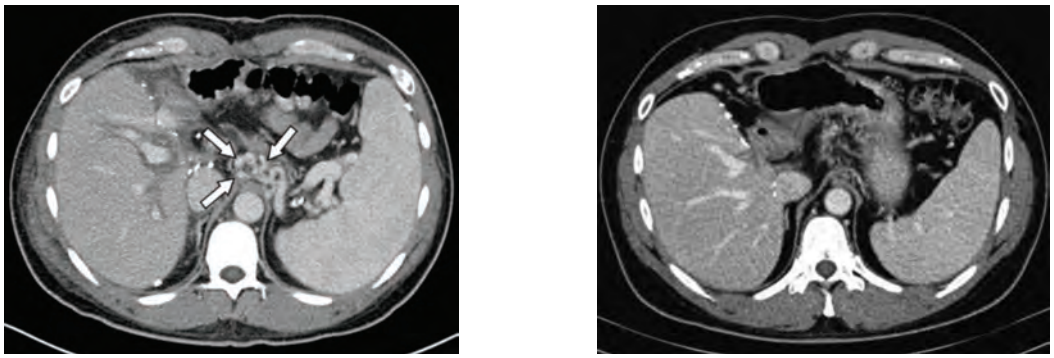
Of the 28 patients with early rejection who showed progression of portal hypertension, 16 (57.1%) were good responders and 12 (42.9%) were poor responders. Of the 63 patients in this group without progression of portal hypertension, 39 (61.9%) were good responders and 24 (38.1%) were poor responders. There was no significant relationship between progression of portal hypertension and response to immune suppression therapy in the early rejection group ($P = .820$). In the late rejection group, poor response to immune suppression therapy was significantly more likely in patients who did than did not show progression of portal hypertension ($P = .033$) (Table 4). Findings in representative patients are illustrated in Figure 2 and Figure 3.

Table 4. Relationship Between Progression of Portal Hypertension and Clinical Outcomes in Patients With Late Acute Cellular Rejection

	No. of Patients (%)		*P* Value
	Good Responder (n = 29)	Poor Responder (n = 21)	
Progression of portal hypertension	6 (20.7%)	11 (52.4%)	.033
S2	4 (13.8%)	8 (38.1%)	.091
V2	2 (6.9%)	7 (33.3%)	.025

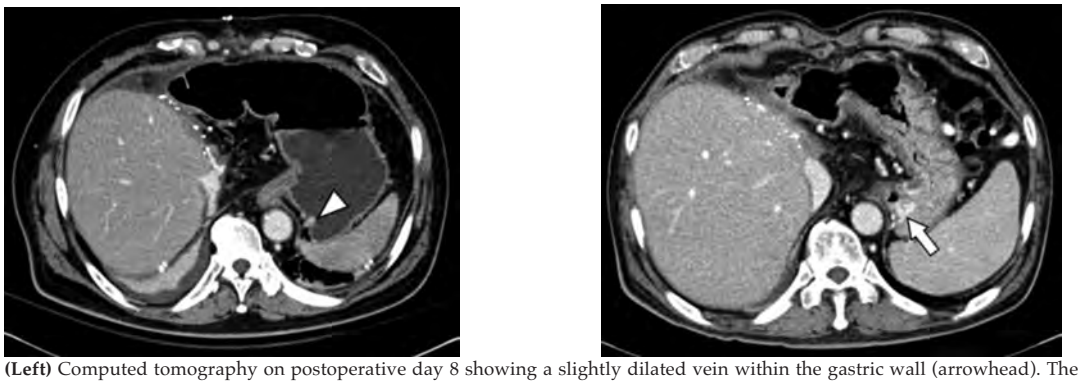
Abbreviations: S2, increase over the interval; V2, interval aggravated

Figure 2. Images From 45-Year-Old Man Diagnosed With Acute Cellular Rejection (Rejection Activity Index = 6) 309 Days After Living Donor Liver Transplant With Right Hemiliver Graft for Hepatitis B Virus-Associated Liver Cirrhosis



(Left) Computed tomography on postoperative day 5 showing splenomegaly and prominent portosystemic collaterals located around the gastric fundus (arrows). **(Right)** Computed tomography around the time of diagnosis of acute cellular rejection, 310 days after liver transplant, showing normalization of spleen size (S0) and decreases in portosystemic collaterals (V0). Patient received immune suppression treatment and was discharged after clinical findings improved.

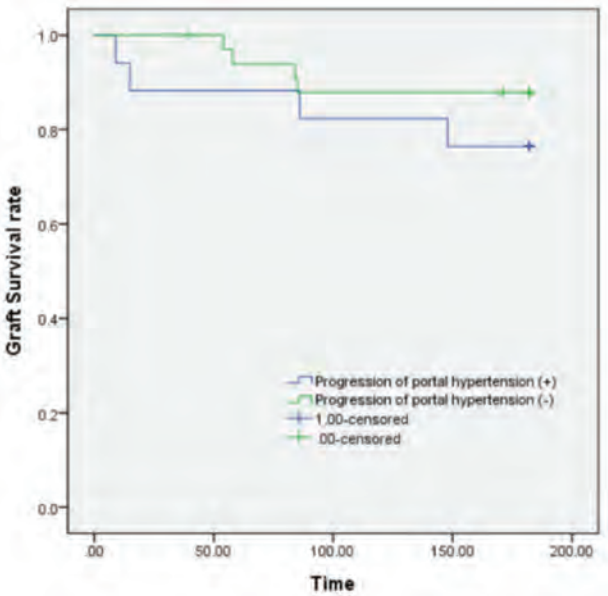
Figure 3. Images From 56-Year-Old Man Diagnosed With Acute Cellular Rejection (Rejection Activity Index = 7) 243 Days After Living Donor Liver Transplant With Right Hemiliver Graft for Hepatitis B Virus-Associated Liver Cirrhosis



(Left) Computed tomography on postoperative day 8 showing a slightly dilated vein within the gastric wall (arrowhead). The craniocaudal diameter of the spleen was approximately 15 cm (not shown). **(Right)** Computed tomography around time of diagnosis of acute cellular rejection, 246 days after LT, showing progressive variceal engorgement within the gastric wall with more prominent tortuous vessels (arrow) (V2) and progressive splenomegaly (craniocaudal diameter of spleen, approximately 17 cm [not shown]). Patient underwent immune suppression treatment, but his liver enzymes and bilirubin concentrations failed to decrease. Follow-up biopsies performed several times revealed pathologic features of chronic rejection.

Graft survival at 6 months between patients with and without progression of portal hypertension did not differ significantly in both the early (P = .608) and late (P = .318) rejection groups (Figure 4).

Figure 4. Graft Survival at 6 Months in Late Rejection Patients



The Kaplan-Meier curves show no significant difference between patients with and without progression of portal hypertension.

Discussion

Our findings showed that CT features suggesting the progression of portal hypertension, such as progressive splenomegaly and variceal engorgement, were occasionally observed in patients with both early and late rejection after LT. Although progressive variceal engorgement was more frequently seen in patients with late than with early rejection, the frequencies of progressive splenomegaly and overall progression of portal hypertension did not differ significantly in the early and late rejection groups. Subgrouping of patients as good or poor responders to immune suppression therapy showed that the frequency of progression of portal hypertension in the late rejection group was significantly more frequent in poor than in good responders, whereas this incidence did not differ significantly between good and poor responders in the early rejection group. Nevertheless, graft survival was not significantly affected by the frequency of progression of portal hypertension in either group.

Portal hypertension after LT can reduce portal flow and impair or delay graft regeneration and can even be life-threatening.[25] Acute cellular rejection, one of the most common complications of LT, as well as various other complications (including small graft size, hepatic venous outflow obstruction, and portal vein stenosis), may be the cause of portal hypertension and decrease portal inflow to the liver graft, particularly in those with persistent portosystemic shunt.[26] Evaluation of the pathophysiologic mechanism of acute cellular rejection has shown that severe periportal inflammation can progress to centrolobular venule obstruction and increased intrasinusoidal pressure, eventually causing portal hypertension.[27] Indeed, decreased portal flow on Doppler US may be a marker for acute cellular rejection after LT. Patients with acute cellular rejection have been reported to experience a marked reduction in portal blood flow velocity, with a 40% reduction[7] and an absolute portal blood flow velocity <20.2 cm/s,[8] proposed as cutoffs for the diagnosis of clinically relevant acute cellular rejection. Reversed portal flow has also been reported during acute cellular rejection episodes after LT.[22,23,28] Consistent with these findings, the present study showed that CT features suggesting the progression of portal hypertension were not uncommon in patients with acute cellular rejection.

Several factors during the early postoperative period may affect portal pressure. For example, graft size can be an important factor in patients who undergo living donor LT. Small-for-size grafts can lead to a sudden increase in intrasinusoidal pressure due to the relatively low capacity of the hepatic sinusoid.[29] Postoperative volume overload or congestion can also lead to high intrahepatic vascular resistance, and variations in the degree of portal vein stenosis can increase portal pressure. Interactions among these various factors can result in the improvement, persistence, or development of portal hypertension during the early postoperative period, making it difficult to interpret results in the early rejection group. Huge portosystemic shunts are usually interrupted surgically or radiologically in our institution. These procedures can have a greater effect on portal pressure than acute cellular rejection-associated changes in graft parenchyma during the early postoperative period, possibly leading to the underestimation of portal hypertension. This may account for the lower frequency of progressive variceal engorgement shown in the early versus the late rejection group.

In contrast, confounding factors may have minimal effects during the late posttransplant period.

Liver transplant recipients have had more time to adapt to the sizes of the grafts. Moreover, because most patients who experience late rejection do so in an outpatient setting, problems such as volume overload due to fluid therapy are less likely. In the present study, CT features of progressive portal hypertension were occasionally observed in the late rejection group and were more frequent in poor than in good responders to immunosuppressive treatment. The progression of portal hypertension during this period likely reflects the acute cellular rejection-associated parenchymal changes in the graft.

This study had some limitations. First, because of its retrospective design, there may have been selection bias in the study populations. Acute cellular rejection is common after LT, and patients with suspected mild acute cellular rejection were empirically treated with immune suppressants before pathologic confirmation. There are no definitive guidelines for performing liver biopsy, with the choice to obtain biopsy samples being at each clinician's discretion. Therefore, patients with mild acute cellular rejection were not included in our study population, suggesting that our findings are applicable only to patients with clinically relevant acute cellular rejection. Second, some patients in the present study underwent procedures to change portal flow, which could have influenced the development or regression of portal hypertension. Therefore, it is hard to generalize the results of this study to patients treated using a different surgical strategy. Third, the present study is a cohort study. Comparisons with a control group are necessary to determine whether the progression of portal hypertension is diagnostic for acute cellular rejection. Fourth, although we analyzed CT features in these patients, we did not assess the consistency between CT features and changes in portal flow on Doppler US. Paired Doppler US scans were not always available, particularly during the late postoperative period. Doppler parameters such as portal blood flow velocity can better show the presence of portal hypertension as decreased or reversed values. Further studies pairing CT and Doppler US features are needed.

Conclusions

Computed tomography features suggesting the progression of portal hypertension are occasionally encountered in patients with acute cellular rejection. In patients with late rejection, the progression of portal hypertension is more frequently associated with poor than with good response to immune suppression treatment. Nevertheless, graft survival is not significantly affected.

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Length of Alcohol Abstinence Predicts Posttransplant Delirium in Living Donor Liver Transplant Recipients with Alcoholic Cirrhosis

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Abstract

Objectives: **History of alcohol abuse is a predictive factor for posttransplant delirium. We aimed to investigate whether preoperative abstinence was associated with posttransplant delirium in liver transplant recipients with alcohol-related cirrhosis.**

Materials and Methods: **From January 2014 to December 2019, 84 patients with alcohol-related cirrhosis who received living donor liver transplant were retrospectively reviewed and divided into a delirium group (n = 46, 54.8%) and a nondelirium group (n = 38, 45.2%) using the Richmond Agitation-Sedation Scale and the Confusion Assessment Method for the Intensive Care Unit.**

Results: **In the delirium group versus the nondelirium group, patients were more likely to have preoperative hepatic encephalopathy (58.7% vs 31.6%; *P* = .013), more likely to have higher Model for End-Stage Liver Disease scores (27.05 ± 10.56 vs 18.85 ± 7.96; *P* < .001), less likely to have preoperative alcohol abstinence (43.5% vs 68.4%; *P* = .022), had longer duration of mechanical ventilation (7.57 ± 7.82 vs 2.50 ± 5.96 days; *P* = .001), and had longer stays in the intensive care unit (14.85 ± 15.01 vs 8.84 ± 7.84 days; *P* = .021) and in the hospital (37.89 ± 18.85 vs 27.15 ± 10.43 days; *P* = .002). Multivariate analysis revealed that preoperative alcohol abstinence (odds ratio 4.953; 95% CI, 1.519-16.152; *P* = .008) was a significant predictor and that more patients had abstinence durations <3 months (60.9% vs 34.2%; *P* = .048) in the delirium group.**

Conclusions: **A high incidence of posttransplant delirium in liver transplant recipients with alcohol-related cirrhosis was associated with preoperative abstinence. Abstinence >6 months before living donor liver transplant is suggested to reduce the risk of posttransplant delirium.**

Key words: *Alcohol, Liver cirrhosis, Liver transplantation, Postoperative delirium*

Introduction

Delirium, characterized by an acute change in mental status, is a common issue in critically ill patients. This condition is often associated with increased costs, mortality, length of hospital stay, and long-term cognitive impairment.[1-4] Delirium after liver transplant has an incidence of 1.6% to 47.4%,[5-12] and it has a negative effect on clinical outcomes.[5-7,9,11-13] An increased incidence of delirium in the intensive care unit (ICU) is related to the complexity of the surgical procedure, severity of illness, neural structural changes after hepatic encephalopathy, metabolic disturbances, and drug neurotoxicity.[14-16] There are several risk factors for delirium after liver transplant, including preoperative encephalopathy,[7,9,11] preoperative renal replacement therapy,[5,8,11] high Acute Physiology and Chronic Health Evaluation II (APACHE II) scores,[9,11,12] extended mechanical ventilation duration posttransplant,[5,9] and blood transfusions.[5,7,10-12]

Alcohol-associated liver disease is also a crucial risk factor for delirium.[6,9,12] However, the incidence of delirium remains controversial among various populations (2.6% to 42.3%) of transplant recipients with alcoholic cirrhosis.[5-12] Alcoholic liver disease is a common indication for liver transplant, with an average of 28.68% among patients from an American database[17] and of 19% among a European database.[18] The risk of alcoholic relapse is considered before

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public organ allocation. In Asia, patients with alcoholic cirrhosis with life-threatening conditions may receive an emergent living donor liver transplant (LDLT) after a rigorous assessment. However, the duration of alcohol abstinence remains controversial. No single study has focused on delirium in transplant patients with alcoholic cirrhosis. Thus, this study aimed to clarify the association between posttransplant delirium in liver transplant recipients with alcoholic cirrhosis and the clinical outcomes of these patients after LDLT.

Materials and Methods

This retrospective study included data collected from a single medical center in Taiwan between January 1, 2014, and December 31, 2019. During this period, 338 patients underwent LDLT. From this cohort, 84 patients with alcoholic liver disease were included in our study. In emergency situations (with rapidly worsening liver function and potentially fatal outcomes), LDLT may be considered as a life-saving treatment after patients undergo a preliminary psychosocial assessment, a cautious preoperative evaluation, and comprehensive conversations that include the patient and their families. Patients who showed insight into their alcohol use, made a commitment to lifelong abstinence, had an absence of comorbid psychiatric disorders, and had sufficient psychosocial support were potential candidates for a liver transplant. Patients required being considered as low risk for relapse after an assessment by psychiatrists and social workers. Appropriately selected patients and matched living donors, who were up to the recipients' third-degree relatives, underwent LDLT. All information was collected from electronic medical records. The study was approved by the Institutional Review Board of Changhua Christian Hospital (document no. 191244).

Delirium assessment

Delirium was diagnosed as disturbances in cognition, attention, and awareness over a short duration in an acute or fluctuating course. However, it was not diagnosed in conditions of severely reduced levels of arousal, such as coma.[19] Several bedside screening tools have been developed by various health care providers for regular monitoring and timely intervention of delirium. The Confusion Assessment Method for the Intensive Care Unit (CAM-ICU),[20] which has a sensitivity of 80% and a specificity of 95.9%,[21,22] has been recommended for routine clinical practice.[23] It is also utilized in patients who are receiving mechanical ventilation or patients with cirrhosis.[24]

A prerequisite for a delirium evaluation is an assessment of a patient's arousal level as defined by the Richmond Agitation-Sedation Scale (RASS).[25,26] This scale has also been validated for clinical use.[27] Patients in a coma who were not able to respond to verbal stimulation were categorized as "unable to assess," with a score of -4 (deep sedation) to -5 (unarousable). Otherwise, if patients could be aroused and they could be categorized with a RASS score of between +4 (combative status) and -3 (moderate sedation status), the delirium evaluation then proceeded to a CAM-ICU assessment.

Inclusion and exclusion criteria

Among the 338 patients who received LDLTs between January 1, 2014, and December 31, 2019, in our medical center, 84 patients with alcoholic liver disease were enrolled in this study. All patients were diagnosed with alcohol use disorder[19] by hepatologists, psychologists, and social workers. Patients with other etiologies of liver disease such as viral hepatitis, autoimmune hepatitis, nonalcoholic fatty liver disease, primary biliary cholangitis, or primary sclerosing cholangitis were excluded. Postoperative delirium development was initially defined as a RASS score between +4 (combative status) and -3 (moderate sedation status), with patients then assessed with the CAM-ICU test. According to this assessment, bedside nurses would evaluate the patient 3 times per day. If the assessment was positive, physicians would reassess the patient for confirmation of the score. After factors contributing to delirium were surveyed by laboratory and imaging examinations, none of the patients with alcohol withdrawal syndrome, hepatic encephalopathy, cardiovascular diseases, neurotoxic conditions related to drugs (such as tacrolimus), intracranial hemorrhage, or infarction were categorized into the delirium group.

Because of difficulties in differentiating among delirium, alcohol withdrawal syndrome, and hepatic encephalopathy, we discreetly evaluated the latest drinking period[28] to decide whether the symptoms

constituted alcohol withdrawal syndrome and ordered a biochemistry test for hyperammonemia. Subsequently, all patients were divided into a delirium (n = 46, 54.8%) and a nondelirium group (n = 38, 45.2%).

Data collection

All patients were preoperatively assessed for their profile information (age and sex), clinical presentations of hepatic encephalopathy, and severity of chronic liver disease (Model for End-Stage Liver Disease [MELD] score). Each patient also received a psychiatric evaluation (duration of alcohol use disorder and alcohol abstinence duration). A patient who achieved preoperative abstinence was defined as one who had attained at least 1 month of sobriety with a low risk of relapse after an initial psychosocial assessment. Perioperative procedures, including operation time and amount of blood loss, were recorded. After the transplant procedure, all patients received critical care with routine assessment of their APACHE II scores. Calcineurin inhibitor-based immunosuppression was initiated with tacrolimus (target level of 5-10 ng/mL), mycophenolate, and methylprednisolone. The serum tacrolimus level on postoperative day 7 was measured. Postoperative infections, including respiratory tract infections, intra-abdominal infections, urinary tract infections, bloodstream infections, wound infections, and catheter-related infections, were assessed through culture examinations. Postoperative sepsis was further defined as life-threatening organ dysfunction accompanied by an increase of 2 points in the Sequential Organ Failure Assessment score. Outcomes posttransplant were assessed by analyzing the mechanical ventilator duration, hospital mortality, and length of ICU and hospital stays. The alcohol abstinence duration was further divided into ≤3, 3 to 6, and >6 months to evaluate the effects of duration of abstinence on postoperative delirium.

Statistical analyses

Patient data are expressed as means ± SD, and categorical variables are expressed as numbers and percentages. A Mann-Whitney U test was used to compare the differences in continuous variables, and a chi-square or Fisher exact test was used to compare the differences in categorical variables. Significant variables in the univariate analyses were then included in a forward, stepwise multiple logistic regression model to identify the most important risk factors for developing delirium in the ICU after LDLT surgery.

A chi-square test was performed to compare the 2 groups. Statistical significance was defined as $P < .05$. We performed statistical analyses on a personal computer using the statistical package SPSS for Windows (version 20).

Results

We included a total of 84 patients, 46 (54.8%) of whom developed delirium after transplant, in this study. Age, sex, duration of alcohol use disorder, abstinence duration, operative duration, APACHE II score, and tacrolimus levels on postoperative day 7 were not significantly associated with delirium.

Before transplant, we observed a higher proportion of preoperative hepatic encephalopathy (58.7% vs 31.6%; $P = .013$), higher MELD scores (27.05 ± 10.56 vs 18.85 ± 7.96; $P < .001$), and lower percentage of preoperative alcohol abstinence (43.5% vs 68.4%; $P = .022$) in the posttransplant delirium group versus the nondelirium group. Furthermore, during the transplant procedure, blood loss (4235.87 ± 2632.00 mL vs 2676.32 ± 2341.97 mL; $P = .001$) was significantly greater in the delirium group. Patients in the posttransplant delirium group had longer durations of mechanical ventilation (7.57 ± 7.82 vs 2.50 ± 5.96 days; $P = .001$) and prolonged ICU stays (14.85 ± 15.01 vs 8.84 ± 7.84 days; $P = .021$) and hospital stays (37.89 ± 18.85 vs 27.15 ± 10.43 days; $P = .002$) compared with the nondelirium group. However, neither postoperative sepsis (17.4% vs 7.9%; $P = .330$) nor hospital mortality (13% vs 5.3%; $P = .284$) were significantly different between the groups (Table 1).

On multivariate analysis, preoperative alcohol abstinence (odds ratio of 4.953; 95% CI, 1.519-16.152; $P = .008$) placed patients at high risk for developing posttransplant delirium (Table 2).

To evaluate the effect of the duration of alcohol abstinence before liver transplant on postoperative delirium, we further analyzed various cutoff durations for alcohol abstinence: <3, 3 to 6, and >6 months. In the delirium group, a higher percentage of patients with statistically significant abstinence times of <3 months (60.9% vs 34.2%, $P = .048$) was observed (Table 3).

Table 1. Demographic and Clinical Features of the Delirium and Nondelirium Groups

Demographic and Clinical Features	Nondelirium Group (n = 38)	Delirium Group (n = 46)	*P*
Age, years	50.13 ± 7.33 (36.0-65.0)	51.00 ± 7.85 (25.0-68.0)	.605
Male sex, No. (%)	35 (92.1)	44 (95.7)	.654*
Duration of alcohol use disorder, years	17.50 ± 9.83 (2.0-40.0)	20.43 ± 8.74 (3.0-40.0)	.162
Preoperative alcohol abstinence, No. (%)	26 (68.4)	20 (43.5)	.022
Duration of abstinence time, months	13.5 ± 22.56 (0-120.0)	12.64 ± 27.70 (0-120.0)	.878
Preoperative abstinence, No. (%)	12 (31.6)	27 (58.7)	.013
Hepatic encephalopathy MELD score	18.85 ± 7.96 (6.17-40.0)	27.05 ± 10.56 (5.48-40.0)	<.001
Operative time, min	369.55 ± 77.01 (214-530)	396.13 ± 84.97 (261-710)	.139
Blood loss, mL	2676.32 ± 2341.97 (400-11 500)	4235.87 ± 2632.00 (400-12 000)	.001
APACHE II score	19.32 ± 6.595 (6.0-30.0)	20.61 ± 6.310 (7.0-35.0)	.180
Tacrolimus level (day 7), ng/mL	5.57 ± 2.17 (1.80-11.00)	5.30 ± 2.19 (1.20-10.20)	.578
Postoperative infection, No. (%)	16 (42.1)	25 (54.3)	.264
Pneumonia, No. (%)	5 (13.2)	14 (30.4)	.071*
Intra-abdomen infection, No. (%)	4 (10.5)	7 (15.2)	.747*
Bacteremia, No. (%)	11 (28.9)	14 (30.4)	.882
Postoperative sepsis, No. (%)	3 (7.9)	8 (17.4)	.330*
Duration of mechanical ventilator, days	2.50 ± 5.96 (0-37.0)	7.57 ± 7.82 (0-35.0)	.001
Hospital mortality, No. (%)	2 (5.3)	6 (13.0)	.284*
ICU stay, days	8.84 ± 7.84 (4.0-44.0)	14.85 ± 15.01 (4.0-92.0)	.021
Hospitalization, days	27.15 ± 10.43 (13.0-51.0)	37.89 ± 18.85 (15.0-92.0)	.002

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; ICU, intensive care unit; MELD, model for end-stage liver disease; SD, standard deviation;

Results show mean ± SD (range), unless indicated otherwise. *P* values were by Pearson chi-squared test or by *Fisher exact test.

Table 2. Logistic Regression Analysis of Factors Contributing to Posttransplant Delirium

Variable	Univariate Analysis			Multivariate Analysis		
	OR	95% CI	*P*	OR	95% CI	*P*
MELD score	1.094	1.039-1.151	.001	1.029	0.959-1.104	.427
Blood loss	1.000	1.000-1.000	.009	1.000	1.000-1.001	.025
ETT duration	1.194	1.047-1.361	.008	1.100	0.952-1.270	.197
ICU stay	1.070	1.002-1.143	.044	0.988	0.911-1.073	.781
Hospitalization	1.053	1.015-1.093	.006	1.036	0.986-1.090	.162
Preoperative hepatic encephalopathy	3.079	1.250-7.583	.014	0.736	0.208-2.608	.635
Preoperative alcohol abstinence	2.817	1.147-6.919	.024	4.953	1.519-16.152	.008

Abbreviations: ETT, endotracheal intubation; MELD, model for end-stage liver disease; OR, odds ratio

Table 3. Comparison of Various Cutoff Durations of Alcohol Abstinence Between the Delirium and Nondelirium Group

Alcohol Abstinence Time	Nondelirium Group (n = 38)	Delirium Group (n = 46)	*P* Value
<3 months	13 (34.2)	28 (60.9)	.048
3-6 months	7 (18.4)	6 (13.0)	
>6 months	18 (47.4)	12 (26.1)	

Results show number (%) of patients in each group.

Discussion

In our study, a high percentage of patients with alcoholic cirrhosis (up to 54.8%) developed postoperative delirium after LDLT. Multivariate analysis revealed that preoperative alcohol abstinence was an independent risk factor. After the cutoffs of abstinence times were divided into 3 and 6 months, a shortened abstinence duration was significantly associated with postoperative delirium. Moreover, postoperative delirium had a negative impact on the duration of mechanical ventilation, ICU stay, and hospital stay, but not on hospital mortality.

In previous studies, the incidence of delirium after liver transplant was shown to range from 1.6% to 47.4%.[5-12] An increasing number of patients with alcoholic cirrhosis of the liver are receiving liver transplants.[17] A history of alcohol abuse is a predictive factor for delirium after liver transplant.[6,9,12] An alcoholic etiology has been positively correlated with the incidence of posttransplant delirium, although the rate has been reported to vary between 2.6% and 42.3%.[5-12] Two studies with a relatively small sample size had a high incidence rate of posttransplant delirium. Wang and colleagues reported a high incidence (47.4%), with alcoholic etiologies of posttransplant delirium accounting for 42.3% of the cases.9 In another prospective study, Beckmann and colleagues also reported a high incidence (45.2%) but reported a low proportion of patients with alcoholic etiologies

(9.5%) according to comprehensive assessments in the ICU and the hospital unit.[5] To clarify the association between posttransplant delirium and its alcoholic etiologies, we focused on patients with alcoholic cirrhosis (incidence rate of 54.8%). In our study, more than half of the patients with alcoholic cirrhosis developed delirium after liver transplant.

The requirement of a 6-month alcohol abstinence before liver transplant has been generally adopted since 1997. This was recommended by the American Society of Transplant Physicians and the American Association for Study of Liver Diseases.[29] The so-called "6- month rule" promoted improvements in liver function and evaluated patients' risks of potential relapse of alcohol consumption before public organ allocation. However, several trials on early transplant in patients with severe acute alcoholic hepatitis (who were not responsive to corticosteroid therapy and had a high 6-month mortality rate of >75%[30]) showed favorable outcomes. Patients in these trials had a 6-month survival rate between 77% and 100%.[31-34] Consensus statements for liver transplant in select patients with acute alcoholic hepatitis and a short interval of abstinence duration between 1 and 3 months[35-37] had a significant impact on clinical practice in Europe[38] and the United States.[39] In Taiwan, an abstinence duration of >6 months remains a requirement before being listed for deceased donor liver transplant. However, LDLTs may be considered as a life-saving treatment for patients with rapid worsening of liver function and those unable to achieve 6-month sobriety. Potential transplant candidates with a low risk of alcohol relapse are selected because sustained alcohol use posttransplant has shown a negative impact on long-term survival rates.[40]

The role of abstinence time and its association with posttransplant alcohol relapse remain controversial in LDLT.[41,42] This might be explained by a strong social and psychological support from close family members who could help protect the individual against alcohol relapse.[43,44] This protective factor is especially true when the donor is living with the recipient in the same household.

In our study, 45.2% of patients did not achieve necessary alcohol abstinence before transplant. The absence of preoperative abstinence was identified as a significant independent risk factor for post-transplant delirium with an odds ratio of 4.953. We might assume that preoperative abstinence may reduce the risk of posttransplant delirium and its negative impact on the duration of mechanical ventilation, ICU stay, and hospital stay. With proper treatment, our data supported that there was no significant difference in hospital mortality in the delirium group. However, further research is required to investigate the association between preoperative abstinence duration and long-term outcomes.

Alcohol-related brain injury has been discussed in recent studies. Proposed mechanisms include nutritional deficiencies, hepatic dysfunction, ethanol-specific effects, systemic neuroinflammation, and synergistic effects.[45,46] Abstinence may improve brain structure and biochemical status.[47] This could explain why a longer duration of abstinence decreased the risk of posttransplant delirium in our study. However, the distinct pathophysiology of alcohol-related brain damage and postoperative delirium requires further investigation.

Similar to the short-term outcomes shown in other studies, our study showed that posttransplant delirium was associated with prolonged mechanical ventilation[5,7,9,11,12] with an average of 5.07 days, prolonged ICU stays[6,7,11,12] with an average of 6.01 days, and prolonged hospital stays[6-8,11,12] with an average of 10.64 days. These issues may be compounded further by frequent episodes of sepsis,[11] urinary tract infection, and pneumonia.[6] However, in our study, neither postoperative sepsis (17.4% vs 7.9%; $P = .330$) nor hospital mortality (13% vs 5.3%; $P = .284$) was significantly different between the groups. We assumed that the appropriate management of postoperative delirium could achieve similar outcomes for hospital mortality. Compared with other studies that reported a higher hospital mortality of 6 months[11] or 1 year,[7] the study by Lee and colleagues showed no significant difference in hospital and 1-year mortality.[12] Whether delirium is a reversible condition and whether it affects long-term outcomes remain to be resolved.[2,3,48] Further research is required regarding this issue.

Considering its negative effect on outcomes, postoperative delirium should be prevented and treated using multicomponent nonpharmacological risk factor methods, comprehensive assessments, and timely pharmacological interventions.[48-50] In the ICU, a standard assessment by ICU-CAM was used to detect delirium in its early stages. Benzodiazepine

use is a risk factor for delirium in ICU patients.[23] Thus, we preferred propofol, haloperidol, or quetiapine as our medications of choice. We also adopted early mobilization and encouraged family support by transferring patients to ordinary hospital units when they were stable. This is compatible with previous study.[12] This strategy may explain why the incidence of postoperative sepsis was not significantly different in patients with delirium versus those without delirium.

Our study had certain limitations. First, the study was retrospective in design, and the data were collected from medical records. Second, post-transplant delirium was assessed by individual and bedside nurses. However, the RASS and CAM-ICU have been consistently applied in clinical practice. Third, the sample size was relatively small (ie, from a single medical center). Fourth, our findings were limited to patients with alcoholic liver disease. We note that patients with viral or autoimmune hepatitis require further analysis. As the concept of early transplant for severe alcoholic hepatitis was advocated and LDLT gained popularity in Asia, we were the first to focus on alcohol hepatitis and LDLT for posttransplant delirium. Moreover, data on long-term outcomes remain lacking. Further studies are needed to discuss the relapse rate and its impact on LDLT.

Conclusions

We concluded that a high incidence of posttransplant delirium in alcoholic cirrhotic recipients was associated with preoperative abstinence. Abstinence >6 months prior to LDLT is suggested to reduce the risk of posttransplant delirium.

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Role of Cytomegalovirus in the Development of Posttransplant Lymphoproliferative Disorders With or Without Epstein-Barr Virus Infection

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Abstract

Objectives: **Many studies have revealed the role of Epstein-Barr virus infection, in combination with chronic immunosuppression, as the main factor in the development of posttransplant lymphoproliferative disorder malignancy. Although many studies have been published on other confounding factors involved in posttransplant lymphoproliferative disorders, the role of coinfection with both cytomegalovirus and Epstein-Barr virus has not been investigated. We evaluated the role of cytomegalovirus infection as a risk factor in transplant recipients who were simultaneously infected with Epstein-Barr virus.**

Materials and Methods: **In the current retrospective study, 143 recipients of various solid-organ transplants at Namazi Hospital from April 2018 to March 2019 were assessed for coinfection with cytomegalovirus and Epstein-Barr virus with the TaqMan real-time polymerase chain reaction assay. We collected clinical and pathology details from their medical records.**

Results: **Of the 143 patients, 81 (57%) were male. Children under 5 years old were the largest group with 32% prevalence, and the most common organ transplant in this study was liver transplant. The prevalence of cytomegalovirus and Epstein-Barr virus coinfection was 12.6% (18/143 patients), of whom 50% experienced posttransplant lymphoproliferative disorder (9/18 patients) during 18 months after transplant. The incidence of posttransplant lymphoproliferative disorder was significantly higher among patients coinfected with cytomegalovirus and Epstein-Barr virus than among patients without coinfection. We observed a significant correlation between cytomegalovirus viral loads, as well as Epstein-Barr virus genome load, in posttransplant lymphoproliferative disorder development.**

Conclusions: **Coinfection with cytomegalovirus and Epstein-Barr virus, as well as the genome load of each virus, can serve as a strong predictive factor of posttransplant lymphoproliferative disorder in solid-organ transplant recipients.**

Key words: *Coinfection, Monitoring, Solid-organ transplant, Virus genome load*

Introduction

Viral infections, especially from the Herpesviridae family, are associated with high morbidity and mortality in immunocompromised patients. Since the first successful organ transplant in 1954,[1] herpesviruses have emerged as the putative opportunistic infection in different types of solid-organ transplants.

After primary infection, both cytomegalovirus (CMV) and Epstein-Barr virus (EBV), as members of the Herpesviridae family, may remain latent with intermittent periods of reactivation that may vary according to the host immune status. The incidence rates of CMV and EBV infection vary widely among solid-organ transplant recipients, from 14% to 82% for CMV[2,3] and from 42% to 61% for EBV,[4,5] and primary infection with CMV or/and EBV may cause various subclinical infections, graft rejection, and even death.[6] Also, CMV is associated with enhanced replication of other viral agents, such as EBV. Cytomegalovirus can directly and/or indirectly accelerate EBV replication and thereby lead to B-cell proliferation and posttransplant lymphoproliferative disorder (PTLD) in solid-organ transplant recipients.[7]

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Posttransplant lymphoproliferative disorder is a heterogeneous disease ranging from indolent reactive hyperplasia to high-grade lymphoma, and the incidence of PTLD varies between 1% and 20%, according to type of organ, degree of immunosuppression, viral infection, recipient/donor EBV serostatus, ethnicity, and genetic variation of the host.[5,8] Although the causal relationship between EBV and PTLD has been proved, limited data are available on the role of CMV infection.[9] Some studies have demonstrated that a high viral load of EBV DNA may be a harbinger of PTLD, but there are few data on the role of CMV viral load.[4,5] Therefore, this study examined the correlation of CMV and EBV viral loads with PTLD progression.

Another purpose of this study was to determine the overall incidence of EBV infection, CMV infection, and EBV-CMV coinfection in Iranian solid-organ transplant recipients as well as the association with incidence of PTLD.

Materials and Methods

We analyzed the results from April 2018 to March 2019 of quantitative EBV and CMV tests recorded from 143 solid-organ transplant recipients who were clinically suspected for CMV and/or EBV infection.

The age range of the participants was 1 to 67 years. The patients had received liver (n = 121), kidney (n = 16), or bone marrow (n = 3) transplant or dual liver-kidney transplant (n = 2). The main reason for exclusion from the study was no suspicion of infection.

The focus of this study was on PTLD cases in patients with CMV-EBV coinfection versus patients with CMV or EBV monoinfection, with special focus on the effect of the viral load on each group of patients, as well as the underlying diseases and rates of mortality and morbidity.

Cytomegalovirus and Epstein-Barr virus load monitoring

The sera samples from the patients referred to the Prof. Alborzi Clinical Microbiology Research Center, which is affiliated with Shiraz University of Medical Sciences, were assessed by TaqMan real-time polymerase chain reaction (PCR) assay for monitoring CMV and EBV infections.

The suspected samples had been stored at -70 °C until the viral DNA extraction process. Viral nucleic acid was isolated from 200 μL serum, according to the manufacturer's instructions (Roche). In each serum sample, CMV and EBV genome loads were evaluated by TaqMan real-time PCR assay, as described previously.[10] The detection limit of each CMV and EBV quantitative PCR assay test was 10 copies/mL sera.

Drug regimen for transplant patients

The routine immunosuppressive regimen after transplant was triple therapy with tacrolimus, mycophenolate mofetil, and prednisolone. In Namazi Hospital, CMV prophylaxis is the routine prevention strategy for CMV infection in pediatric patients under 18 years old, and preemptive therapy is the routine prevention strategy in adult patients.

Posttransplant lymphoproliferative disorder diagnosis

World Health Organization criteria and details from medical records showed that 9 patients were affected by PTLD malignancy. At the time of PTLD presentation, computed tomography is the primary choice for the diagnosis of PTLD. Tissues from all affected patients were histopathologically examined by an expert pathologist (BG) for final disease confirmation. It is noteworthy that most transplant donors in this study were brain dead.

Statistical analyses

The data were analyzed using SPSS for Windows (version 16.0). The most important statistical tests used in this study were the *t* test, the chi-square test, and the Mann-Whitney test.

Results

We assessed 143 transplant recipients of various organ types who were suspected for CMV-EBV coinfection at least once (1-9 times) during 1.5 years after organ transplant. There were 81 male patients (56.6%) and 62 female patients (43.3%). The patient population consisted of pediatric and adult recipients, with an age range of 1 to 67 years and a mean age of 11.82 years (SD, 11.92 years) (Table 1). There was 1 patient for whom we did not obtain/record any age data.

Table 2 shows that 16.9% (n = 24) of the patients had CMV monoinfection, 23.9% (n = 34) had EBV monoinfection, and 12.6% (n = 18) had CMV-EBV coinfection.

Epstein-Barr virus infection was the most common infection (n = 52, of whom 18 were coinfected with

CMV). There was no statistically significant correlation of age with CMV infection or with CMV-EBV coinfection ($P \geq .05$); however, there was a significant relationship between EBV infection and age ($P \leq .05$).

The prevalence of CMV infection, EBV infection, and CMV-EBV coinfection for each type of transplant is shown in Table 3.

Table 1. Different Organ Transplants in Different Age Groups of Iranian Transplant Recipients

Age Group	Number of Recipients				Total, No. (%)
	Liver	Kidney	Bone Marrow	Liver/Kidney	
1-5 y	43	2	0	0	45 (31.7%)
6-10 y	33	5	2	1	41 (28.9%)
11-15 y	20	1	0	1	22 (15.5%)
16-20 y	15	3	0	0	18 (12.8%)
21-25 y	2	5	0	0	7 (4.9%)
>26 y	8	0	1	0	9 (6.3%)
Total	121	16	3	2	142 (100%)

Table 2. Prevalence of Cytomegalovirus Infection, Epstein-Barr Virus Infection, and Coinfection With Both Among Different Age Groups of Iranian Solid-Organ Transplant Recipients

Age Group	Number of Infected Recipients (%)		
	CMV	EBV	CMV-EBV
1-5 y	12/45 (26.7%)	18/45 (40%)	8/18 (44.4%)
6-10 y	5/41 (12.2%)	10/41 (24.4%)	4/18 (22.2%)
11-15 y	3/22 (13.6%)	3/22 (13.6%)	3/38 (16.6%)
16-20 y	2/18 (11.1%)	1/18 (5.5%)	1/18 (5.5%)
21-26 y	1/7 (14.3%)	1/7 (14.3%)	1/18 (5.5%)
>26 y	1/9 (11.1%)	1/9 (11.1%)	1/18 (5.5%)
Total	24/142 (16.9%)	34/142 (23.9%)	18/142 (12.6%)

Abbreviations: CMV, cytomegalovirus infection; CMV-EBV, coinfection with both viruses; EBV, Epstein-Barr virus infection

Table 3. Prevalence of Cytomegalovirus Infection, Epstein-Barr Virus Infection, and Coinfection With Both According to Organ Type in Iranian Solid-Organ Transplant Recipients

Type of Transplant	No. of Transplants	CMV	EBV	CMV-EBV
Liver	121	22	33	16
Kidney	16	0	0	0
Bone marrow	3	1	1	1
Liver/kidney	2	1	0	1
Total	142	24	34	18

Abbreviations: CMV, cytomegalovirus infection; CMV-EBV, coinfection with both viruses; EBV, Epstein-Barr virus infection

Lymph node biopsy was the primary method of PTLD diagnosis in 9 transplant recipients included in this study; in addition, 8 of the 9 patients experienced CMV infection simultaneous with EBV infection. Statistical analyses revealed a significant correlation between CMV-EBV coinfection and PTLD incidence ($P \leq .05$), whereas 1 of 134 patients who were not coinfected with CMV-EBV experienced at least 1 type of PTLD disorder, but this result was not statistically significant ($P \geq .05$).

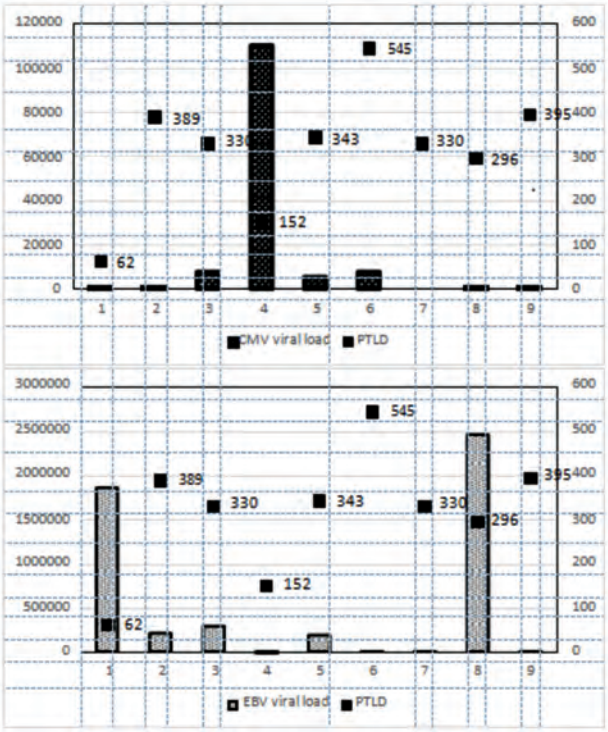
The maximum EBV viral loads were higher than the CMV genome load in the patients with PTLD. Notably, there was a significant correlation between CMV and EBV maximum viral load and the occurrence of PTLD (Figure 1, Table 4). In patients with PTLD, the CMV-EBV coinfection occurred before PTLD development, except for a single case (Table 4).

Table 4. Cytomegalovirus and Epstein-Barr Virus Peak Titers in 19 Patients With or Without Posttransplant Lymphoproliferative Disorder During 18 Months After Transplant

Patient	Age	Sex	PTLD After Tx, d	PTLD Before and/or After CMV-EBV	CMV-EBV Peak Titer, serum copies/mL	Organ Tx Type	Underlying Disease	Rejection	Outcome
P1	6 y	M	62	7 d after	400-185 500	Liver	ND	ND	Survival
P2	4 y	F	389	6 d after	911-210 000	Liver	Biliary atresia	Rejection	Survival
P3	12 y	F	330	113 d after	7800-290 000	Liver	CHF	ND	Survival
P4	2 y	F	152	1 d after	110 500-2 550 000	Liver	ND	Rejection	Death
P5	1 y	M	343	6 d after	5400-185 000	Liver	Tyrosinemia	ND	Death
P6	6 y	M	545	395 d after	7800-950	Liver	Crigler-Najjar	Rejection	Death
P7	15 y	M	330	30 d after EBV infection	0-131 000	Liver	ND	ND	Death
P8	2 y	F	296	5 d after	500-2 450 000	Liver and BMT	Biliary atresia, non-Hodgkin lymphoma	Rejection	Death
P9	22 y	F	395	169 d before	890-760	Liver	PFIC	ND	Survival
P10	3 y	M	Not PTLD		10 500-12 500	Liver	ND	ND	
P11	67 y	M	Not PTLD	ND	450 000-41 000	Liver	HBV	ND	Survival
P12	4 y	M	Not PTLD	ND	840-450	Liver	ND	ND	
P13	10 y	M	Not PTLD	ND	950-600	BMT	Leukemia	Rejection	Death
P14	19 y	F	Not PTLD	ND	450-750	Liver	ND	ND	
P15	9 y	M	Not PTLD	ND	1100-122 000	Liver	PFIC	Rejection	Death
P16	5 y	M	Not PTLD	ND	1000-8900	Liver	Cirrhosis	ND	Survival
P17	2 y	M	Not PTLD	ND	1000-2300	Liver	ND	Rejection	Survival
P18	15 y	F	Not PTLD	ND	110 500-7600	Liver and kidney	ESLD hyperoxaluria	ND	Death
P19	19 y	F	Not PTLD	ND	450-750	Liver	ND	ND	ND

Abbreviations: BMT, bone marrow transplant; CHF, congenital hepatic fibrosis; CMV-EBV, coinfection with both cytomegalovirus and Epstein-Barr virus; ESLD, end-stage liver disease; F, female; HBV, hepatitis B virus; M, male; ND, no data; PFIC, progressive familial intrahepatic cholestasis; PTLD, posttransplant lymphoproliferative disorder; Tx, transplant

Figure 1. Cytomegalovirus and Epstein-Barr Virus Loads in 9 Coinfected Iranian Patients Who Developed Posttransplant Lymphoproliferative Disorder at Different Times After Transplant



Abbreviations: CMV, cytomegalovirus; EBV, Epstein-Barr virus; PTLD, posttransplant lymphoproliferative disorder

Discussion

The CMV and EBV are respective members of the Betaherpesvirinae and Gammaherpesvirinae subfamilies of Herpesviridae in the order Herpesvirales and cause opportunistic viral infections in immunocompromised patients such as transplant recipients.

In response to CMV and EBV primary, coprimary, or secondary infections, there are substantial defensive responses in patients without transplant; however, in transplant recipients, these responses are limited and may lead to diverse clinical manifestations of infection.

In this study, the EBV and CMV infection levels were less than expected (17% and 24%, respectively), which may have been caused by the CMV preemptive therapy regimens applied in pediatric patients, who comprised most of the participants. There is scant information published about the incidence of CMV-EBV coinfection in solid-organ transplant recipients, which had a rate of about 12.6% over the 1.5-year study period after transplant in our study.

The present study revealed the incidence of PTLD increased significantly among transplant recipients with CMV-EBV coinfection versus recipients without coinfection. Limited data are available about the role of CMV in PTLD development. Jaksch and colleagues have shown that the use of immunoglobulin G prophylaxis against CMV can inhibit development of PTLD.[11] In a large data analysis study on kidney transplant patients who received immunoglobulin G prophylaxis against CMV, the PTLD incidence for the inpatient group was remarkably alleviated versus that shown in the control group.[9] Manez and colleagues showed that CMV infection increased the post-transplant risk of PTLD after EBV primary infection.[12]

Arcenas and Widen demonstrated that CMV infection is associated with EBV reactivation in vitro. They focused on the potency of the CMV infection as an important cofactor in EBV reactivation among transplant recipients.[13] Preiksaitis and Keay reported that CMV mismatch between donors and recipients is a factor in the PTLD incidence rate.[14] There are several molecular and cellular explanations for these observations, including (1) both CMV and EBV infections can polyclonally activate B cells including EBV-infected B cells; and (2) suppression of T-cell activity via interleukin 10 (IL-10) gene homologs exists in both EBV and CMV, which may impair the MHC capacity of the major histocompatibility complex, which in turn may disrupt the antiviral immune response of the host.

In the interaction between CMV and EBV in transplant recipients, the clinical sequelae are not well known, but an increase in the expression of immediate early genes, including the gene for EBV ZEBRA protein, diffuse and restricted early genes were seen, and overall the pool of EBV-infected B cells was increased.[15] Cytomegalovirus increases neutrophil migration, delays neutrophil apoptosis, and thereby accelerates tissue damage relevant to CMV immunopathology.[16]

Some studies have shown that IL-8 is a main cytokine that is excreted after CMV infection, which in addition to accelerating the production of CMV progeny virus, can modulate the immune system via the attenuation of the antiviral effect of interferon α. Costa and colleagues revealed that the expression of UL76 leads to IL-8 production during CMV infection.[17] Some studies have shown the role of an induced inflammatory cytokine such as IL-8 in cancer development. Waugh and Wilson described the IL-8 pathway in tumor progression.[18]

Recent studies have demonstrated that stimulation of the pathways for the family of mammalian

inducible transcription factors known as nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) after CMV infection, which may lead to proinflammatory cytokines production, can be blocked via viral microRNAs miR-UL122-3p and miR-US5-1,[19] as well as CMV UL26 viral proteins.[20] It is noteworthy that NF-κB is a critical key factor involved in the transcription of CMV immediate early genes and a broad array of other genes.[21]

Kim and colleagues showed that the maximum load of CMV was not associated with a higher risk of PTLD.[22] However, in our study, CMV peak titer was associated with risk of PTLD development.

Overall, there are some common pathological routes between CMV and EBV with a possible synergistic effect.

Conclusions

We found frequent infection with CMV, EBV, and CMV-EBV in transplant patients who were suspected of these infections. Also, we showed correlations between PTLD and viral loads of CMV and EBV. Further studies are needed to clarify the pathogenesis and interactions involved in CMV-EBV coinfection.

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Intraoperative Tissue-Immunosuppressive Therapy Reduces Rejection Episodes in Heart Transplant Recipients

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Abstract

Objectives: **Our study was conducted to determine the effects of intraoperative antithymocyte globulin administration on donor hearts procured after cardiocirculatory death. We evaluated the impact of antithymocyte globulin on graft function and related parameters during isothermic blood cardioplegia.**

Materials and Methods: **In this prospective and randomized single center study, 30 patients with orthotropic heart transplant were divided into 2 groups: group 1 included 15 patients who received retrograde antithymocyte globulin infusion via coronary sinus intraoperatively and immediately after organ procurement and group 2 included 15 patients who received traditional antithymocyte globulin infusion after implantation.**

Results: **Study patients had a mean age of 33.8 years (range, 15-56 y). All patients had panel reactive antibody less than 10% except for 3 patients. The cluster of differentiation 3-positive cell count decrease was more than 20%. The inotropic therapy dose required and the myocardial pressure (stiffness) were less for group 1 patients. These patients had less acute rejection episodes than group 2 (0% vs 13.3%; *P* < .05).**

Conclusions: **Favorable clinical outcomes were observed in terms of less acute rejection episodes and better graft function at least during the early posttransplant period. Intraoperative antithymocyte globulin treatment may have a preventive effect for acute cellular rejection in heart transplant patients.**

Key words: *Antithymocyte globulin, CD3, Immunosuppression*

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Introduction

Allograft rejection is one of the crucial dilemmas and concerns of early mortality after heart transplant.[1] The main purposes of any immunosuppressive protocol are adapting the host's immune reaction by minimizing non-self recognition and intervention against foreign antigen structures; the long-term survival of patients with full functioning graft is the final aim of organ and tissue transplant. With the reduction of rejection risk, immunosuppressive therapy has made organ transplant feasible.[2]

The inclusion of cytolytic antibodies as immunosuppression induction treatment, such as anti-T-cell globulins, in the prophylactic therapy protocol has increased success with solid-organ transplant.[3] Prevention of steroid-resistant rejection was the initial target in treatment and has led to the development of polyclonal antibodies. The use of antilymphocyte drugs has enhanced immunosuppression and optimized outcomes in allograft recipients. Antileukocyte serum was first defined by the Russian immunologist Élie Metchnikoff in 1899.[4]

Induction treatment is a "supplemental prophylactic treatment strategy" that decreases the hazard of acute rejection in the early posttransplant period. Although the mechanisms of action of antiimmune serum have not yet been fully explained, without a doubt there is now evidence that antithymocyte globulins (ATG) are useful agents for managing these clinical circumstances. However, current immunosuppressive regimens are still suboptimal in graft failure rates and have adverse effects, and a general consensus for the best treatment protocol has not been reached.[5]

Antibody therapy is usually applied at a fixed dose for 1 or 2 weeks posttransplant. This regimen has been successfully modified for renal transplant by substitution of a perioperative single high dose

(9 mg/kg) of ATG in nonsensitized patients.[6] In general, ATG has a strong suppressive impact on activated lymphocytes, a fact that endorses its use in clinical situations where activated lymphocytes play a predominant role, as in the case of T-cell-mediated graft rejection.[3] When high-dose intraoperative ATG is used, the introduction of calcineurin inhibitors can be postponed, thereby protecting cardiac function and completely avoiding use of corticosteroids in the primary immunosuppression regimen.[7]

In cardiac transplant, however, "intraoperative continuous infusion" at the start of surgery, as successfully used in renal and renal-pancreatic transplant, is not preferred as a protocol. To assess the clinical impact and efficacy of intraoperative continuous ATG infusion versus the established conventional prophylactic ATG regimen, we conducted a prospective randomized study. This investigation will allow us to elucidate whether this new protocol is associated with efficacy and safety similar to the conservative therapy.

Materials and Methods

Patients

Our study was performed at a tertiary reference cardiac surgery hospital and approved by our local ethics committee. This was a prospectively designed study that included 32 consecutive patients who had orthotropic heart transplant at our center between July 1, 2011 and July 30, 2014. Patients were randomized into 2 groups based on the infusion timing of ATG (ATG-Fresenius S; Fresenius Biotech GmbH, Gräfelfing, Germany). Group 1 initially included 17 patients who had ATG infused via coronary sinus both intraoperatively and postoperatively. Group 2 included 15 patients who had only postoperative ATG infusion (conventional treatment group). To allow concise and balanced progression of the study, the randomization of the 2 groups was done consecutively, with group 1 patients being the last 17 patients of the study period. Patients were informed about the procedure and gave informed consent preoperatively. Patients with preoperative thrombocytopenia, leukopenia, or active bacterial, fungal, or viral infections were not included in this study. Two patients were excluded from study results due to death from a surgical complication (bleeding) and death due to renal failure (Table 1).

Table 1. Patient Demographics and Transplant Values

	Group 1 (n = 15)	Group 2(n = 15)	*P* Value
Mean age, y	32.4 ± 11	37.3 ± 13	NS
Sex (female/male)	4/11	2/13	NS
Aortic cross-clamp time, min	121.7 ± 10	135.18 ± 26	NS
Total perfusion time, min	198 ± 25	181 ± 31	NS
Cold ischemic time, min	131 ± 62.3	103 ± 59.5	NS
Total ischemic time, min	261 ± 65.1	234 ± 61.4	NS
Hospital stay, d	30 ± 5.1	50 ± 19.8	.02

Abbreviations: NS, not significant

Surgical procedure

Under general anesthesia with full monitorization of all hemodynamic parameters, total cardiopulmonary bypass was initiated. Isothermic blood cardioplegia was applied immediately after aortic cross-clamping. All anastomosis procedures were made under cross-clamping. All bicaval orthotropic heart transplants were performed by the same surgical team.

Study design

This study was conducted in donor hearts obtained after cardiocirculatory death (category III and category IV according to modified Maastricht classification)[8] to determine the effects of intraoperative ATG administration applied during isothermic blood cardioplegia on graft function and related parameters. Retrograde isothermic blood cardioplegia infusion with the ATG solution via the coronary sinus was started as soon as the donor heart arrived to the surgical department.

Total doses were the same for both groups, with the only difference being that 7 to 10 mg of the total dose were infused intraoperatively for group 1 patients. For this procedure, 7 to 10 mg of ATG were infused intraoperatively via cardioplegia cannulas for group 1 patients until the end of surgery. Postoperatively, group 1 patients received 3 mg/kg ATG for 7 days and group 2 patients (control group) received standard ATG therapy consisting of 7 daily doses of ATG beginning immediately after termination of surgery and on arrival to the intensive care unit. Intraoperatively, all patients received a single intravenous bolus of 1000 mg methylprednisolone immediately before removal of the aortic cross-clamp.

Blood samples were taken from the aortic ostium at the beginning of the infusion, before the anastomosis, and after the anastomosis. Total lymphocyte count, platelet counts, and granulocyte numbers were determined just before heart transplant and every 24 hours thereafter for 30 days. The diagnosis of acute cardiac allograft rejection was made according to

the criteria of the International Society for Heart and Lung Transplantation.[9]

Postoperative period

All patients had the same follow-up protocol posttransplant. Immediate posttransplant prophylaxis for infections included short-term antibiotic agents such as ceftazidime and piperacillin and oral nystatin. Patients who were negative for cytomegalovirus (CMV) infection but had donors who were CMV positive were given acyclovir at 5 mg/kg/day.

Efficacy parameters included vital signs and the need for postoperative transfusions. Acute rejection was not considered as an adverse event but as treatment failure. Safety analysis was based on adverse events directly noted by the medical staff or explained by the patients.

Statistical analyses

All patient data were recorded at a computerized database system from laboratory findings and hard copies of medical records. All statistical analyses were performed using commercially available SPSS statistical software (version 16.0.1, SPSS Inc., Chicago, IL, USA). Continuous variables are expressed as means and standard deviation (SD). For categorical data, absolute and relative frequencies were considered and categorical variables were compared using chi-square test and Fisher exact test where appropriate. In addition, cluster of differentiation 3 (CD3) count was analyzed in group 1 patients using chi-square test.

Continuous data, including mean results and SD, median, quartiles, minimum, maximum, and number of valid values, were compared using independent sample *t* tests or Mann-Whitney U tests. $P < .05$ was considered to be statistically significant. All *P* values reported were 2-sided and intended to be descriptive.

Results

Patient characteristics

Our study population included 25 men (84.5%) and 5 women (16.6%). Mean age (SD) was 33.8 (6.3) years (range, 15 to 56 y). Preoperative causes of heart failure were chronic ischemic heart disease in 20 patients (66.6%), primary cardiomyopathy in 8 (26.6%), and other causes in 2 (7%). Eight of 15 patients (53.3%) in group 1 (continuous infusion) and 9 of 15 patients (60%) in group 2 (conventional infusion) had at least 1 attendant disease at orthotopic heart transplant. Most patients were classified as III or IV according to the New York Heart Association criteria. At the time of enrollment, all patients were nonsmokers except for one. No significant differences were shown between the 2 groups regarding mean age, sex, indication for cardiac transplant, and cardiac functional class. Mean age of donors was 44 years (range, 23-61 y). No significant differences were shown among donors regarding age, sex, cause of death, total cold ischemia time, and other surgical parameters during transplant (Table 1).

Early survival information

No perioperative deaths were reported except for the 2 excluded patients. Rejection was monitored during hospital stay. There were no deaths in the final patient groups. No differences were observed between the 2 groups with regard to clinical performance or electrocardiographic assessment.

Group 1 patients showed less echocardiographic abnormalities, insofar as left ventricular shortening fraction and expected wall thickness alterations, after transplant than group 2 patients. In addition, the doses needed for inotropic therapy and the myocardial pressure (stiffness) measurements were less for group 1 patients than for group 2 patients. At last follow-up before hospital discharge, patients had New York Heart Association grade I/II disease.

Laboratory findings

Immediately after the first ATG administration, total lymphocyte counts quickly and significantly decreased in group 1 patients; however, a similar T-lymphocyte depletion affecting CD3 and CD8 subpopulations was shown for both groups (Table 2) but was only significant for group 1.

Both groups showed thrombocyte count decreases at the beginning of induction therapy. However, on the day of transplant, thrombocyte counts were particularly lower in group 2 patients (Table 2). Marked increases in thrombocyte counts were shown over the subsequent days in both groups, although results were only significant for group 1. No cases of severe thrombocytopenia were shown in any of the patients that required discontinuation of ATG treatment ($< 50 \times 10^3/\mu L$). Moderate leukocytopenia was reported in 4 patients

in group 1 and 6 patients in group 2; however, no patients required discontinuation of ATG infusion.

All patients in group 1 except for 3 had panel reactive antibody (PRA) less than 10%. CD3-positive cell count was decreased by more than 20% for group 1 patients (Table 3). Unfortunately, group 2 patients did not undergo CD3 cell analyses. Although this was a study limitation, we were able to compare total lymphocyte counts between the 2 groups ($P < .03$).

Group 1 patients had no acute rejection episodes (0%) versus 2 of 15 patients (13.3%) in group 2 ($P < .05$). The 2 patients underwent endomyocardial biopsies, which showed acute rejection according to early postoperative clinical and echocardiographic findings, and received antirejection therapy.

Table 2. Comparison of Thrombocyte and Lymphocyte Counts in Treatment Groups Before and After Antithymocyte Globulin Administration

	Preoperative Level	Postoperative Level	Change in Value
		Thrombocyte, $10^3/\mu L$	
Group 1	260 ± 85	71 ± 19	72.6%
Group 2	159 ± 71	98 ± 24	38.3%
P value			< .05
		Lymphocyte, µL	
Group 1	2100 ± 765	340 ± 312	83%
Group 2	1490 ± 470	350 ± 240	73%
P value			.03

Table 3. Panel Reactivity Antibody and Cluster of Differentiation 3 Values in Group 1 Patients

Patient Number	PRA (Class I/ Class II), %	CD3-Positive T Cell, %
1	3.5/7.2	1.5/0.3/0.3
2	8/5.3	3.5/1.1/0.2
3	9/12	12/6.5/0.1
4	3.7/15	23/4.3/2.1
5	7.2/5.1	16/2.3/1.2
6	4.5/8.2	11.3/2.3/1.2
7	11/6.8	14/1.6/1.1
8	8/6.2	16/2.8/1.4
9	7/4.3	10/3.1/1.3
10	9/2.3	18/2.6/1.4
11	6.8/4.1	19/2.2/1.0
12	9/5	20/4.3/1.1
13	8/5	12/2.5/0.4
14	7/8.1	9/3.1/1.1
15	5.7/8	14/2.0/0.8

Abbreviations: CD, cluster of differentiation 3; PRA, panel reactive antibody

Discussion

When risk for allograft rejection is increased during the initial posttransplant period, nearly all immunosuppressive therapies for solid-organ transplant recipients follow the use of additional strength treatment. CD4-positive T cells play a primary role in acute cardiac allograft rejection, and acute CD4-positive T-cell-mediated rejection requires major histocompatibility complex (MHC) II expression in the allograft, pointing to the importance of direct graft recognition. A key point for acute cellular CD4-mediated rejection is whether the rejection happens via direct MHC class II presentation by the graft and/or via indirect donor antigen presentation by host MHC class II-bearing antigen-presenting cells.[10]

Specific antibody induction agents or high-dose intravenous corticosteroids or combinations of both can be used to allow immunosuppressive efficacy at this early stage. Implementation of induction treatment during the immediate postoperative period or perioperatively has become useful in cardiac transplant. This approach can improve graft survival after transplant, with a noteworthy reduction in calcineurin inhibitor dosage and reduction of associated adverse events without compromising allograft survival.

The use of ATG to prevent rejections has shown promise in solid-organ transplant,[11,12] including cardiac transplant.[13-15] After rabbit ATG as a prophylaxis treatment was first defined in 1987 by Kawaguchi and associates,[16] antilymphocyte antibodies are now administered in almost 22% of transplant recipients.[17] Currently, ATG is the only induction drug approved for cardiac transplant.

The immunosuppressant ATG is a polyclonal anti-T-lymphocyte immunoglobulin product procured from rabbits immunized with human Jurkat cells.[18] Its mechanisms of action on T cells include complement-mediated cytolysis of T-cells, stimulation of apoptosis, blocking of signal transduction pathways, opsonization of activated cells, and suppression of adhesion.[19]

Antithymocyte globulin can reduce levels of lymphocyte subsets expressing surface proteins. It temporarily decreases leukocyte and platelet numbers, which return to normal levels after application. Specific changes in lymphocyte action can occur that block these surface molecules called clusters of differentiation (CD).[10,20] This efficacy of ATG is likely to be a result of the complement binding to the cell-ATG composite, and reduced CD2, CD3, CD4, and CD8 counts have been noted. Indeed, a single high-dose implementation may affect cytokine levels, decreasing interleukin 1β, tumor necrosis factor-α, and interferon-γ levels, suddenly increasing interleukin 10, but not affecting interleukin 12-p70.[10]

Antithymocyte globulin can have a better effect than activated T lymphocytes by blocking mechanisms like antigen recognition (MHC classes I and

II) and complement-dependent cytolysis of activated lymphocytes, blocking signal transduction pathways accountable for activation of T cells, inhibiting leukocyte adhesion on endothelial cells and subsequent extravasation[21] and/or opsonization of activated cells, and stimulating Fas-mediated apoptosis of activated lymphocytes.[5]

In our study, we analyzed the efficacy and safety of 2 induction therapy regimens in patients early after heart transplant (standard therapy with rabbit ATG for 7 days versus ATG infusion started immediately at transplant followed by low-dose therapy). Effectiveness of treatment was assessed by improved graft survival. The rationale of an initial intraoperative retrograde infusion approach was whether, in addition to T-cell depletion, ATG could more efficaciously avoid initial damage.

The above-mentioned mechanisms of ATG appear to work together to protect the allograft from initial inflammatory harm and to allow allorecognition processes and occurrence of an immune response. In general, initiation of ATG infusion at an early phase may decrease the strength of the initial immune reaction. Many experimental studies have reported that ATG preparations may have a useful impact against ischemia-reperfusion injury in nontransplant models.[2,6] Abudher and associates[22] found that high-dose intraoperative ATG may enhance cyclosporine sensitivity. In a study of 30 cardiac transplant recipients, patients given ATG for 7 days tended to have less cardiac allograft vasculopathy than those who received ATG for 3 days (28% vs 50%; $P = .05$).[23] Martins and associates reported that the accumulative dose of rabbit ATG may also be related to better renal graft and subsequent patient survival rates.[24]

Both of the regimens demonstrated comparable efficacy results, with a low incidence of acute rejection and without graft loss despite low cyclosporine concentrations. This could explain the relatively low incidence of calcineurin inhibitor-related adverse events. Particularly notable was that there was no mortality among patients in the high-dose group. In addition, intraoperative application of ATG was not related with hemodynamic complications and was well tolerated. For both patient groups, severe adverse effects related to ATG use were not detected.

Faggian and associates, in a study that compared a single high intraoperative dose of rabbit ATG followed by 1.5 mg/kg for 5 days (n = 14) versus standard 7-day therapy (n = 16), noted similar efficacy between regimens. Early high-dose ATG may preserve effectiveness, but a fixed therapy of 1.5 mg/kg for 5 days alone may be a less effective rejection prophylaxis than 7-day therapy.[23] Krasinskas and associates reported that monitoring ATG based on peripheral T-lymphocyte counts in cardiac transplant recipients led to a decrease in the total ATG dose from 10 to 15 mg/kg to 1 to 5 mg/kg without an increase in acute rejection.[25] In our study, we have applied the same dose of ATG for both groups postoperatively. Koch and colleagues confirmed this finding that lymphocyte-adapted monitoring can preserve efficacy with a significant reduction in cumulative rabbit ATG dose compared with a conventional fixed-dose regimen.[26]

The impact of ATG therapy on peripheral blood lymphocyte subsets was analyzed by flow cytometry. A higher percentage of patients in group 1 had transient leukopenia; however, despite the existence of comorbidity, no differences between the 2 groups were detected. Intraoperative ATG infusion decreased total lymphocyte count, with initial and rapid thrombocyte decrease. No patients required discontinued therapy because of marked lymphopenia, neutropenia, or thrombocytopenia. Although several strategies can decrease circulating antibodies, studies have reported that patients with increased pretransplant PRA levels > 10% tend to have earlier and more severe rejections with significantly lower posttransplant survival.[26] We obtained similar results concerning PRA levels in our study.

A simultaneous reduction was observed regarding CD3-positive (total T lymphocytes), CD3/CD4-positive (T helper cells), and CD3/CD8-positive (cytotoxic T cells) levels, although occurring faster and lasting longer in group 1 patients.

Although higher dosing of ATG might cause CMV infections, a lower incidence of CMV infection was noted by Zuckermann and associates with high-dose ATG use.[15] In our study, we observed no differences in incidence of clinical infections between the 2 groups, and there was no patient loss due to any infectious complications.

Conclusions

Induction treatment has been part of the immunosuppressive protocol for more than 40 years, but when and how it should be used in heart transplant

recipients are not clear. Although a growing pool of data point to its efficacy and tolerability, its use as an induction regimen in heart transplant recipients remains unproven.

The potential of rabbit ATG to inhibit progression to cardiac allograft vasculopathy is of substantial importance, and future research is awaited with interest. Modern therapies in which rabbit ATG dosing is adjusted with lymphocyte count may allow reduced dosing, allowing potential safety and cost benefits without compromising efficacy.

Despite our small sample size, favorable clinical outcomes were observed in terms of less acute rejection episodes and better graft function, at least during the early posttransplant period. Patients with intraoperative ATG treatment needed less inotropic therapy and had less posttransplant complications. Our results support the feasibility of ATG as an early therapy as intraoperative infusion in orthotopic heart transplant. Intraoperative continuous infusion of ATG treatment may have a preventive effect for acute cellular rejection in cardiac transplant patients. Further controlled trials are required to identify the most suitable dosage and to optimize the starting time of this induction protocol. Our study, even with its limited patient number, allowed preliminary insight of the therapy modality and duration that could be used for further larger patient group studies.

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Case Report

Therapeutic Lymphangiography for Persistent Lymphatic Leak After Kidney Transplant: A Novel Technique

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Abstract

Lymphatic leakage is a common and well-described complication after kidney transplantation, occurring in up to 25% of patients. Accumulation of lymph is due to the surgical disruption of recipient lymphatic channels accompanying the external iliac vessels, complicated by lower extremity edema, wound breakdown, infection, and, if unresolved, graft loss due to extrinsic compression. In this report, we describe the novel use of diagnostic and therapeutic lymphangiography to successfully treat lymphatic leak after renal transplant that was resistant to drain placement, sclerotherapy, and laparoscopic peritoneal window creation. We also describe the methodology, indications, and contraindications and conclude that this technique is well-tolerated and offers a good option for complex lymph leaks that do not respond to conventional treatment. Further studies are required to compare its efficacy with other standard methods, including sclerotherapy and laparoscopic peritoneal fenestration, as the primary treatment modality.

Key words: *Lipiodol, Lymph leak, Lymphocele, Renal transplantation*

Introduction

Lymphatic leakage is a common and well-described complication after kidney transplantation, occurring in up to 25% of patients.[1] Accumulation of lymph is due to the surgical disruption of recipient lymphatic channels accompanying the external iliac vessels, complicated by lower extremity edema, wound breakdown, infection, and, if unresolved, graft loss due to extrinsic compression. Standard management involves observation, if found incidentally, with aspiration or drain placement utilized as first-line treatment if the lymphatic collection is large or compressing the graft kidney. In most cases, drainage of lymphatic fluid resolves spontaneously. In the setting of ongoing lymphatic leakage, sclerotherapy can be performed or a peritoneal window can be created. Laparoscopic creation of a peritoneal window, which allows the lymphatic fluid to drain into the peritoneal cavity where it can be absorbed, has the lowest recurrence rate at 8% to 16% in a systematic review.[1] However, it is uncertain how to treat persistent lymphatic leakage despite standard management. In this report, we describe the novel use of diagnostic and therapeutic lymphangiography to successfully treat lymphatic leak after renal transplant that was resistant to drain placement, sclerotherapy, and laparoscopic peritoneal window creation.

Case Report

A 77-year-old man with chronic kidney disease due to focal segmental glomerulosclerosis underwent an unrelated living donor kidney transplant from his spouse in a standard fashion with suture ligation and division of the lymphatics overlying the iliac artery. A 10F flat surgical drain was placed in the extraperitoneal space adjacent to the ureteroneocystostomy, as is standard for our practice. Within the first few days postoperatively, the drain put out 200 to 400 mL per day of serosanguinous fluid, and he developed lower extremity edema, most significantly in the ipsilateral leg. Fluid analysis excluded a urine leak and confirmed a lymphatic leak. He was discharged home, and his drain was removed as an outpatient

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once the drainage decreased to less than 50 mL per day.

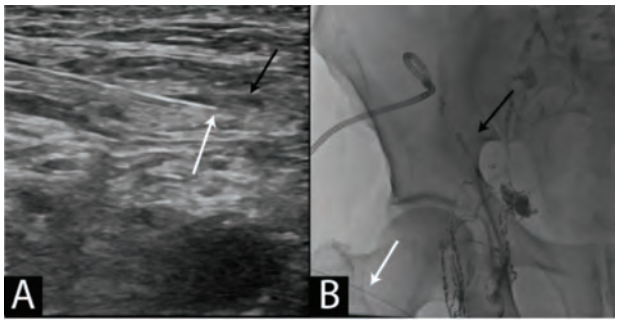
One month posttransplant, because of increased creatinine levels, the patient underwent ultrasonography, which demonstrated a large perinephric fluid collection. The patient underwent ultrasonography-guided drain placement with subsequent improvement of his graft function.

Over the second month posttransplant, his drain output was 300 mL per day, and he was admitted for laparoscopic creation of a peritoneal window. Under direct visualization, methylene blue was injected through the drain into the lymphocele cavity, demonstrating the retroperitoneal collection. The colon was medialized, and the retroperitoneum was opened, with a wide communication between the lymphocele and the peritoneal cavities. The drain was again flushed with methylene blue to demonstrate free drainage into the peritoneum.

Throughout the third month posttransplant, his drain output had not significantly improved after peritoneal window creation, and he was admitted for a drain study and sclerotherapy. The drain was checked under fluoroscopy, which demonstrated the pigtail catheter in place within a small fluid cavity. Povidone iodine (4 mL) was injected into the drain, which was then clamped for 1 hour, before placement to gravity suction. The patient continued to have persistent high-volume lymphatic drainage 1 week after sclerotherapy.

He then underwent diagnostic and therapeutic lymphangiography. A 25-gauge needle was advanced into a normal-sized ipsilateral inguinal lymph node under ultrasonographic guidance (Figure 1A), and Lipiodol (Guerbet LLC, Princeton, NJ, USA) was injected in small aliquots. With serial fluoroscopic spot images, the radiopaque Lipiodol was demonstrated to course from the injected lymph node up the external iliac lymphatic plexus before extravasating from a disrupted channel adjacent to the drain, thereby confirming the lymphatic leak (Figure 1B). Lipiodol, which has an oily appearance, was also confirmed visually with aspiration of the drain. A total of 10 mL of Lipiodol was administered. The procedure was well-tolerated by the patient, and the drain output significantly improved immediately after the procedure and stopped completely after 2 days. Six days after the procedure, ultrasonography demonstrated no persistent fluid collection, and the drain was removed.

Figure 1. Radiological Images of Therapeutic Lymphangiography



(A) Ultrasonographic image showing 25-gauge needle (white arrow) positioned between the cortex and the hilum of the ipsilateral inguinal lymph node (black arrow). **(B)** Fluoroscopic spot image demonstrating the intranodal access catheter (white arrow) and disrupted lymphatic system with lipiodol leaking adjacent to retroperitoneal drain (black arrow).

Discussion

Lymphangiography has been used in the diagnosis of lymphoceles, with a water-soluble contrast agent infused to visualize the disrupted lymphatic channels, and as a therapeutic intervention with glue embolization or sclerosis with povidone iodine or 95% ethanol. Originally developed in 1901, Lipiodol is a mixture of iodine and poppy seed oil-derived fatty acids and was used as the first iodinated contrast agent. Its use in the sclerosing of postoperative lymphatic leakage has been described as the primary management in a small cohort of 3 patients after kidney transplant in Korea with promising results[2]; however, it has yet to be described in complex or resistant lymphoceles. Our proposed standard methodology, including indications and contraindications, is shown in Table 1.

The mechanism by which Lipiodol improves lymphatic leakage has been thought to involve a local inflammatory and granulomatous process that obstructs the lymphatic outflow, combined with mechanical occlusion due to Lipiodol's high viscosity.[3] If successful, the drainage decreases immediately postprocedure[3] and completely resolves within 2 weeks.[2] Standard complications of lymphangiography include contrast allergy, access site hematoma, or infection. Lipiodol injection can cause cardiovascular or pulmonary complications, the most frequent of which is pulmonary oil embolism, which can be mitigated by infusing less than 20 mL of Lipiodol.[4] Lymphangiogram would only be effective for a lymphatic leak; sclerosis is ineffective due to the lack of a true epithelial lining. Other causes of perinephric fluid collections, including seroma or urine leak,

Table 1. Proposed Indications, Contraindications, and Methodology for Lymphangiography

Indications:	Contraindications:
• Symptomatic lymphocele following kidney transplant • Persistent lymphatic leak following standard treatment with sclerotherapy and/or laparoscopic peritoneal fenestration	• Iodine or Lipiodol allergy • Nonlymphatic leak (eg, ascites, urine) • Inability to identify inguinal lymph nodes

Methodology for Therapeutic Lymphangiography:

1. Position the patient supine and prepare/drape the ipsilateral groin.
2. Perform ultrasonography to identify a deep inguinal lymph node medial to the femoral vein.
3. Introduce a 25-gauge needle into the lymph node, with the needle tip positioned at the junction of the cortex and hilum.
4. Inject Lipiodol in 0.1-mL aliquots and obtain serial fluoroscopic images to visualize the lymphatic channel leading to the lymphocele. Do not use more than 20 mL of Lipiodol.
5. If a drain is present, aspirate the drain to visualize the Lipiodol to confirm communication between the lymphatic channel and the drain.
6. Remove the needle and hold pressure on the access site.

should be evaluated and ruled-out prior to proceeding with a lymphangiogram. Limitations to this technique include having an inadequate lymph node for nodal access, Lipiodol extravasation from the lymph node into the venous system, and a lymphatic leak originating from the renal graft, which would not be visualized with an injection of recipient lymph node.

Conclusions

Our novel use of lymphangiography with Lipiodol was effective in the treatment of a persistent lymphocele after kidney transplant. This technique was well-tolerated and offered a good option for a complex lymph leak that did not respond to conventional treatment. Further studies are required to compare its efficacy with other standard methods, including sclerotherapy and laparoscopic peritoneal fenestration, as the primary treatment modality.

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A First Case Report of Cytomegalovirus Infection Presenting With Perianal Fistula and Abscess Formation in a Kidney Transplant Recipient

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Abstract

Cytomegalovirus infection after transplant has been dramatically reduced in the modern era with improved understanding of immunosuppression and perioperative transplant care. However, cytomegalovirus syndrome with or without tissue invasive disease can still lead to significant morbidity and mortality. Several organs can be involved: most commonly, the gastrointestinal tract, liver, pancreas, lung, and the transplanted renal allograft. Postoperative cytomegalovirus colitis after renal transplant is well recognized and described, with symptoms including abdominal pain, nausea, and diarrhea. Biochemistry can demonstrate pancytopenia with a leukopenia with or without histopathology confirmation. A high index of suspicion is required for a timely diagnosis. This is the first published case report of a patient with cytomegalovirus tissue invasion presenting with a perianal fistula and abscess formation. The diagnosis and management of this case with a literature review is discussed.

Key words: *Cutaneous cytomegalovirus, Cytomegalovirus colitis, Perianal cytomegalovirus*

Introduction

Kidney transplant has been demonstrated to have a significant effect on quality and quantity of life for patients with end-stage renal failure. Despite the benefits, the Achilles heel of transplant medicine remains the morbidity associated with immunosuppression. Cytomegalovirus (CMV) colitis, from activation of latent CMV infection, is a well-recognized complication associated with immunosuppression and secondary morbidity for kidney transplant recipients.[1] Gastrointestinal (GI) involvement with CMV-related morbidity has been well described. Cutaneous tissue manifestation has been very infrequently described, with sparse case reports of perineal, penile, tongue, and scrotal ulceration.[2,3] We describe an unusual case of a patient with CMV colitis presenting with perianal fistula formation. A subsequent review of the literature on this unusual cutaneous presentation of CMV colitis is also presented.

Case Report

A 53-year-old male patient with end-stage kidney disease secondary to hypertensive disease received a renal transplant from a deceased donor (brain death). Peritoneal dialysis was the renal replacement therapy prior to transplant. His past medical history included obstructive sleep apnea, monoclonal gammopathy of unknown significance, prior laparoscopic peritoneal dialysis, and catheter and laparoscopic cholecystectomy (for history of gallstone pancreatitis). The recipient was positive for CMV immunoglobulin G (IgG) and negative for Epstein-Barr virus IgG. The donor/recipient (D/R) match profile was human leukocyte antigen mismatch 6/6, CMV D^+/R^+, Epstein-Barr virus D^+/R^-. At time of transplant, the patient was CMV IgG positive and CMV IgM negative on serology. The patient underwent low-risk immunosuppression induction with basiliximab and began a triple maintenance protocol with tacrolimus, mycophenolate mofetil,

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and prednisone. There were concerns regarding persistent idiopathic leukopenia, so the patient did not receive CMV prophylaxis.

The patient underwent an uncomplicated kidney transplant via a modified Rutherford Morison incision in the right iliac fossa and concurrent removal of the peritoneal dialysis catheter. He had delayed graft function and required hemodialysis via a temporary femoral venous catheter (Vascath) until postoperative day 8. His postoperative stay was complicated by *Clostridioides difficile* colitis, which was treated by oral vancomycin (1 g twice daily for 14 days). He also underwent 2 courses of pulse corticosteroid treatment for treatment of biopsy-proven borderline acute rejection on postoperative day 5 and day 20.

He developed new perianal pain on postoperative day 34 with ongoing associated diarrhea. Bedside examination revealed extensive perianal excoriation. Magnetic resonance imaging of his pelvis revealed a possible intersphincteric abscess. He underwent formal examination under anesthesia, and a perianal fistula was identified, arising 2 cm proximal to the anal verge, and this was laid open. Hematoxylin and eosin staining of fistula tract tissue revealed evidence of chronic active inflammation and CMV inclusion bodies suggestive of CMV colitis (Figure 1). This diagnosis was confirmed by immunohistochemical staining with CMV protein monoclonal antibody (Figure 2). At this point, the patient was CMV IgG positive and CMV IgM positive on serology, indicating CMV reactivation, and his plasma CMV viral load was 75 000 copies/mL. His biochemistry at the time of diagnosis demonstrated normal electrolytes with anemia (hemoglobin, 107 g/L), thrombocytopenia (111 × 10^9 platelets/L), and a white blood cell count of 8.2 × 10^9 cells/L. Postoperatively he underwent commencement of intravenous ganciclovir (400 mg twice daily) with immediate resolution of perianal pain. His perianal wound site continued to heal and improve, and reduction in viral load continued to improve. His plasma viral load and white blood cell count during his treatment are shown in Table 1. After 20 days of intravenous ganciclovir therapy, he was transitioned to oral valganciclovir (900 mg twice daily) due to down-trending CMV viral load.

Due to his protracted stay, the patient developed significant frailty and immobility. He continues to receive ongoing inpatient rehabilitation.

Figure 1. Hematoxylin and Eosin Staining Shows Inclusion Bodies

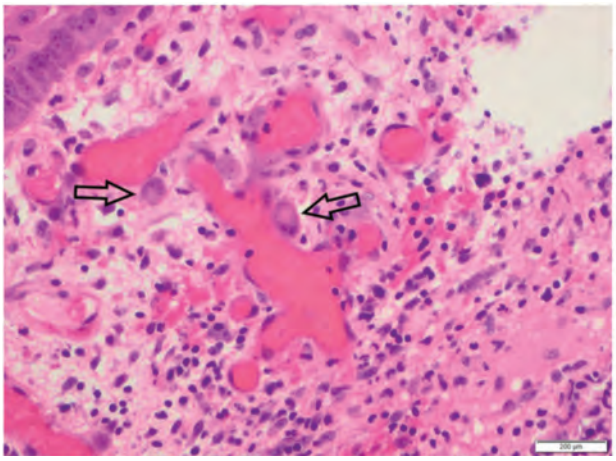

Figure 2. Immunohistochemical Staining Shows Cytomegalovirus Inclusion Bodies

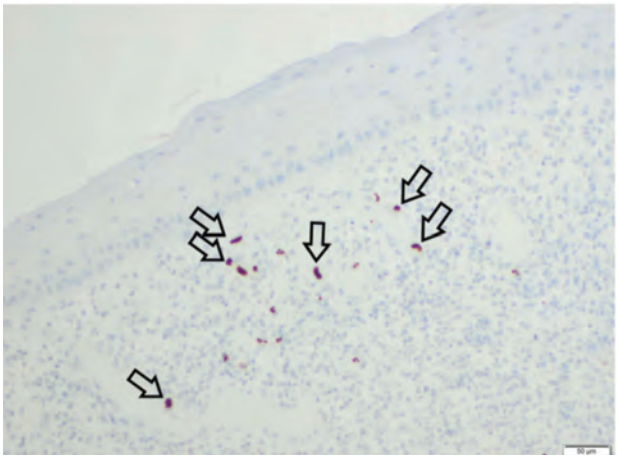

Table 1. Cytomegalovirus Viral Load and White Blood Cell Count

Time After CMV Diagnosis and Ganciclovir Therapy	CMV DNA PCR Test, EDTA Plasma Viral Load, copies/mL	White Blood Cell Count, ×10^9 cells/L	Lymphocyte Count, ×10^9 cells/L
Day 0	75 000	8.6	1.0
Day 6	8700	6.6	0.9
Day 9	5800	6.8	1.2
Day 13	12 000	5.6	0.7
Day 16	6500	3.4	1.3
Day 20	2100	3.6	1.2

Abbreviations: CMV, cytomegalovirus; EDTA, ethylenediaminetetraacetic acid; PCR, polymerase chain reaction

Discussion

Cytomegalovirus, also known as *Human herpesvirus* 5, is a common DNA virus from the Herpesviridae family, affecting over 50% of adults in developed countries.[4] Viral reactivation of CMV is a well-known complication of immunosuppression following kidney transplant and has clinical manifestations

Table 2. Cutaneous Manifestations of Cytomegalovirus in Renal Transplant Patients

Author	Age/Sex	Time After Transplant	Manifestation	Treatment	Outcome (complication)
Lee et al[8]	68 y, female	3 wk	Perianal ulcers	Intravenous ganciclovir	Recovery
Neumann et al[2]	68 y, male	2 mo	Tongue and penis ulcers	Intravenous ganciclovir	Death (pulmonary sepsis)
Bhandari et al[9]	46 y, male	3 y	Median ankle cutaneous growth	Intravenous ganciclovir	Death (superimposed bacterial infection)
Prasad et al3	52 y, male	2.5 mo	Ulceration of axilla, scrotum, and penis	Intravenous ganciclovir	Recovery
Ferguson et al[10]	66 y, female	20 y	Extensive shallow ulceration on back, buttock, and proximal lower limbs	Piperacillin and tazobactam, followed by meropenem and vancomycin and acyclovir (not diagnosed as CMV until autopsy)	Death (respiratory failure and shock)
Cervera-Hernandez et al[11]	44 y, male		Abdominal wall swelling, redness and pain	Intravenous ganciclovir, then oral valganciclovir	Recovery
Moscarelli et al[12]	54 y, female	1 mo	Painful median gluteal ulceration	Intravenous ganciclovir, then oral valganciclovir	Recovery
Trimarchi et al[13]	56 y, male	4 mo	Trunk maculopapular rash	Intravenous ganciclovir	Recovery
Choi et al[14]	31 y, male		Multiple perineal ulcers	Intravenous ganciclovir	Recovery
Choi et al[14]	62 y, female		Multiple penile ulcers	Intravenous ganciclovir	Recovery
Kaisar et al[15]	39 y, female	7 y	Perineal ulceration	Valacyclovir, then oral valganciclovir, then oral ganciclovir	Recovery

Abbreviations: CMV, cytomegalovirus

similar to primary CMV infection in this population.[1] Prophylactic antiviral therapy and preemptive CMV treatment are common practice and have significantly reduced CMV incidence; however, CMV infection remains common in these groups, and a high index of suspicion should be maintained to facilitate early identification.[5] In the current era with prophylaxis, CMV infection affects 8% to 32% of kidney transplant recipients, with peak incidence occurring at the postoperative period from day 30 to day 90.[6] Without prophylaxis, this rate is up to 70%.[6] Its presentation is variable, with involvement of the GI tract and ocular system being the most frequent and with abdominal pain being the most common presenting symptom.[4] Less frequent cases have been reported with involvement of the respiratory, hepatic, central nervous, and cardiac systems.[4] Cutaneous involvement has also been rarely reported, involving perineal and oral mucosal lining.

Risk factors and etiology

Involvement of the upper GI tract is most frequent. Symptoms include abdominal pain, nausea, and vomiting.[4] Lower GI tract involvement and symptoms are less common and can include diarrhea and hematochezia. The strongest identifiable independent risk factor is serological mismatch between donor and recipient, with the CMV D^+/R^- profile being highest risk.[6] In addition, the use of mechanistic target of rapamycin immunosup-pression or high-risk induction (with polyclonal antibodies such as antithymocyte globulin) is an additional risk factor.[6] This patient had CMV IgG positive serology results that indicated a moderate risk of CMV reactivation; however, only standard immunosuppression was used. His risk was elevated by several other factors, including inability to commence CMV prophylaxis in the initial postoperative period, several rounds of pulse corticosteroid treatment, and deconditioning with prolonged hospital stay.

Cases of CMV viremia with concurrent cutaneous tissue invasion have been sparsely reported. Cytomegalovirus colitis and active inflammation may have led to development of perianal fistula as a cutaneous manifestation of the disease. Conversely, CMV viremia may have secondarily infected the perianal/rectal tissue, or the preexisting excoriated perianal skin (from recurrent diarrhea in the context of recent *C. difficile* colitis), leading to cutaneous involvement. It is interesting to note that routine histopathological assessment of perianal fistulas is not common, and thus CMV involvement may be underreported in both immunocompromised and immunocompetent hosts.

Regardless of the sequence of events, histo-pathology revealed CMV inclusion bodies in this patient, which was vital to the diagnosis of pathology. The process of subsequent confirmation with serological testing and treatment with intravenous ganciclovir was a critical factor to successfully manage this condition. Furthermore, there is the possibility of oncogenic transformation of this cutaneous lesion

into anal squamous cell carcinoma secondary to chronic immunosuppression and inflammation.[7]

Diagnosis

The diagnosis of CMV-related pathology relies on a combination of clinical, serological, and histopathological examinations. Despite the broad array of signs and symptoms, initial clues that may manifest serologically include leukopenia, thrombocytopenia, and/or derangement of liver function tests.[1] The presence of idiopathic leukopenia may have contributed to CMV reactivation early in this patient's clinical course.

Several modalities exist to diagnose CMV reactivation and related GI pathology, including tissue or serum CMV polymerase chain reaction (PCR) quantification of CMV DNA, CMV culture, and endoscopy with histology assessment.[1] Histological assessment of tissue with hematoxylin and eosin and immunofluorescence is considered the gold standard to establish CMV diagnosis in tissue biopsies. The use of serological PCR CMV DNA quantification can assist this diagnosis and guide treatment efficacy but relies on the presence of viremia in the patient.

There have been rare, reported cases of cutaneous CMV in renal transplant patients, as described in Table 2. To our knowledge, this is the first reported case of a perianal fistula with histopathology-confirmed CMV diagnosis in a transplant recipient. Some examples include Lee and colleagues, who described a case of cutaneous CMV infection presenting as perianal ulcers 3 weeks after deceased donor renal transplant in a 68-year-old female recipient.[8] Further cutaneous manifestations of CMV in a renal transplant recipient were described by Neumann and colleagues. They reported the case of a 68-year-old man who developed ulcers on the tongue and penis 2 months after transplant. Ulcer biopsy revealed CMV inclusion bodies, and the patient's PCR results were positive for CMV viremia.[2] Bhandari and colleagues have described another fatal complication of cutaneous CMV in a 46-year-old man who had received a renal transplant 3 years previous to presentation. He presented with a cutaneous growth on his medial ankle, which showed CMV inclusion bodies on histopathology. This patient was treated with ganciclovir; however, he developed severe sepsis secondary to a superimposed bacterial infection.[9]

Conclusions

In summary, cutaneous manifestations of CMV have been reported rarely in transplant patients. Fistula formation has been previously described as a complication of CMV infection in immunocompromised patients, however, not in the transplant population. We describe the first case of a perianal fistula with confirmed CMV inclusion bodies in a postoperative renal transplant patient. This highlights that a high index of suspicion for CMV pathology should be considered in this patient population for timely diagnosis and appropriate treatment, regardless of confounding diagnoses such as recent *C. difficile* infection. Furthermore, this report demonstrates the value of CMV prophylaxis in this vulnerable group, which is especially important given the high morbidity and mortality associated with CMV infection in the immuno-compromised population and the specific management involved.

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Case Report

Rescue Hepatectomy and Anhepatic Phase Management After Primary Nonfunction in a Liver Transplant

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Abstract

Primary nonfunction is a rare but lethal complication that occurs in a small number of liver transplants. When primary nonfunction occurs, the only definite treatment is retransplant; however, another liver might not be readily available at that time. Hence, a surgeon should be aware of the various options available at hand for patient care during the time interval between the primary nonfunction and retransplant. Here, we describe the management strategy that was devised to take care of an unstable anhepatic patient in the intensive care unit, care of the patient during anhepatic phase, and successful outcome with a second liver transplant. Our index patient was a recipient of a liver donated after cardiac death. While in the operating room, after reperfusion of the liver, the patient had right heart dysfunction leading to hemodynamic instability and congestion of the liver, which culminated in primary nonfunction. Graft hepatectomy had to be done on postoperative day 1 because of deteriorating condition of the patient, and the patient was maintained in anhepatic phase in the intensive care unit for 27 hours.

Key words: *Donation after brain death, Donation after cardiac death, Retransplant, Right ventricle systolic function*

Introduction

Primary nonfunction (PNF) is a life-threatening complication after liver transplant known to occur in 4% to 8% of cases.[1] In PNF, the nonfunctioning liver can severely compromise recipient hemodynamics and necessitate urgent retransplant. Rescue graft hepatectomy has been described as a means to stabilize recipient hemodynamics. While the anhepatic patient awaits retransplant, meticulous critical care management is essential. A rate of 35% long-term patient survival following rescue hepatectomy with anhepatic time has been reported.[2] Here, we describe our management strategy following a recent experience with PNF and a 27-hour anhepatic phase.

Case Report

Our recipient was a 67-year-old man with hepatitis C cirrhosis and segment VII lesion, radiographically consistent with hepatocellular carcinoma. Preoperative echocardiography was notable for a normal ejection fraction, grade 2 diastolic dysfunction, a hypertrophic septum, and no evidence of pulmonary hypertension.

The original donor was a 35-year-old man, with donation after cardiac death and body mass index (calculated as weight in kilograms divided by height in meters squared) of 36.9, who died from drug overdose with 25 minutes of cardiopulmonary resuscitation time. The terminal value for the aspartate aminotransferase (AST) was 264 IU/dL and alanine aminotransferase ratio (ALT) was 42 IU/dL (peak AST and ALT values were 339 and 123 IU/dL, respectively), total bilirubin was 0.5 mg/dL, and terminal creatinine was 1.2 mg/dL. Total warm ischemia time in the donor was 22 minutes.

Transesophageal echocardiography performed immediately prior to the start of the recipient operation demonstrated a normal left ventricular ejection fraction with mild hypertrophy of the anteroseptal wall. The recipient hepatectomy was uneventful with minimal blood loss (without any blood transfusion) and was performed using

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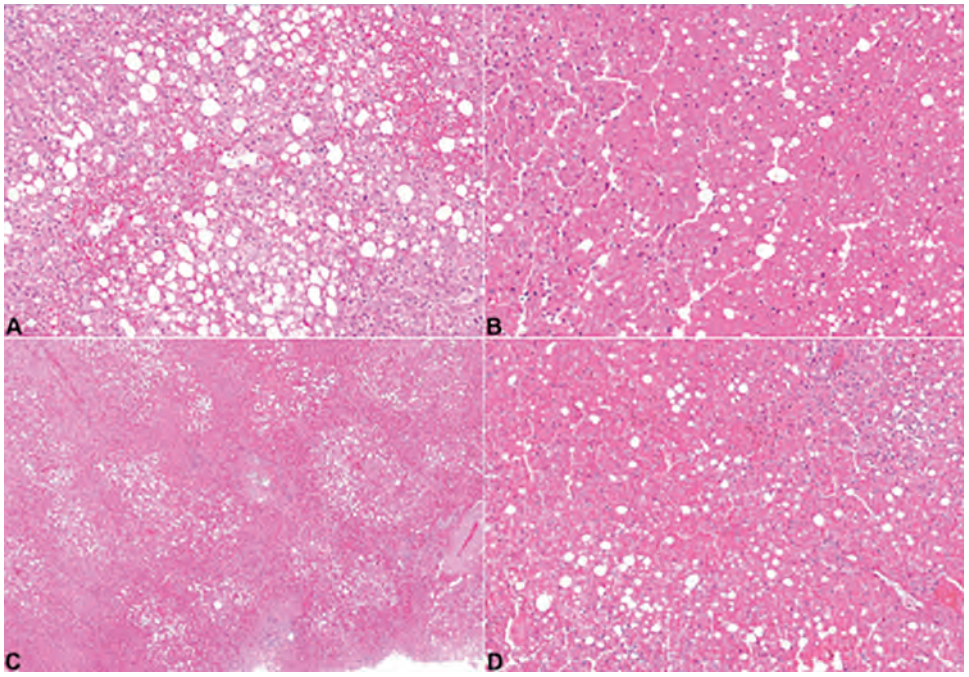
standard techniques. Electrolytes, including magnesium and calcium, were corrected prior to the implantation phase. Intravenous heparin (3000 U) was given just before clamping and division of the recipient portal vein. A side-to-side caval anastomosis (piggyback technique) was used for implantation. The recipient remained hemodynamically stable throughout the implantation phase, which lasted for 25 minutes. Just prior to reperfusion, a 500-mL antegrade blood flush through the inferior vena cava was completed. Rapid volume replacement was given, and the mean arterial blood pressure did not deviate more than 20% from preflush values.

Immediately after reperfusion, there was a significant drop in systolic pressure from 116 to 83 mm Hg. Transesophageal echocardiography revealed right ventricular dilatation and mildly reduced right ventricle systolic function. The central venous pressure increased to 32 mm Hg, and the pulmonary artery pressure rose to 65/39 mm Hg. The electrocardiogram first demonstrated widening of the QRS complex and subsequently ventricular tachycardia. The arrhythmia resolved with calcium and amiodarone; however, the pulmonary artery pressure remained significantly elevated, and an epinephrine infusion was started. Right ventricular dysfunction persisted for 20 minutes and then resolved. After reperfusion of the hepatic artery, hyperfibrinolysis was evident in the surgical field, and rotational thromboelastometry (ROTEM) showed severe coagulopathy (EXTEM clotting time of 180 seconds [normal range, 43-82 s] and maximum clot firmness of 7 mm [normal range, 52-80 mm]). Despite vigorous product replacement and administration of aminocaproic acid, the coagulopathy worsened, lactate rose to a peak of 12.1 mg/dL, and there was persistent hypoglycemia. A liver biopsy was performed (Figure 1B). The abdomen was packed, and the patient was transported to the surgical intensive care unit. Lactate rose to > 20 mg/dL and the AST and ALT levels peaked at 13713 IU/dL and 1650 IU/dL. A bedside laparotomy was required for suspected abdominal compartment syndrome; upon visualization, the liver was congested and ischemic. Continuous veno-venous hemodialysis was started, and the patient was relisted for transplant with a Model for End-Stage Liver Disease score of 27. As the recipient's clinical status deteriorated, the decision was made to proceed with rescue graft hepatectomy (Figure 1D). An end-to-side portocaval shunt was created, and the patient's relisting status upgraded to United Network for Organ Sharing (UNOS) status 1A.

Figure 1. Images of Postreperfusion Liver Biopsies and Explanted Liver



(A) Reperfusion biopsy of liver showing macrosteatosis in a background of hemorrhage and necrosis. **(B)** Reperfusion biopsy of liver showing hemorrhagic necrosis. **(C)** Explanted liver showing macrosteatosis in a background of hemorrhage. **(D)** Explant liver showing hemorrhagic necrosis.

After rescue graft hepatectomy, our patient arrived in the surgical intensive care unit on epinephrine (0.05 μg/kg/min) and vasopressin (0.04 U/min).

The following treatment goals were set for management during anhepatic phase: (1) sodium bicarbonate or 3% hypertonic saline to keep the serum sodium between 152 and 157 mg/dL to reduce the risk of intracranial hypertension/herniation; (2) vasopressors as needed for a mean arterial blood pressure goal of 65 mm Hg; (3) continuous venovenous hemodialysis to manage volume and acidosis; (4) continuous fresh frozen plasma administration for an international normalized ratio goal of < 2; (5) continuous dextrose infusion to maintain serum glucose between 110 and 180 mg/dL; (6) initial labs every 2 hours; and (7) therapeutic plasma exchange (the molecular adsorbent recirculating system [MARS] is not currently available at our center).

With these goals met, our patient's hemodynamics markedly improved. Broad spectrum antimicrobial coverage was provided with ampicillin/sulbactam and fluconazole. Just before retransplant, and after a 27-hour anhepatic phase, the patient was on vasopressin (0.04 μg/kg/min) with mean arterial blood pressure of 70 to 80 mm Hg.

The second donor was a 42-year-old man, with donation after brain death and BMI of 32.7, who died from drug overdose. The terminal AST/ALT values were 141/233 IU/dL (peak AST/ALT, 520/457 IU/dL), total bilirubin was 0.8 mg/dL, and terminal creatinine was 2.2 mg/dL. Total cold ischemic time was 4 hours.

The second transplant was completed expeditiously with a total intraoperative warm time of 20 minutes. Soon after reperfusion, serum lactate dropped from > 20 to 10.1 mg/dL and eventually to 6.6 mg/dL at the completion of the case. Serum glucose rose, coagulopathy resolved, and the surgical field dried. Significant tissue and bowel edema remained, and therefore a staged abdominal closure was completed. The patient was extubated in the surgical intensive care unit on postoperative day 4 and transferred to the transplant floor with serum ALT/AST of 33/20 mg/dL, a total bilirubin of 0.6 mg/dL, serum lactate < 1 mg/dL, international normalized ratio of 1.4, and a fibrinogen of 300 mg/dL. Substantial acute kidney injury occurred and was managed with hemodialysis. The patient was transferred to a skilled nursing facility on postoperative day 17 following the second operation. No neurologic deficits were observed in the postoperative course.

Discussion

Primary nonfunction is a common cause for early retransplant,[3] and often its cause cannot be elucidated. Kulik and colleagues[4] have shown that donor hepatic steatosis is an important risk factor for PNF. Steatosis makes livers more vulnerable to ischemia-reperfusion injury.[5] In our case, liver biopsy showed 40% macrosteatosis (Figure 1, A and C), and it is likely that donor hepatic steatosis contributed to PNF.

Cardiac dysfunction also contributes to PNF. End-stage liver disease is characterized by a state of high cardiac output and low systemic vascular resistance. During liver transplant, sudden changes in preload and afterload and rapid release of cytokines and other vasoactive mediators into the blood[6,7] create significant cardiac stress that frequently unmasks occult cardiac dysfunction.[8] Our patient experienced acute and transient right heart dysfunction despite normal preoperative echocardiography and stress testing.

Primary nonfunction is rarely subtle and is diagnosed with progressive lactic acidosis, absence of hepatic glycogenolysis, hypotension, absence of bile production, and prolonged coma. Once PNF is diagnosed, retransplant is the only option for patient survival.

In our patient, recognition of toxic liver syndrome drove our decision to proceed with rescue hepatectomy. The technique of graft hepatectomy with temporary portocaval shunting was first described by Ringe and associates in 1988.[9]

Goal-oriented critical care management is essential to patient survival in anhepatic phase. Anhepatic patients rapidly develop hypocalcemia, oliguria, renal failure, hypoglycemia, and hypothermia.[10,11] Severe hypocalcemia develops because of loss of citrate metabolism in the liver, and hence meticulous replacement is crucial. Continuous dialysis is almost always necessary for management of both acidosis and volume. Fresh frozen plasma and fibrinogen are needed to combat coagulopathy, and continuous glucose infusion is required. Our patient underwent therapeutic plasma exchange with 1.5 times the total plasma volume. Plasmapheresis removes free and protein-bound toxins and provides fresh clotting

factors and albumin, thus improving coagulopathy in anhepatic patients.[12]

In anhepatic patients, broad-spectrum antibacterial and antifungal coverage is indicated and close neurologic monitoring is needed to help ensure that retransplant is not futile. Survival after retransplant is inferior to that after primary transplant, with 64.6% patient survival at 1 year and 47.8% at 5 years.[13] Uemura and colleagues[14] reported that survival after retransplant for PNF (1 year, 66%; 5 years, 60%; 10 years, 48%) is reduced but not excessive, similar to that after retransplant for other reasons (1 year, 67%; 5 years, 51%; 10 years, 37%) ($P = .635$).

Conclusions

Transplant hepatectomy can be a life-saving procedure in patients with PNF. Meticulous critical care management with attention to intracranial pressure, glucose, calcium, acidosis, and coagulopathy are essential to facilitate successful retransplant outcomes.

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Case Report

First Successful Organ Procurement From a Pediatric Patient With a Nonpulsatile Ventricular Assist Device

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Abstract

Left ventricular assist devices have become an important therapeutic option as a mechanical circulatory support system in the treatment of end-stage heart failure. Organ transplants from brain dead donors on mechanical circulatory support are rare. In the literature, many successful solid-organ transplants have been reported using these donors. However, to our knowledge, this is the first report of successful solid-organ transplant from a child donor with a nonpulsatile ventricular assist device.

Key words: *Brain dead donor, End-stage heart failure, Mechanical circulatory support*

Introduction

The number of patients on organ transplant wait lists has increased around the world.[1] In Turkey, there are almost 1000 children waiting for organ transplant. Organ shortages remain the major limitations in pediatric transplant procedures, and transplant centers are now evaluating high-risk donors. With organ shortages and increased mortality of patients on wait lists, every potential organ donor should be carefully evaluated. We report the first case of visceral organ transplant from a pediatric donor whose cardiac function was supported by a nonpulsatile left ventricular assist device (LVAD).

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Case Report

A 9-year-old girl was admitted to the emergency department with right hemiparesis. The patient had implantation of the Hearth Mate II (Thoratec Corp) LVAD 6 months earlier as a bridge to heart transplant because of severe dilated cardiomyopathy. The patient had also received anticoagulation therapy with warfarin. Brain computed tomography (CT) angiogram demonstrated a thrombus in the terminal of the left internal carotid artery and ipsilateral middle cerebral artery. A noncontrast brain CT scan showed acute ischemia. The patient was transferred to the pediatric intensive care unit, and her anticoagulation therapy was switched to low-molecular-weight heparin. The interventional radiology department determined that the patient was not suitable for the thrombectomy procedure. Laboratory tests were in normal ranges, activated partial thromboplastin time was 38 seconds, and international normalized ratio was 2.8.

On day 2 of hospitalization, the patient suddenly became unresponsive, and an examination revealed anisocoria. After intubation, an emergency brain CT was performed that demonstrated enlargement of ischemic areas and a large subarachnoid hemorrhage. Despite decompressive craniectomy and medical treatment, on day 6 of hospital admission, brain death was confirmed; her family consented to visceral organ and eye donation.

The liver recipient was a 7-year-old girl with autoimmune hepatitis. After transplant, graft function quickly improved and the patient was discharged home 1 week after transplant without complications. The kidney recipients were a 15-year-old boy and a 17-year-old girl who were diagnosed with vesicoureteral reflux and chronic glomerulonephritis, respectively. Both kidney recipients were discharged home 3 weeks after transplant with no

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health concerns. The intestinal recipient, a 1-year-old girl with microvillus inclusion disease, died on day 3 after transplant.

Discussion

Early after development of cardiopulmonary support systems, those donors on extracorporeal membrane oxygenation and on cardiac assisted devices have been considered to be high-risk solid-organ donors. Concerns with regard to these donors include noncardiac organ dysfunction because of nonpulsatile perfusion.

In the literature, many successful solid-organ transplant procedures have been reported using these donors. In 2004, Rayhill and associates reported the first successful organ transplant from an adult donor who was supported by an LVAD.[2] In 2009, Misra and associates reported the first successful transplant of a left lateral segment graft from a pediatric donor who was supported by a Berlin Heart pulsatile ventricular assist device.[3] To our knowledge, this is the first report of a successful solid-organ transplant from a child donor who had nonpulsatile LVAD support.

Left ventricular assist devices have become an important therapeutic option in the treatment of end-stage heart failure as a bridge to transplant and a bridge-to-recovery. Because of organ shortages, there are often long waits for deceased donors, especially in developing countries like Turkey. Longer wait times for heart transplant have resulted in increases in the number of patients with long-term LVAD complications.[4]

Radovancevic and associates suggested that long-term nonpulsatile support may not be inferior to pulsatile support and can be used efficiently and safely to maintain adequate renal function in patients who are receiving long-term LVAD support.[5] Patel and associates reported the first case of a successful solid-organ transplant from a donor who had continuous-flow LVAD treatment for 22 months.[6] Results from a successful case report reported that nonpulsatile cardiac assist devices are not a contraindication to visceral organ donation.[7]

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Intraoperative Type I Acute Myocardial Infarction During Liver Transplant Requiring Intra-Aortic Balloon Pump: A Case Report

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Abstract

We describe a complex case of liver transplant in a 70-year-old male patient with no known history of coronary artery disease, normal preoperative left ventricular function, and negative preoperative cardiac workup who developed progressive intraoperative left ventricular myocardial dysfunction secondary to class I acute myocardial infarction, ultimately requiring intraoperative intra-aortic balloon pump insertion to optimize myocardial perfusion. Management of myocardial ischemia was complicated by bleeding in the setting of coagulopathy necessitating correction. Once hemostasis was achieved, the patient immediately underwent coronary angiography and bare metal stent placement in the mid-left anterior descending coronary artery for an acute plaque rupture.

Key words: *Hypertension, Myocardial infarction, Transesophageal echocardiography*

Introduction

Liver transplant for patients with coronary artery disease (CAD) is high risk, with reported 1-year mortality rate of approximately 40%.[1] Despite best efforts to risk-stratify liver transplant candidates for myocardial ischemia with stress provocation studies, sometimes preexisting CAD will not be apparent until exposure to intraoperative physiologic stress, presenting as acute coronary ischemia. In such cases, managing physicians may encounter multiple clinical dilemmas. The Institutional Review Board has waived the requirement for written consent from the patient, and we have received HIPPA authorization for this case report.

Case Report

Preoperative evaluation

A 70-year-old man with hypertension, type 2 diabetes, and alcohol-induced end-stage liver disease complicated by hepatic encephalopathy, hepatorenal syndrome, and recurrent ascites with spontaneous bacterial peritonitis presented for deceased donor orthotopic liver transplant (OLT). His Model for End-Stage Liver Disease-Na score was 33.

Pretransplant cardiac work-up included a negative nuclear stress test with coronary calcium score of 145, indicating a high negative predictive value for significant CAD.[2] The patient's transthoracic echocardiogram demonstrated low-normal left ventricular (LV) ejection fraction (LVEF) of 55% and no regional wall motion abnormalities. Hence, coronary angiography was not indicated.

Intraoperative course

After induction of general anesthesia, a transesophageal echocardiography (TEE) probe was placed, demonstrating moderately diminished LVEF with greater hypokinesis of the anteroseptal and apical segments. No concomitant electrocardiogram (ECG) changes or major hemodynamic changes were present. The suspicion of myocardial ischemia was low; hence, a decision was made to proceed with OLT. As the case progressed, the patient required incremental doses of vasopressors. His LVEF further declined to 10% to 15% prior to reperfusion with

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some preservation of function in the myocardial base. At this point, the patient required norepinephrine 2 μg/kg/min, epinephrine 1 μg/kg/min, and vasopressin 0.04 U/min. The suspicion for acute myocardial ischemia increased with time. Continuation of the surgery was necessary, as the hepatic artery and bile duct had been ligated. Furthermore, the cold ischemic time of the graft was approaching 8 hours, increasing the risk of severe myocardial instability during reperfusion.

During graft reperfusion, the portal venous clamp was gradually released, reducing the hemodynamic impact. Despite this, the patient required multiple boluses of epinephrine 1 mg and calcium chloride 1 g to maintain mean arterial pressure above 55 mm Hg. The ECG demonstrated a new intraventricular conduction delay, and amiodarone was initiated. Transesophageal echocardiography demonstrated severe LV hypokinesis. To improve myocardial perfusion, an intra-aortic balloon pump (IABP) was placed by the cardiac surgeons. Subsequently, epinephrine and norepinephrine were rapidly weaned down with LVEF improvement.

Fascial closure was delayed, minimizing time to possible percutaneous coronary intervention. Bleeding secondary to fibrinolysis was evident on thromboelastogram, which was corrected through transfusion of blood products and tranexamic acid. The patient was then transported to the coronary catheterization lab as soon as possible.

Left heart catheterization demonstrated an eccentric ulcerative 90% stenosis in the mid-left anterior descending coronary artery (Figure 1). A bare metal stent was deployed after cangrelor was initiated (Figure 2). He also received loading with clopidogrel 600 mg.

Figure 1. Left Heart Catheterization With Arrow Showing Mid-Left Anterior Descending Artery 90% Stenosis

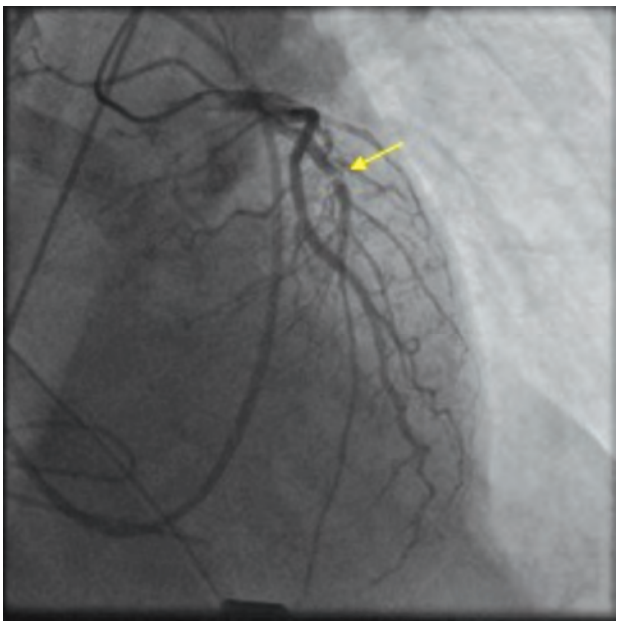
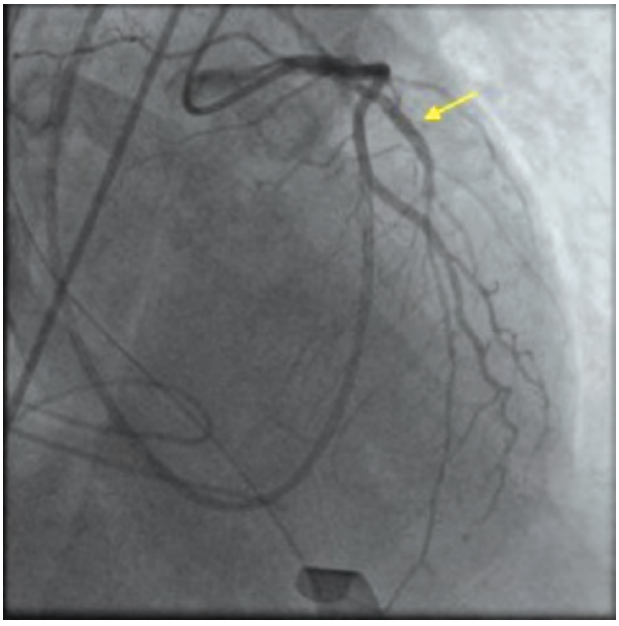


Figure 2. Left Heart Catheterization With Arrow Showing Stent Deployed in Mid-Left Anterior Descending Artery



Postoperative course

In the surgical intensive care unit, cangrelor infusion was continued for 6 hours. P2Y12 assays showed persistent elevation (Table 1), suggesting insufficient antiplatelet activity, prompting a transition to

Table 1. Timeline of P2Y12 Assay Results on Postoperative Day 1

POD0					POD1				
6:45 PM	7:39 PM	12:00 AM	1:07 AM	3:15 AM	10:23 AM	12:37 PM	3:19 PM	5:48 PM	9:35 PM
Cangrelor initiated, BMS deployed	Clopidogrel 600 mg loading dose	Cangrelor infusion stopped	P2Y12: 385	Clopidogrel 300 mg	P2Y12: 356	Clopidogrel 300 mg	P2Y12: 333	Ticagrelor 180 mg	P2Y12: 214

Abbreviations: BMS, bare metal sten; POD, postoperative day

A P2Y12 result of ≥ 235 P2Y12 reaction units after loading dose of clopidogrel was associated with higher risk of stent thrombosis or cardiovascular death.[11]

ticagrelor. Therapy with IABP allowed stable myocardial perfusion pressures and rapid reduction in cardioactive support within the first day. On postoperative day (POD) 1, his abdomen was closed surgically and he was weaned off IABP. Transthoracic echocardiogram showed anteroseptal wall motional abnormality, near akinesia, consistent with the territory of infarct, with LVEF of 35%. On POD3, he was weaned off vasopressors and extubated. He was transferred to the floor on POD13 and discharged to an inpatient rehabilitation center 4 weeks postoperatively.

Discussion

Management of non-ST elevation acute myocardial infarction presents particular challenges during OLT involving a multidisciplinary approach with tight coordination of all activities, hemodynamic support with considerations for mechanical support, and management of the hemostatic system.

Role of perioperative transesophageal echocardiography

When ECG changes are not present, intraoperative TEE becomes a key diagnostic tool to evaluate for myocardial ischemia.[3] A TEE can elucidate new-onset regional and global LV systolic dysfunction, as well as diastolic dysfunction, as markers of ischemia. Furthermore, TEE is indicated in management of hemodynamic instability to guide selection of interventions.

Intraoperative management of myocardial ischemia

Maintenance of the optimal myocardial supply-to-demand ratio is the cornerstone of intraoperative management. This involves use of vasoactive, inotropic, and antiarrhythmic agents and cardioversion or defibrillation as necessary. On occasion, use of mechanical hemodynamic support is necessary. In cardiogenic shock, IABP is the first line of treatment for hemodynamic support[4] and, on rare occasions, has been used in noncardiac surgical procedures.[5] This procedure improves myocardial perfusion through augmentation of the systemic diastolic pressure, thus optimizing myocardial supply-to-demand ratio until coronary revascularization becomes possible. In our patient, the use of IABP reduced requirements of vasopressor and inotropic medications, improved LV systolic function, and provided sufficient time to achieve surgical hemostasis until definitive intervention could be performed in the cardiac catheterization lab. However, it is prudent to be aware of the possible complications of IABP, which are mainly related to malposition and mechanical destruction of platelets and red blood cells. Of note, there have been case reports of liver injury secondary to malposition of IABP.[6]

Role of imaging in diagnosis of myocardial ischemia and coronary intervention

Although preoperative testing for myocardial ischemia is widely implemented in evaluations of liver transplant candidates, perioperative myocardial ischemia still occurs.[7] Current preoperative work up, such as nuclear stress testing, has been shown to lack sensitivity and has not been shown to predict outcomes after OLT.[8] Coronary angiography is the gold standard for diagnosis of CAD and acute coronary syndrome, with subsequent interventions including angioplasty and stenting dependent on the coronary anatomy.[9] However, because of its invasive nature, risk of complications, and cost, it is restricted to high-risk patients. Per our institutional guidelines, coronary angiography is recommended for patients who have a positive provoked ischemia on noninvasive ischemic testing or nondiagnostic stress testing if clinically indicated and those without stress testing and with a calcium score of more than 400.

Management of coagulopathy

Management of coagulopathy during OLT is complex in the setting of ongoing myocardial ischemia due to opposing concerns: correction of coagulopathy may cause plaque-associated thrombus propagation, but not correcting coagulopathy leads to the cascade of bleeding, hypotension, reduced preload, and myocardial perfusion pressure, as well as exacerbation of ischemia. Under circumstances of reduced LV systolic function, massive transfusion creates an additional risk of pulmonary edema and poor gas exchange. The use of antifibrinolytics in an attempt to achieve hemostasis had to be made cautiously in the setting of myocardial ischemia, with the understanding that it could potentially worsen myocardial blood supply via thrombosis propagation. Platelet transfusions in the setting of antiplatelet medications also appear counterintuitive but necessary to correct coagulopathy, A modest goal of platelet count above 50×10^3/mL was chosen to

balance the benefit of hemostasis with the risk of in-stent thrombosis. The decision to correct coagulopathy lies on balancing these opposing priorities and should be goal-directed using clinical findings and point-of-care laboratory tests, particularly viscoelastic tests such as the use of thromboelastogram.

Antiplatelet therapy during the perioperative period of orthotopic liver transplant

Care of the liver transplant recipient after percutaneous coronary intervention is challenging, as the prodrug clopidogrel requires hepatic activation and the pharmacokinetics are thus unpredictable in patients with cirhossis[10] and likely in newly transplanted patients. In this setting, point-of-care P2Y12 assays are useful in monitoring the adequacy of antiplatelet therapies. Ticagrelor may be preferred as it does not require metabolic activation by the liver. In our posttransplant patient with expected thrombocytopenia, the risk of bleeding from thrombocytopenia and antiplatelet therapy required balance against the risk of in-stent thrombosis from fresh stent placement, with consideration of judicious transfusion if needed.

Importance of a coordinated team effort

The successful outcome of this medically challenging patient was largely dependent on the coordinated effort of a multidisciplinary team, which included the transplant surgeons, anesthesiologists, cardiac surgeons, interventional cardiologists, critical care physicians, and transplant hepatologists. Timely management was crucial to patient stabilization, prompt diagnosis, and targeted intervention necessary to treat the unexpected and severe intraoperative myocardial dysfunction. Shared decision-making among the different disciplines was of utmost importance to ensure the smooth and successful delivery of care for this patient.

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Case Report

COVID-19 Pneumonia and Intensive Care Treatment of a Lung Transplant Recipient

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Abstract

In the COVID-19 pandemic presently affecting the whole world, solid-organ transplant recipients under immunosuppressive therapy are at higher risk than the general population. COVID-19 infection primarily affects the lungs, and so the risk is further increased in lung transplant recipients. The course of COVID-19 in lung transplant recipients is unclear. Here, we present the intensive care follow-up and treatment process of a bilateral lung transplant recipient who developed acute respiratory failure due to COVID-19, for whom the final outcome was favorable. Antiviral treatment was initiated for the 53-year-old male patient with COVID-19 pneumonia, and in the following hyperinflammatory phase, high-dose pulse steroid therapy was administered. The patient was followed up with high-flow nasal oxygen, and then he was supported by intermittent noninvasive mechanical ventilation as hypoxia became more severe. With these noninvasive ventilation strategies and good intensive care procedures, the patient was successfully discharged.

Key words: *Acute respiratory failure, Coronavirus disease 2019, Pneumonia, Severe acute respiratory syndrome coronavirus 2*

Introduction

COVID-19 first emerged in Wuhan, China, in December 2019 and spread rapidly to other countries in a worldwide pandemic.[1] Patients who undergo solid-organ transplant are usually treated with immunosuppressive therapy and therefore face a high risk of infection. The lungs are the primary affected organ in COVID-19 infection, and so the risk is greater in patients after lung transplant than for other patients. As well as COVID-19 infection, coinfections due to the immunosuppressive state can cause an increase in morbidity and mortality.[2] There are inadequate data on the course of COVID-19 in lung transplant recipients. Here, we present the intensive care unit (ICU) management and treatment modalities of the COVID-19 infection that occurred in a lung transplant recipient.

Case Report

A 53-year-old male patient, diagnosed with known hypertension and diabetes mellitus, had received a bilateral lung transplant in response to chronic obstructive pulmonary disease 2 years previously. He was admitted to the hospital with complaints of fever and newly developed dyspnea. Nasopharyngeal swabs were obtained from the patient and tested with reverse transcriptase polymerase chain reaction (PCR), and the results were positive for SARS-CoV-2. The patient was hospitalized on the same day and transferred to the ICU to treat existing dyspnea, tachypnea, and low oxygen saturation despite oxygen therapy. Thoracic computed tomography was consistent with widespread bilateral multisegmented and multilobar involvement and was typical for COVID-19 pneumonia (Figure 1).

At the time of ICU admission, his arterial blood gas results were 40 mm Hg Pao_2, pH 7.36, and 42 mm Hg $Paco_2$. His lymphocyte count was 0.21 $\times 10^9$ cells/L (10.2%) with levels of 0.1 g/L C-reactive protein, 485 U/L lactate dehydrogenase, 1.4 mg/L D-dimer, 0.8 mg/dL creatine, 28 U/L alanine aminotransferase, 21 U/L aspartate aminotransferase, 0.47 μg/L procalcitonin, 146 μg/L ferritin, and 19 pg/mL interleukin 6. High-flow nasal oxygen (HFNO) treatment was initiated, and oxygen

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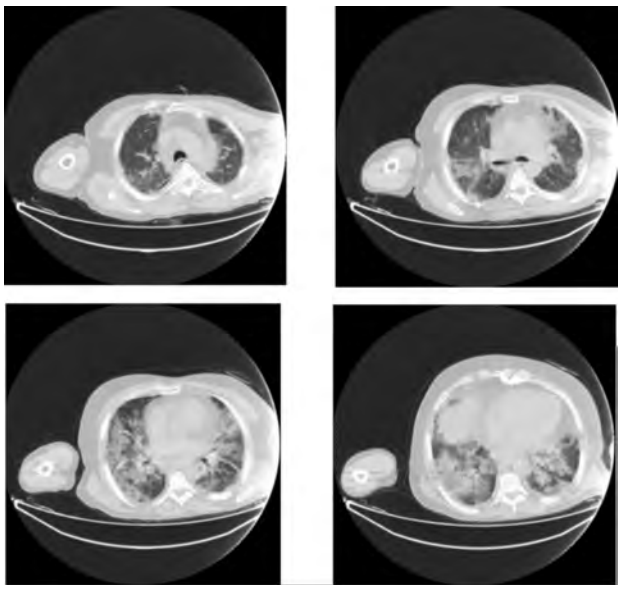
saturation was between 78 and 80 mm Hg. The fraction of inspired oxygen (Fio_2) was set to 80% and the flow rate to 50 L/min. Favipiravir (2 × 1600 mg/day loading dose, 2 × 600 mg maintenance), methylprednisolone (1 mg/kg), acetylsalicylic acid (1 × 100 mg), enoxaparin (1 mg/kg/12 h), and vitamin C (4 × 1.5 g) were added to the treatment.

Figure 1. Computed Tomography Images Obtained During Admission to Intensive Care Unit Show Multisegmented, Multilobar, and Bilateral Diffuse Involvement

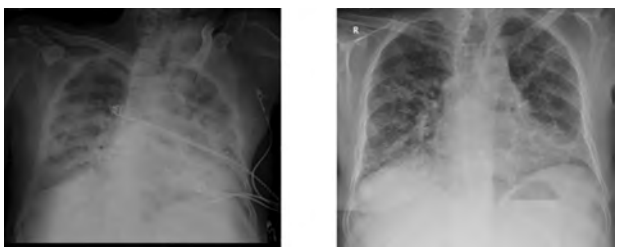


Because of the patient's immunosuppressive state, all cultures were sent during ICU hospitalization to be screened for opportunistic infections with cytomegalovirus, *Aspergillus*, and *Pneumocystis jirovecii*. Piperacillin-tazobactam was initiated empirically with the recommendation of the infectious diseases consultant. The patient received tacrolimus, mycophenolate mofetil, and 5 mg prednisolone to maintain immunosuppressive therapy after lung transplant, and he had a tacrolimus drug level of 3.41 μg/L (reference range, 5-20 μg/L). Drug levels were checked at regular intervals, and doses were adjusted. He had received trimethoprim/sulfamethoxazole 2 days a week for *P. jirovecii* prophylaxis. The patient developed fever symptoms and increased procalcitonin levels despite the follow-up treatment, so the piperacillin-tazobactam treatment was stopped on day 4, and meropenem, teicoplanin, and inhaled colistin were initiated. A prophylactic dose of voriconazole was administered for *Aspergillus*. Favipiravir treatment was completed in 10 days.

On day 10 after ICU admission, chest radiography showed increased infiltration, the patient developed hypoxemia, and his respiratory symptoms worsened. The Fio_2 was increased to 100% and flow rate to 60 L/min in the HFNO treatment. Intermittent noninvasive mechanical ventilation was initiated. Because of COVID pneumonia progression, which was in the hyperinflammatory phase, pulse steroid therapy was planned for the patient, whose acute phase reactants and D-dimer increased. Procalcitonin was within normal limits (0.07 μg/L). Methylprednisolone was administered as a pulse (10 mg/kg) for 3 days. Methylprednisolone, 1 mg/kg, was given as maintenance in the follow-up period. To treat the elevated D-dimer (15 mg/L), enoxaparin was continued at 1 mg/kg dose twice a day at 12-hour intervals, and antithromboembolic compression stockings were worn for mechanical prophylaxis. During follow-up for this patient, no thromboembolic complications occurred and D-dimer level regressed and decreased below 1 mg/L.

During follow-up, the HFNO rate and Fio_2 decreased gradually, and the patient's symptoms regressed and saturations increased. On day 14 of his ICU admission, the HFNO treatment was switched to a reservoir mask (10 L/min O_2). The patient was transferred to the inpatient clinic with greater than 94 mm Hg oxygen saturation as measured by pulse oximetry while given 4 L/min HFNO on day 18 of hospitalization. The COVID-19 immunoglobulin G and M antibody level was 9.67 (normal range, 0-0.99). No additional complaint was observed during the inpatient clinical follow-up, and the patient was discharged with complete recovery (Figure 2).

Figure 2. Chest Radiographs



Chest radiographs from **(Left)** the day of intensive care unit admission and **(Right)** the day of discharge.

Discussion

Solid-organ transplant recipients are at higher risk for infections because of the immunosuppressive

treatments they receive. Infections that primarily affect the lung, such as COVID-19, require rigorous management of the disease in lung transplant recipients. In our patient, COVID-19-positive tests occurred while under tacrolimus treatment. The tacrolimus level was carefully monitored during his hospitalization, and the therapeutic range of 5 to 20 μg/L was maintained. We believe that 2 details contributed to the healing process: (1) initiation of antiviral therapy in the early period as soon as polymerase chain reaction tests showed positive results for COVID-19 and (2) administration of pulse steroid therapy during the hyperinflammatory phase. Pulse steroid therapy via anti-inflammatory effects prevents fibrosis in COVID-19 pneumonia.[3] In a study conducted on COVID-19 patients, it was reported that the use of 1 to 2 mg/kg/day methylprednisolone for 5 to 7 days had positive effects on the course of COVID-19, such as a decrease in oxygen need and faster improvement in radiological findings.[4]

In the case series from Aversa and colleagues,[5] in which lung transplant recipients developed COVID-19, a total of 32 patients were reported. Eleven patients (34%) died within 14 days, and high levels of white blood cells, C-reactive protein, and D-dimer, as well as low lymphocyte count, were associated with greater severity of the disease and higher mortality. High-dose steroid was used in 44% of the patients, and tocilizumab was used in 19%. Aversa and colleagues reported that high-dose steroid was used only for 3 or 5 days in patients with elevated C-reactive protein, ferritin, D-dimer, or lactate dehydrogenase with worsening respiratory symptoms, and the dose was increased up to 15 mg/kg in patients who required intubation.[5] In our patient, 10 mg/kg methylprednisolone was administered for 3 days during the hyperinflammatory phase. Anticytokine therapies such as tocilizumab and anakinra were not needed in our patient because there was a favorable clinical response to steroid treatment.

In a multicenter study by Messika and colleagues, there were 35 lung transplant recipients who developed COVID-19, and 31 patients (88.6%) were hospitalized.[6] Of these 31 hospitalized patients, 13 (41.9%) required ICU admission and 4 developed acute thromboembolic complications during follow-up.[6] Although severe elevations in D-dimer levels developed in our patient, the use of antithromboembolic compression stockings and administration of enoxaparin prevented possible thromboembolic complications. In their multicenter study, Messika and colleagues reported that 7 of 13 patients (53.9%) followed up in the ICU received invasive mechanical ventilation.[6] Our patient was followed up with HFNO after ICU admission. On follow-up day 10, our patient's clinical symptoms had worsened, and desaturation occurred. Both the amount and rate of HFNO were increased for our patient, who was near the threshold for invasive mechanical ventilation, and he was successfully supported with intermittent noninvasive mechanical ventilation. The successful management of the acute symptoms with HFNO and noninvasive mechanical ventilation prevented the need for invasive mechanical ventilation.

Conclusions

Lung transplant patients are at great risk during the COVID-19 pandemic. High morbidity and mortality rates are possible if COVID-19 infection develops in these patients. The prognosis for our patient was good with early interventions. We believe that hospitalization of the symptomatic patient on the same day of the diagnosis of COVID-19, prompt ICU admission when needed, and the rigorous ICU management via noninvasive ventilation strategies contributed to the successful outcome.

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Endovesical Bacillus Calmette-Guérin for Nonmuscle Invasive Bladder Cancer in Kidney Transplant Recipients: Is It Safe and Efficacious?

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Dear Editor:

Guidelines from the European Association of Urology (EAU) recommend adjuvant intravesical bacillus Calmette-Guérin (BCG) after transurethral resection of bladder in immunocompetent patient with intermediate- and high-risk nonmuscle invasive bladder cancer (NMIBC).[1]

Bacillus Calmette-Guérin is a live attenuated form of *Mycobacterium bovis*; the precise mechanisms by which this form of immunotherapy works are complex.[2-4] It has been posited that BCG adheres to the urothelium and, once internalized, induces antigen-presenting cell-mediated induction of innate and adaptive immune responses, leading to decreased recurrence and progression rates of NMIBC.[2,4] However, intravesical BCG may have local and systemic toxicity. Local BCG toxicity, such as persistent irritative symptoms, may render succeeding treatments intolerable to the patient, and systemic BCG toxicity exposes patients to a life-threatening situation and prolonged antituberculosis drug administration.

With regard to NMIBC in kidney transplant (KT) recipients, this cancer is associated with a higher risk of recurrence compared with that shown in the nontransplant population affected by similar disease, probably because of underutilization of adjuvant endovesical treatment.[3,5] Furthermore, in cases of progression to muscle invasive bladder cancer (MIBC), radical cystectomy with pelvic lymphadenectomy is the gold standard treatment.[6-8] In KT recipients, radical cystectomy with pelvic lymphadenectomy could be challenging, showing a high risk of vascular or graft injury and graft loss.[8,9] As such, a safe and effective adjuvant treatment to prevent recurrence and progression of NMIBC in these patients is an important need.[10]

Two main questions arise regarding the utilization of intravesical BCG in KT patients with high-risk NMIBC. First, does BCG have the same efficiency as that shown in the regular population, taking into consideration that immunosuppressive treatment after KT promotes an anti-inflammatory response? Second, is the morbidity of BCG instillations greater due to the immunocompromised status of KT recipients?

In a recent systematic review, Jue and colleagues[6] reported that KT recipients treated with adjuvant intravesical BCG in NMIBC had significantly lower recurrence and progression to MIBC compared with patients who were not treated with BCG. Similarly, in 2017, Rodriguez Faba and colleagues[7] reported the largest series of adjuvant endovesical treatment in KT recipients (88 patients) with a median follow-up of 126 months. Six patients had adjuvant intravesical BCG. The recurrence rate was 35% with a mean delay of 10 months. The investigators reported that 5.6% of patients progressed to MIBC and 16 recipients underwent radical cystectomy. As confirmed also by Roumeguere and colleagues, in a group of 8 KT recipients with NMIBC, local induction of immune response by BCG seemed to be effective even in immunocompromised patients.[11]

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The safety of intravesical BCG has been evaluated in nontransplant, immunocompromised patients with HIV and hematological malignancy.[10] In HIV patients, use of adjuvant intravesical BCG was responsible for severe BCG toxicity, involving the need for prophylactic antitubercular therapy during the period of BCG instillation.[10,12] Herr and Dalgbani[13] published the largest series, consisting of 45 immunosuppressed patients, who underwent BCG instillations for bladder cancer; the investigators confirmed the tolerability of the adjuvant treatment. Similarly, in KT patients, several reports have supported the safety of BCG instillation, with good tolerance and minimal side effects.[7,14-17] However, rare cases of subacute interstitial pneumonitis[18] and fatal sepsis[19] have been reported. In this context, prophylactic administration of antituberculous treatment to minimize BCG-induced toxicity[11,20,21] has been discussed. Al Khalifa and colleagues[22] showed a reduction of local side effects when patients were given a 3-day course of isoniazid for each BCG instillation. However, other authors reported an increased rate of side effects, such as fever and malaise, in patients who received isoniazid.[23] Notably, tuberculostatic medication can cause changes in the metabolism of immunosuppressive agents, requiring dose adjustments to avoid rejection of the graft.[21] To date, no specific recommendations on peri-instillational prophylaxis have been made.

According to the literature, the efficacy and safety of BCG in KT recipients with NMIBC have only been evaluated in a limited number of case series. Although the available data have shown promising results, to date, sufficient levels of evidence on its effectiveness in KT recipients are not available, in contrast to available evidence in the general population.

With the considerations outlined here, a multicenter study may address the oncological benefits and harms of endovesical BCG treatments in KT recipients affected by NMIBC.

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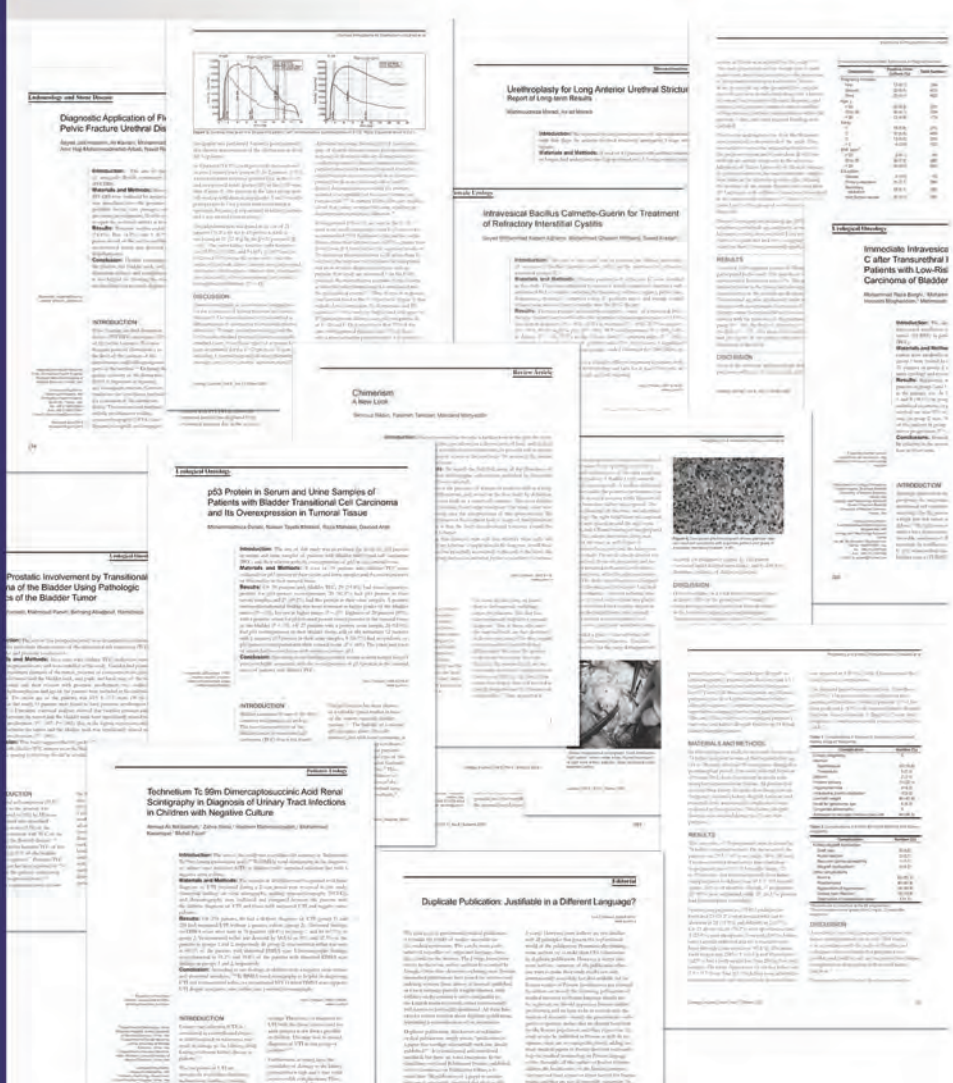

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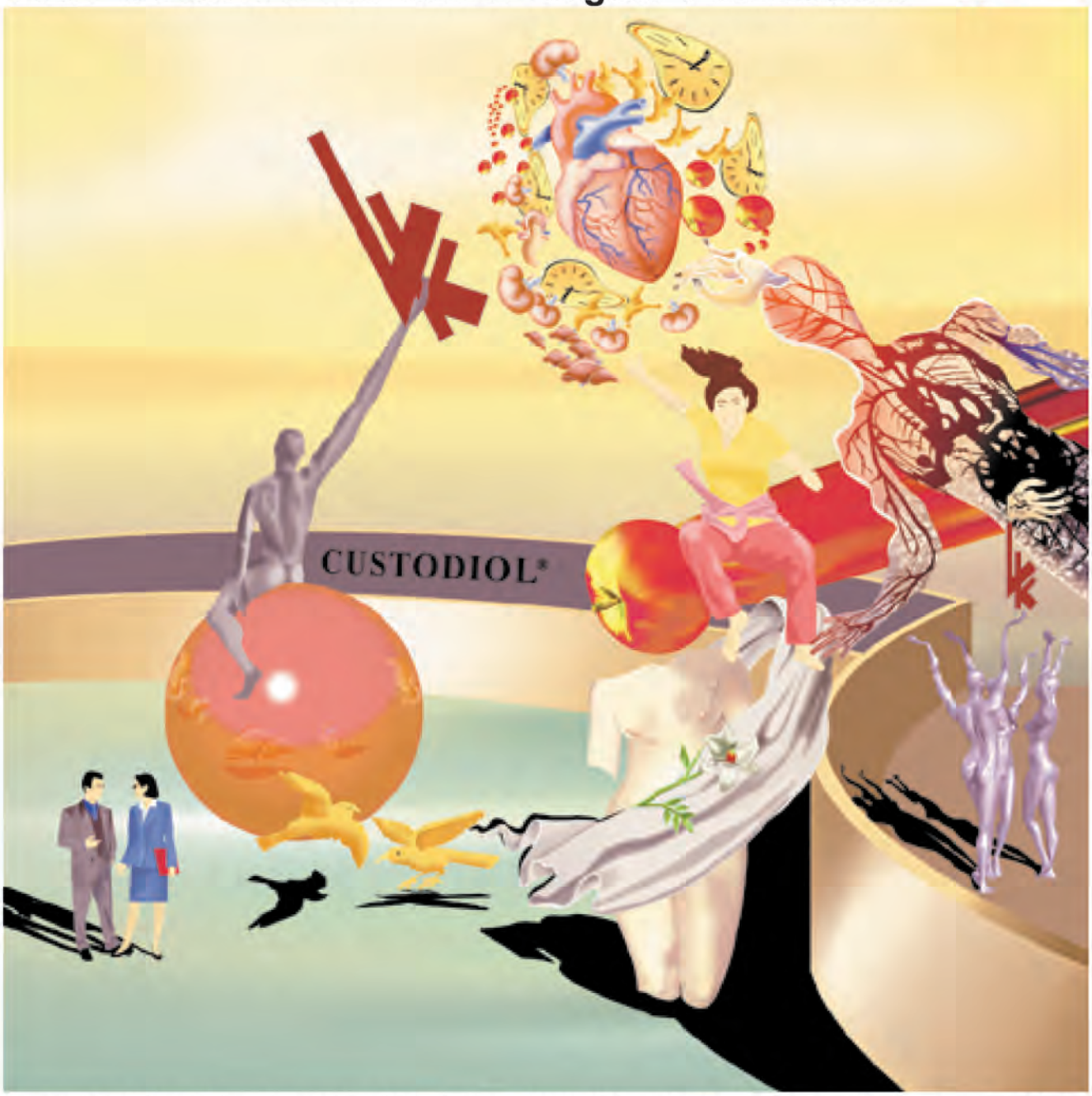

Composition: 1.000 ml of the solution contain: 0,8766 g sodium chloride (15,0 mmol), 0,6710 g potassium chloride (9,0 mmol), 0,8132 g magnesium chloride, 6 H_2O (4,0 mmol), 3,7733 g histidine hydrochloride monohydrate (18,0 mmol), 27,9289 histidine (180,0 mmol), 0,4085 g tryptophan (2,0 mmol), 5,4651 g mannitol (30,0 mmol), 0,0022 g calcium chloride, 2 H_2O (0,015 mmol), 0,1842 g potassium hydrogen 2-ketoglutarate (1,0 mmol). **Uses:** For cardioplegia during cardioplegic operations, organ protection during operations in bloodless organs (heart, kidney, liver), for preservation of organs for transplantation (heart, kidney, liver, lung, pancreas) and also for vein and artery transplants and for multiorgan protection. **Contraindications:** None known. **Dosage guidance, mode and duration of use:** Please see detailed instructions for use and specialist information. **Warning:** Custodiol® is not intended for intravenous or intra-arterial administration, but only for selective perfusion of the relevant organs, though also for surface cooling and preservation of the donor organ en route from donor to recipient. Custodiol® must therefore not be used for systemic infusion. **Presentation and pack sizes:** Bottles of 100 ml, 500 ml and 1.000 ml, bags of 5.000 ml. As at: 01/02.

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DR. F. KÖHLER CHEMIE

Arzneimittel

Nikkiso-Innovations for Human Care

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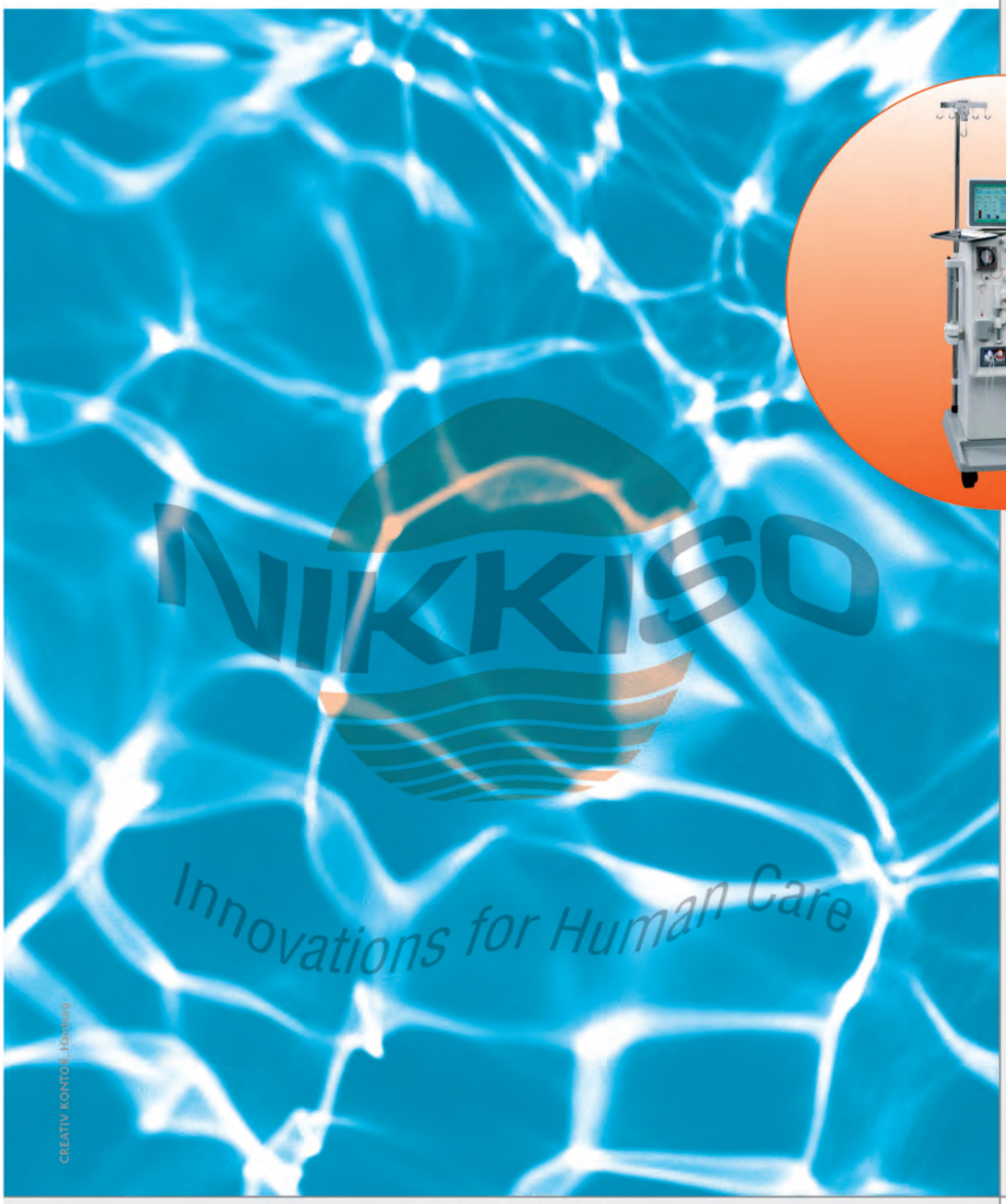

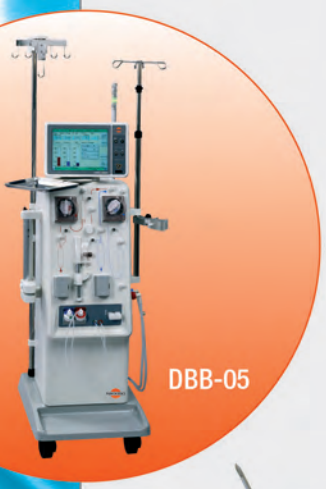

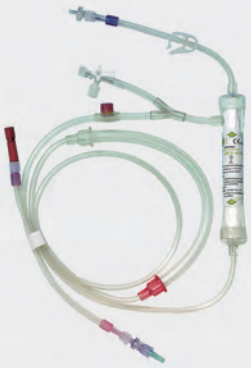

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