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REVIEW

Role of immunotherapy in downsizing hepatocellular carcinoma prior to liver transplantation

Konstantinos Ouranos, Anthi Chatziioannou, Ioannis Goulis, Emmanouil Sinakos

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Abstract

Hepatocellular carcinoma (HCC) is an aggressive primary liver neoplasm that, according to tumor stage, can be treated with resection, transplantation, locoregional treatment options, or systemic therapy. Although interventions only in early-stage disease can offer complete tumor regression, systemic therapy in advanced disease can significantly prolong overall survival, according to published clinical trials. The emergence of immunotherapy in the field of cancer therapy has had a positive impact on patients with HCC, resulting in atezolizumab–bevacizumab currently being the first-line option for treatment of advanced HCC. In light of this, application of immunotherapy in the preoperative process could increase the number of patients fulfilling the criteria for liver transplantation (LT). Implementation of this approach is faced with challenges regarding the safety of immunotherapy and the possibly increased risk of rejection in the perioperative period. Case reports and clinical trials assessing the safety profile and effectiveness of neoadjuvant immunotherapy, highlight important aspects regarding this newly evolving approach to HCC management. More studies need to be conducted in order to reach a consensus regarding the optimal way to administer immunotherapy prior to LT. In this review, we summarize the role, safety profile and future considerations regarding the use of neoadjuvant immunotherapy prior to LT in patients with HCC.

Key Words: Hepatocellular carcinoma; Immunotherapy; Tumor downsizing; Liver transplantation; Neoadjuvant; Rejection

Core tip: Immunotherapy has been used in the treatment of advanced hepatocellular carcinoma (HCC) with promising results. Extending its use in the preoperative period prior to liver transplantation (LT), either alone or in combination with other locoregional treatment modalities, could increase the pool of potential LT candidates. Data from case reports and ongoing clinical trials assessing neoadjuvant immunotherapy prior to LT could revolutionize the current consensus regarding HCC downsizing practices and improve survival of patients with this type of malignancy.

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INTRODUCTION

Hepatocellular carcinoma (HCC), the most common primary liver malignancy, constitutes the sixth most common cancer worldwide and the fourth most common cause of cancer-related mortality[1]. Incidence of HCC has been on the rise in some parts of the world, such as Europe and the USA, where the main risk factors for HCC development include HBV and HCV infection, alcohol consumption and nonalcoholic fatty liver disease (NAFLD)[2-4]. Due to the fact that HCC has been the fastest-rising cause of cancer-related mortality[2], and that most patients present at an advanced stage at the time of diagnosis, multiple treatment approaches have been thoroughly investigated by the scientific community in an effort not only to detect the cancer at an earlier stage, when more treatment modalities are applicable, but also ensure complete eradication of the tumor.

Optimal treatment options for HCC depend on tumor morphological characteristics, liver functionality and overall physical status of the patient, as suggested by the Barcelona Clinic Liver Cancer staging system (BCLC); one of the most used staging systems. According to BCLC, very early (0) and early (A) stages are potentially curative with radiofrequency ablation (RFA), surgical resection or liver transplantation (LT), with an overall survival (OS) > 60 mo. Patients with intermediate (B), advanced (C) and terminal (D) disease, however, who are not candidates for curative resection or transplantation, are best treated with transarterial chemoembolization (TACE), systemic therapy and supportive care, respectively, and face a grim prognosis with an OS of 20 mo for stages B and C and < 3 mo for stage D[5-7].

Patients with early-stage disease who are not candidates for surgical resection can undergo liver transplantation (LT) as a curative option, given that they fulfill the respected criteria, with a 4-year survival rate of 75%. These criteria, widely known as the Milan criteria (MC), screen patients for liver transplantation eligibility based on morphological characteristics of the tumor. However, strict application of the MC can exclude many patients from receiving the potentially curative treatment of LT, solely on the basis of tumor size and number[8,9]. In an effort to include more patients within the MC and further utilize the clinical benefits of LT, the concept of downstaging has been introduced in the treatment of HCC. Downstaging refers to a decrease in the tumor burden to the point where patients meet the MC and can receive LT. Downstaging options include, but are not limited to, TACE combined or not with doxorubicin eluting beads (TACE ± DEB), RFA, microwave ablation (MWA), transarterial radioembolization (TARE), irreversible electroporation (IRE), high-intensity focused ultrasound (HIFU), stereotactic body radiotherapy (SBRT), and systemic therapy[10]. Post-transplant survival rate in patients who had undergone LT after successful downstaging to MC have been shown to be comparable to that of patients undergoing LT and initially presenting within the MC[11].

In the modern era of cancer immunotherapy, alteration of signals that modulate the interaction between cancer cells and cells of the immune system, has led to many advances in the treatment of various cancer types, including HCC[12]. Although immunomodulating therapies are mainly used in advanced HCC, neoadjuvant immunotherapy is a promising approach as a means of downstaging the tumor prior to LT, yielding positive outcomes in the post-transplant period[13,14]. The aim of this review is to summarize the role of immunotherapy as a downstaging technique and also highlight future considerations regarding its safety and clinically beneficial endpoints in the perioperative period and beyond.

ORTHOTOPIC LT FOR HCC

The MC have been widely used as a tool for determining which patients are eligible for LT. According to these criteria, patients may undergo LT if the following requirements are met: (1) Single tumor with a diameter ≤ 5 cm; or (2) up to three tumors, each ≤ 3 cm in diameter and no extrahepatic spread or

vascular involvement. Although patients with HCC transplanted within the MC have a 4-year survival rate of 75% and a recurrence-free survival rate of 83%, there are studies suggesting that patients not fulfilling the MC may still benefit from LT[15,16]. Overdependence on the MC may mask the true number of patients that would benefit from a transplant. In light of this, several expanded criteria have been proposed in an effort to include patients in the transplant process. What makes these criteria stand out from MC, is that they take into account not only morphological characteristics of the tumor, but also integrate biological aspects of the disease and response to locoregional treatment (LRT) in their algorithm[17]. One of the most commonly used biological parameter is -fetoprotein (AFP). AFP serves as marker of HCC differentiation and can be used in the pretransplant period to identify patients at high risk for HCC recurrence after LT. AFP levels ≥ 1000 ng/mL are associated with poor outcomes following LT, although there are no established guidelines that indicate the optimal AFP threshold that accurately predicts post-LT outcomes[18,19]. Other well-studied biological parameters that can be taken into consideration include des--carboxyprothrombin (DCP) levels, neutrophil-to-lymphocyte ratio (NLR), prognostic nutritional index, aspartate aminotransferase-to-platelet ratio index, and aspartate aminotransferase-to-neutrophil ratio index[18]. Evaluation of tumor response to LRT is a newly evolving concept in optimal selection of patients for LT, that aims to downstage patients within the MC, promising comparable survival rates to patients with HCC receiving LT and already within the MC. Response to treatments that result in decreased tumor burden can be viewed as a complementary marker of the biological aggressiveness of the tumor and risk of HCC recurrence after LT[15]. All of the proposed expanded criteria that include the aforementioned parameters have 5-year survival rates that approximate that of MC, resulting in many institutions adopting them for the purpose of selecting patients with HCC for LT[18].

Application of the expanded criteria, however, requires an adequate reserve of available organs for transplantation, since more patients are included in the transplant process. And while this is not a problem for countries located in Asia, where living donor LT (LDLT) is the main organ source, western countries mainly depend on deceased donor LT (DDLT), which necessitates strict selection of eligible patients for LT[19]. Moreover, patients receiving DDLT typically have longer wait times when compared to patients receiving LDLT, raising concern for tumor progression in such circumstances. The above remarks highlight the importance of careful selection of patients for LT, in order to maximize the positive outcomes following LT. Downstaging therapy, ideally within the MC, is common practice nowadays and has a robust armamentarium of treatment approaches that serve to reduce tumor burden and make HCC amenable to transplantation. Also, bridging therapy aims to halt tumor progression and allow patients to receive curative treatment. Although there are no clear-cut indications for downstaging or bridging therapy, results from various studies suggest that patients presenting with tumor characteristics beyond the established criteria for LT, as well as patients with waiting times ≥ 6 mo until LT, should receive neoadjuvant therapy[20,21]. Outcomes following implementation of pretransplant treatment modalities have been mixed. A study from Yao *et al*[8] revealed post-transplant survival and recurrence-free probabilities of patients with HCC successfully downstaged within MC to be comparable to those observed in patients with HCC and already within the MC at the time of diagnosis[22]. Other studies conducted by Lao *et al*[23], Chapman *et al*[24], and Gordon-Weeks *et al*[25] have also reached to similar conclusions. However, several other studies examining the effect of LRT on post-LT outcomes found out that neoadjuvant therapy is not associated with improved outcomes and may even increase recurrence of HCC following downstaging protocol implementation[26-30]. The lack of consistent outcomes following LRT application prior to LT has generated an extensive discussion of whether conventional LRT should be modified or enriched with the aim of enhancing the downstaging and bridging options for HCC[31]. Immunotherapy has been on the spotlight of HCC in recent years and is mainly used for late-stage disease when curative treatment is unfeasible, resulting in improved OS and progression-free survival (PFS)[32]. Neoadjuvant immunotherapy as a form of LRT prior to LT is a promising new approach that aims to leave behind the flaws associated with conventional LRT and increase the number of patients receiving curative treatment.

IMMUNOTHERAPY FOR ADVANCED HCC

Tumor microenvironment in HCC

The liver is an immunogenically active organ. Under normal conditions, antigen-presenting cells (APCs) take up, process and present the antigens that enter the hepatic sinusoids on T cells, in an effort to elicit a robust immune response and prevent tissue damage. Kupffer cells, which are liver-specific macrophages, liver sinusoidal endothelial cells (LSECs) and hepatic stellate cells (HSCs) constitute the most important APCs in the liver parenchyma and, apart from their antigen-presenting role, complement the immunological repertoire of the liver by other means as well[33]. Kupffer cells produce anti-inflammatory molecules, mainly interleukin (IL)-10 and transforming growth factor (TGF)-β, attracting regulatory T (Tregs) cells that possess immunosuppressive properties, whereas LSECs and HSCs express high levels of programmed cell death ligand (PDL)1, contributing to attenuation of the immune response[34]. As a result, the liver can fight off antigens that could cause tissue damage and

also maintain immune tolerance, thereby avoiding autoimmunity.

HCC development is governed by alterations in the normal liver environment that promote tumoral spread *via* upregulation of immunosuppressive molecules that hinder the immune response against cancer cells[35]. Maintenance of this immunosuppressive tumor microenvironment (TME) is achieved not only by liver-residing immune cells, but also from migrating populations of lymphocytes, collectively referred to as tumor-infiltrating cells (TICs)[36]. According to the subpopulation being studied, TICs can elicit an antitumoral immune response or result in upregulation of immune evasion by cancer cells. Figure 1 depicts the dynamic and complex interactions of the components of the TME and their effect on tumor spread[35-38] (Figure 1).

Mechanisms of immune evasion are of special concern, since many cancer treatment modalities depend on them. Immune checkpoint molecules modulate T-cell activation and function, attenuate the immune response against cancer cells and allow for unchecked cellular proliferation[39,40]. More specifically, PDL1, expressed by cancer cells or cells of the TME, binds to PD1 on the surface of T cells, leading to T-cell exhaustion and inability to mount an effective immune response. Also, cytotoxic T-lymphocyte-associated protein (CTLA)-4 on T cells outcompetes CD28 for B7 on the surface of APCs, leading to loss of the co-stimulatory signal necessary for T-cell activation[41]. In order to halt tumorigenesis, alteration of the signals that promote immune evasion was made possible with the introduction of antibodies known as immune checkpoint inhibitors (ICIs). Such antibodies that mainly target PD1 (cepilimumab, nivolumab and pembrolizumab), PDL1 (atezolizumab, durvalumab and avelumab) and CTLA-4 (ipilimumab), have been used in the treatment of various cancers, including HCC, and have been shown to correlate with improved OS in major studies assessing their efficacy[42].

Role of immunotherapy in advanced HCC

Although systemic therapy targeting signal conduction pathways appeared in the treatment of HCC in 2007, immunotherapy lagged for about a decade before making a debut in 2017[43-45]. Nivolumab, a PD1 immune checkpoint inhibitor, was the first monoclonal antibody to be assessed in the treatment of advanced HCC. The CheckMate 040 was a noncomparative, dose escalation and expansion trial that included 262 patients (48 in the dose escalation and 214 in the dose expansion phase) and revealed that nivolumab had an objective response rate (ORR) of 15%–20% according to the mRECIST criteria and a median OS of 13.2–15 mo; findings that were comparable to the outcomes produced by sorafenib, the first-line treatment for HCC at that time. Due to the fact that no control arm was available in that trial, subsequent analyses comparing nivolumab to sorafenib were conducted. The CheckMate 459 phase III trial, assigning 743 patients with HCC to receive either nivolumab (intervention arm) or sorafenib (control arm), however, failed to show a statistically significant improvement in median OS [hazard ratio (HR) 0.85 (95% confidence interval (CI): 0.72–1.02); *P* value above the protocol-defined significance level] and PFS [HR 0.93 (95% CI: 0.79–1.1); *P* value above the protocol-defined significance level], but revealed a clinically significant median OS of 16.4 mo versus 14.7 mo in the intervention and control arms, respectively. Even more, grade 3/4 adverse effects were reported in 22% of patients treated with nivolumab compared with 49% of patients treated with sorafenib, justifying the use of this immunomodulating therapy in patients who are not candidates for sorafenib[32,46-48]. Pembrolizumab, another PD1 immune checkpoint inhibitor, was also assessed in the KEYNOTE 224 study, yielding an ORR of 17% and median OS of 12.9 mo[49]. Phase III trials assessing the comparative efficacy of pembrolizumab to best supportive care, failed to show significance in the primary endpoints of OS and PFS; albeit a clinically significant increase in OS[32,50,51]. Several other monoclonal antibodies have been thoroughly investigated as potential first-line treatment options for advanced HCC, including tislelizumab, durvalumab, avelumab, tremelimumab and atezolizumab. Results from these studies have revealed promising outcomes regarding the effect of these immunotherapies in OS and PFS when compared to currently established first-line options for HCC. Table 1 summarizes the major trials that harness immunotherapy, either alone or in combination with other modalities (*e.g.*, addition of a second ICI or systemic therapy), for the treatment of advanced HCC[32,33,39-42,46,47,49,52-54] (Table 1).

The IMbrave150 trial was a cornerstone in the management of advanced HCC. This global, open-label phase III randomized trial compared atezolizumab–bevacizumab with sorafenib in the treatment of advanced HCC. Atezolizumab is a PDL1 ICI and bevacizumab is a vascular endothelial growth factor inhibitor. 501 patients were randomly assigned in 2:1 ratio to receive either atezolizumab-bevacizumab or sorafenib until there was clinical benefit or emergence of unacceptable side effects. The primary endpoints were OS and PFS, whereas secondary endpoints included ORR, duration of response, deterioration of quality of life, physical functioning, and role functioning. According to the results, median OS was 19.2 mo (95% CI: 17.0–23.7) with atezolizumab–bevacizumab and 13.4 mo (95%CI: 11.4-16.9) with sorafenib [HR 0.66 (95% CI: 0.52–0.85), $P < 0.001$], whereas PFS was 6.9 mo (95% CI: 5.7–8.6) with atezolizumab–bevacizumab and 4.3 mo (95% CI: 4.0–5.6) with sorafenib [HR 0.65 (95% CI: 0.53–0.81), $P < 0.001$]. Results of secondary endpoints were also significant and favored the atezolizumab–bevacizumab arm. Grade 3/4 adverse effects occurred in 56.5% and 55.1% of patients in the intervention versus control arm, respectively, with the most frequent severe adverse effect in the atezolizumab–bevacizumab group being high-grade hypertension (15.2% of patients)[55]. The overall outcome of this study resulted in atezolizumab-bevacizumab being the current first-line treatment option for managing advanced HCC[56-59].

Table 1 Clinical trials assessing the effectiveness of immunotherapy in patients with advanced hepatocellular carcinoma

Trial name	Phase	Intervention	Status
Single-agent immunotherapy			
NCT02576509	III	Nivolumab *vs* sorafenib	Completed
NCT02702414	II	Pembrolizumab (single-arm study)	Completed
NCT02702401	III	Pembrolizumab *vs* BSC	Completed
NCT03062358	III	Pembrolizumab and BSC *vs* BSC and placebo	Not yet completed; estimated completion date: June 2023
NCT03412773	III	Tislelizumab *vs* sorafenib	Not yet completed; estimated completion date: May 2022
NCT02989922	II/III	Camrelizumab (single-arm study)	Not yet completed
NCT01008358	II	Tremelimumab (single-arm study)	Completed
Combination of immunotherapy with other treatment modalities[1]			
NCT02423343	I/II	Galunisertib and nivolumab (dose escalation and cohort expansion study)	Completed
NCT03893695	I/II	Ascrinvacumab and nivolumab (single-arm study)	Not yet completed; estimated completion date: June 2022
NCT03059147	I	PI3 kinase/BRD4 inhibitor small molecule and nivolumab (single-arm study)	Not yet completed; estimated completion date: October 2022
NCT03211416	I/II	Pembrolizumab and sorafenib	Not yet completed; estimated completion date: December 2022
NCT03713593	III	Lenvatinib and pembrolizumab *vs* Lenvatinib and placebo	Not yet completed; estimated completion date: December 2023
NCT03316872	II	Pembrolizumab and SBRT (single-arm study)	Not yet completed; estimated completion date: December 2023
NCT03099564	I	Pembrolizumab and Radioembolization (single-arm study)	Not yet completed; estimated completion date: June 2022
NCT03939975	II	Pembrolizumab or nivolumab or toripalimab with thermal ablation, RFA or MWA	Completed
NCT02715531	I	Atezolizumab with bevacizumab or other chemotherapy agents	Completed
NCT03434379	III	Atezolizumab and bevacizumab *vs* Sorafenib	Not yet completed; estimated completion date: June 2022
NCT03755791	III	Atezolizumab and cabozantinib *vs* sorafenib *vs* cabozantinib	Not yet completed; estimated completion date: December 2023
NCT04310709	II	Reforafenib and Nivolumab (single-arm study)	Not yet completed; estimated completion date: May 2023
NCT03869034	II	HAIC and sintilimab *vs* HAIC	Completed
NCT03794440	II/III	Anti-VEGF monoclonal antibody and sintilimab *vs* sorafenib	Not yet completed; estimated completion date: December 2022
NCT03764293	III	Apatinib and PD1 monoclonal antibody *vs* sorafenib	Not yet completed; estimated completion date: June 2022
NCT03755739	II/III	Pembrolizumab and/or ipilimumab administered *via* arterial infusion or intra-tumor fine needle injection *vs* pembrolizumab and/or ipilimumab administered *via* vein infusion	Not yet completed; estimated completion date: November 2033
NCT04273100	II	PD1 monoclonal antibody and TACE and lenvatinib (single-arm study)	Not yet completed
NCT03857815	II	PD1 monoclonal antibody and SBRT (single-arm study)	Not yet completed
NCT01853618	I/II	Tremelimumab and/or TACE and/or RFA (sequential assignment)	Completed
NCT04124991	I/II	Durvalumab and TARE (single-arm study)	Not yet completed
NCT03475953	I/II	Regorafenib and avelumab (sequential assignment)	Not yet completed; estimated

completion date: December 2022

[1]Combination therapy includes using two or more ICIs, an ICI plus systemic therapy and/or ICI plus LRT. BSC: Best supportive care; TACE: Transarterial chemoembolization; TAE: Transarterial embolization; PI3 kinase: Phosphoinositide 3 kinase; BRD4 inhibitor: Bromodomain-containing protein 4 inhibitor; SBRT: Stereotactic body radiotherapy; RFA: Radiofrequency ablation; MWA: Microwave ablation; HAIC: Hepatic arterial infusion chemotherapy; VEGF: Vascular endothelial growth factor; PD1: Programmed cell death receptor; ICI: Immune checkpoint inhibitor; LRT: Locoregional therapy.

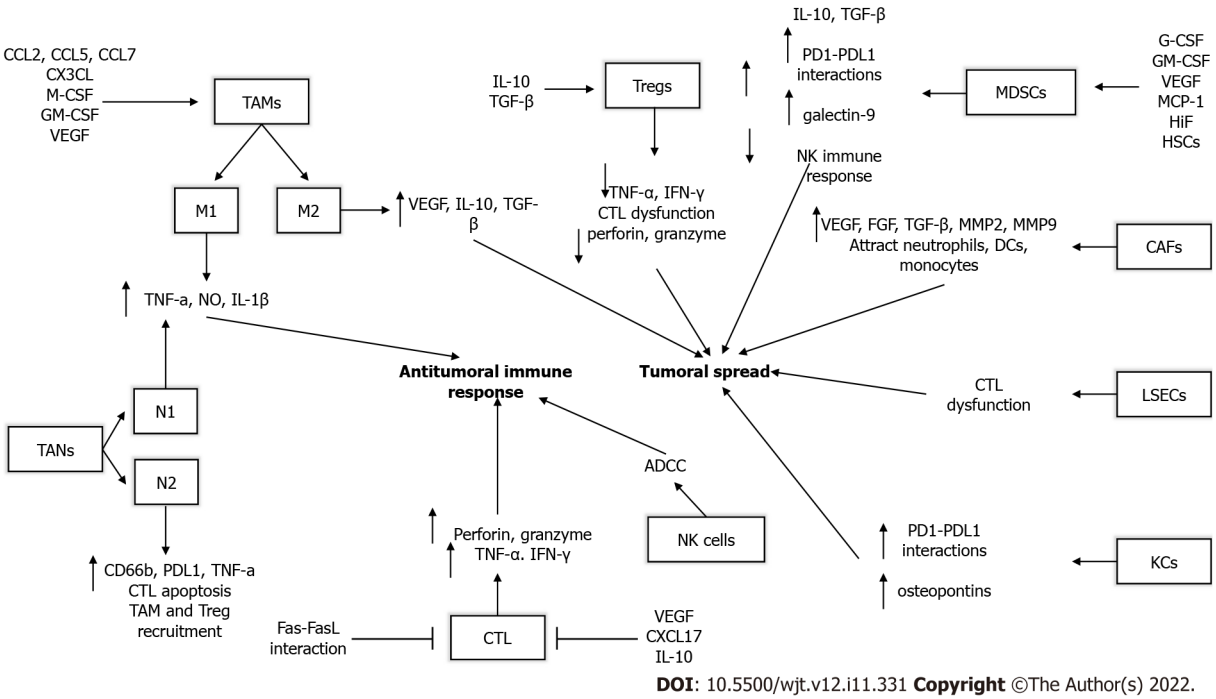

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Figure 1 Schematic representation of the major components of the tumor microenvironment in patients with hepatocellular carcinoma. The main elements of the TME can affect tumoral spread both positively and negatively. The migration of TAMs and TANs can enhance the antitumoral immune response (M1 and N1 subpopulations) through the production of inflammatory mediators, such as TNF-α, NO and IL-1β, whereas M2 and N2 subpopulations promote tumoral spread by producing immunosuppressive molecules and modulating T-cell function. The immune upregulating effects of NK cells and CTLs are typically blunted in patients with HCC due to the presence of factors secreted by components of the TME. MDSCs mute NK responses, increase levels of galectin-9, IL-10, TGF-β, and promote PD1-PDL1 interactions, favoring tumor spread. Treg cells, LSECs and KCs all promote HCC development by inducing CTL dysfunction, immune evasion, and expression of immune-downregulating factors. CCL2: Chemokine receptor type 2; CCL5: Chemokine receptor type 5; CCL7: Chemokine receptor type 7; CX3CL: Chemokine (C-X3-C motif) ligand 1; M-CSF: Macrophage colony stimulating factor; GM-CSF: Granulocyte macrophage colony stimulating factor; VEGF: Vascular endothelial growth factor; TAMs: Tumor associated macrophages; M1: Subpopulation 1 of TAMs; M2: subpopulation 2 of TAMs; IL-10: Interleukin 10; TGF-β : Transforming growth factor beta; TNF-a: Tumor necrosis factor alpha; NO: Nitric oxide; IL-1β: Interleukin 1 beta; TANs: tumor associated neutrophils; N1: Subpopulation 1 of tans; n2: subpopulation 2 of TANs; CD66b: Cluster of differentiation 66 type b; PDL1: Programmed cell death ligand 1; PD1: Programmed cell death receptor 1; CTL: Cytotoxic CD8+ T cells; Tregs: T regulatory cells; FasL: Fas ligand; IFN-γ: Interferon gamma; CXCL17: Chemokine (C-X-C motif) ligand 17; NK cells: Natural killer cells; MCP-1: Monocyte chemoattractant protein-1; HiF: Hypoxia inducible factor; HSCs: Hepatic stellate cells; MDSCs: Myeloid derived suppressor cells; CAFs: Cancer associated fibroblasts; FGF: Fibroblast growth factor; MMP2/9: Matrix metalloproteases 2 and 9; LSECs: Liver sinusoidal endothelial cells; KCs: Kupffer cells.

Recently, the HIMALAYA study assessed the efficacy of combination tremelimumab and durvalumab in advanced HCC. This phase III study involved 1234 patients that were randomly assigned to receive durvalumab and tremelimumab or sorafenib or durvalumab monotherapy. The ORR was 20.1% in the durvalumab–tremelimumab group compared with 5.1% and 17% in the sorafenib and durvalumab groups, respectively. The PFS and OS were 3.78 and 16.4 mo in the durvalumab and tremelimumab group, 4.07 and 13.8 mo in the sorafenib group, and 3.65 and 16.6 mo in the durvalumab group. Grade 3/4 adverse events occurred at a lower rate in the durvalumab–tremelimumab and durvalumab groups when compared with the sorafenib arm. Overall results of this breakthrough study open up new treatment options that could be integrated into the treatment algorithm of HCC management[60].

As suggested by the above remarks and Table 1, clinical trials assessing the combination of immunotherapy and systemic therapy or the use of two ICIs concurrently, have shown greater outcomes when compared to trials that use single-agent therapy (immunomodulating or systemic) in the intervention arm. An ambitious treatment approach is the combination of ICIs with LRT, the latter of which is traditionally used in early-stage disease or as a means of downstaging or bridging therapy prior to LT

[61]. The idea behind this approach is that LRT can alter the TME by inducing a robust antitumoral immune response and reduce the number of immunosuppressive molecules. Although these effects could theoretically justify LRT as a single therapy to control tumor progression, evidence suggests that such responses are weak and transient and cannot completely control the tumor. The addition of immunotherapy could amplify the antitumoral responses produced by LRT, thus creating a synergistic interaction between ICIs and LRT that could effectively control tumor spread[62,63]. There are a few trials assessing the combination of LRT with ICIs, since most of them take advantage of immunotherapy in the form of adoptive cell and vaccine therapy. However, results from these studies have demonstrated favorable outcomes in terms of OS and safety, thus encouraging the implementation of this combination in case other first-line treatment modalities fail[62].

Although combination immunotherapy is a superior approach than single-agent immunotherapy for the treatment of HCC, there are a few remarks that need to be pointed out. The need of combining various immunotherapeutic drugs in specific dosages may come as a challenge for smaller hospitals that are neither readily equipped, nor familiar with the specific combination regimens used to treat HCC. The lack of availability of highly efficacious drugs in resource-limited hospitals prevents the widespread application of immunotherapy, leaving healthcare providers with a restricted panel of drug options, mainly systemic chemotherapeutic agents, that, although effective, do not demonstrate the superiority of immunotherapy in treating HCC. Unfortunately, this hurdle inevitably affects pre-transplant ICI use for the same reasons mentioned above.

IMMUNOTHERAPY AS A DOWNSTAGING THERAPY PRIOR TO LT

It seems evident that immunotherapy has an integral role in the management of advanced HCC. The success of ICIs use in the long-term survival of patients with HCC has brought into question whether immunotherapy could also produce significant outcomes in early-stage disease and mainly as neoadjuvant treatment modality prior to LT. Although data on this topic are scarce, valuable information can be extracted regarding the future applications of ICIs in HCC management.

Goals of neoadjuvant immunotherapy

Delivery of immunotherapy prior to LT serves the same goals as application of conventional LRT, and, at the same time, establishes new perspectives in terms of prediction of post-LT outcomes and survival following transplantation. Bridging and downstaging ICI therapy is a novel approach to maintaining or even increasing the pool of transplant HCC candidates able to undergo curative LT. Beyond that, ICIs may have additional benefits post-LT, since they may be able to decrease disease recurrence by treating micrometastatic disease that was not detected prior to LT[14]. The basis behind the already mentioned promising benefits of neoadjuvant immunotherapy stems from the ability of ICIs to reconstitute the immune response towards an antitumoral microenvironment that halts disease progression. More specifically, histological analysis of a specimen from a subject enrolled in a study evaluating the perioperative use of ICIs in patients with HCC revealed an increase in the number of cytotoxic $CD8^+$ T cells and levels of interferon (IFN)-γ, which are both known to mitigate the immunosuppressive TME seen in HCC and at the same time mount an effective antitumoral, inflammatory response that controls tumor spread. Also, although the cluster of Treg cells, which are known to induce an immunosuppressive environment and promote cancer spread, was increased, there was an eventual complete pathologic response observed in the analyzed specimen. This could be due to the high $CD8^+$ T cell/Treg cell ratio, favoring the antitumoral immune response, or to the presence of a mixed population of regulatory T cells that serve to halt disease progression[64]. Other studies have also evaluated the mechanisms responsible for producing favoring outcomes following periprocedural ICI administration and have concluded that the overwhelming infiltration of tumor-specific CD8+ T-cells, the release of inflammatory cytokines, such as IFN-γ and tumor necrosis factor (TNF)-α, the elevated number of tumor neoantigens that attract T cells and the relative decrease in the number of immunosuppressive and Treg cells, all contribute to the positive immunomodulating outcomes of neoadjuvant ICI use[65-68]. Overall, neoadjuvant immunotherapy prior to LT in HCC serves three main goals: (1) Preventing patients from waitlist dropout, when the time interval to LT is substantial (bridging therapy); (2) increasing the number of patients eligible for transplantation by including them in established LT criteria (downstaging therapy); and (3) ensuring micrometastatic spread eradication after LT, thereby increasing the chances of prolonged survival after surgery.

Considerations regarding the safe use of neoadjuvant immunotherapy prior to LT in patients with HCC

When contemplating ICI administration prior to LT, one has to take into account the time interval between the last dose of ICI therapy and LT, factors that predict response to ICI therapy, in order to prevent graft rejection, and the possible adverse events associated with ICI and how they could be effectively managed.

Post-LT ICI administration has been linked to donor allograft rejection[69]. Indications for using immunotherapy after transplant include recurrence of malignancy or emergence of a new tumor that is responsive to ICI therapy. When a transplant process takes place, immunosuppression typically follows to prevent the host immune response against the transplanted allograft. ICI administration, by upregulating the T-cell response and dampening the signals that create a state of relative immunosuppression that is desirable post-LT, can result in T cells attacking the graft, resulting in dysfunction, subsequent rejection, and eventual graft and/or patient loss. Despite this feared outcome, studies evaluating graft function after ICI administration in patients undergoing LT have been mixed, and no consensus has been reached regarding the safety profile of immunotherapy in the perioperative period[70]. A case series study evaluating 13 HCC patients who received ICI post-LT revealed that four patients (31%) developed graft rejection[71]. Another study identified a cohort of 14 patients who received ICIs post-LT, with four of them (29%) experiencing graft rejection[72]. Moving to the downstaging setting, it is important to consider a washout period between the last dose of immunotherapy and LT in order to downregulate the immune response that was accentuated during ICI therapy, thus allowing the allograft to be successfully transplanted. The ideal time interval until LT has not been decided, mainly due to the limited number of studies harnessing ICIs as a downstaging tool, but there are some important aspects to consider regarding this topic. The half-life of the immunomodulating agent could be used as an adjunctive parameter to calculate the time of immunotherapy discontinuation to LT. However, further understanding of the mechanism of action of ICIs may prove the above remark unreliable. Indeed, occupancy of drug-specific targets by these medications can be prolonged, resulting in a duration of effect that extends beyond the period one would calculate based on the half-life of the ICI[73]. For example, although the half-life of nivolumab is ~25 d, it has been observed that its effects may last for up to 2 mo following a single infusion of the drug, due to sustained occupancy of PD1 on the surface of T cells. Although a short washout period would theoretically correlate with increased risk of graft rejection, there are notable examples that prove this point wrong. A study by Tabrizian *et al*[13] assessed the outcome of nine HCC patients who were transplanted in a single center between 2017 and 2020 after receiving nivolumab 240 mg every 2 wk as downstaging therapy. Washout period did not exceed 30 d for any patient after discontinuation of treatment and, notably, two patients discontinued nivolumab 1 and 2 d prior to LT. Following transplantation, no severe graft rejection, tumor recurrence or death occurred, with one patient developing mild rejection that was appropriately managed with an increase in the dose of tacrolimus. Intraoperative blood transfusion was administered in the two patients who received LT within 2 d of nivolumab discontinuation, which could have accelerated the rate of drug washout[13]. In another study by Chen *et al*[74], a patient who underwent LT and discontinued preoperative toripalimab 93 d before the procedure, suffered ICI-induced acute hepatic necrosis. Results of these studies could indicate that half-life of a drug could not by itself predict the optimal time to LT after downstaging therapy implementation. Other potential parameters or markers should be investigated in order to attain a more precise estimate of the washout period.

Predicting if a liver graft is suitable for transplantation after ICI administration is a promising feat that could smooth out the perioperative process. PDL1 molecule expression on the transplanted graft could act as surrogate biomarker of the safety of ICIs in terms of inducing or not graft rejection. The idea behind this approach is that PDL1-negative grafts will have fewer rejections when compared to positive ones, since ICIs will not be able to mount an inflammatory immune response in the absence of drug-binding molecules on the cells of the transplanted parenchyma, thus maintaining the immunosuppressive environment required for LT. A study by Shi *et al*[75] was conducted to compare the graft rejection rate in five cancer patients who received PDL1-negative allografts when compared to controls with an unknown PDL1 status in their transplanted liver, after receiving the immunomodulating agent toripalimab. Results showed that none of the five patients who received PDL1-negative grafts experienced rejection, whereas another patient treated off-record who received PDL1-positive graft, experienced rejection after ICI administration. In another study conducted by Friend *et al*[76], graft rejection was detected in two HCC patients who received nivolumab after being transplanted with PDL1-postive allografts. DeLeon *et al*[77]. conducted a retrospective evaluation of seven cancer patients undergoing LT to assess the safety of post-transplant ICI use. Five out of seven patients in the study were assessed for PDL1 expression and two of them were positive. One of the two patients who received PDL1-poisitive grafts also demonstrated high levels of tumor-infiltrating lymphocytes in the transplanted liver. The results of the final study indicate that apart from PDL1 status, other potential biomarkers should be assessed to predict the outcomes of ICI use in the operative period. Although no major studies have been conducted up to date that could reliably emphasize the role of miscellaneous biomarkers that predict the safety of ICI use during LT, immunohistochemical analysis of the transplanted allograft could be used as a surrogate parameter that aims to better delineate the outcome of LT following ICI administration.

Although rejection is an undesirable outcome of ICI therapy, other adverse events can also occur, collectively known as immune-related adverse effects (iRAEs). Such adversities can prolong or even terminate the transplant process, not only because iRAEs may make the patient ineligible for LT, but also because effective management of such outcomes may prolong the time interval to LT, resulting in progression of the malignancy and dropout from the transplantation criteria. Most iRAEs present within the first 2 wk of treatment initiation, although they can occur at any time. Every organ can be involved,

and severity can range from mild to life-threatening[78,79]. Results from major clinical trials have found that grade 3/4 adverse events occur at an acceptable rate that would justify their use in HCC treatment. In the IMBrave150 trial, grade 3/4 adverse effects occurred in 56.53% of patients who were treated with atezolizumab–bevacizumab when compared with 55.13% of patients in the control group who were treated with sorafenib. The percentage of high-grade adverse effects in the intervention group was not attributed solely on atezolizumab, since hypertension, the most common high-grade adverse event observed in the study, was most likely attributable to bevacizumab[47,58]. In the KEYNOTE 240 trial, grade 3/4 adverse effects occurred in 52% of patients treated with pembrolizumab compared with 46.27% in the control arm[47].

It is not yet clear which class of ICIs is safer. While CTLA4 plays an important role in the induction of graft tolerance, PD1/PDL1 interactions result in both induction and maintenance of graft tolerance. Theoretically, this could imply that immunotherapy targeting PD1 and/or PDL1 molecules is more likely to cause organ rejection than agents that target CTLA4[80]. However, there are still no published studies that assess the comparative safety profiles of various classes of immunotherapy, so no definite conclusions can be drawn[71]. Regardless of which class will be chosen, treatment of iRAEs is the same, with glucocorticoids being the most common immunosuppressant agent that can effectively ameliorate negative outcomes of ICIs[78]. Patients undergoing LT for HCC usually have compromised liver function. Nonetheless, ICI use is safe in this patient population, since these drugs are not metabolized in the liver.

As already mentioned before, the paucity of available donors for LT substantially limits this treatment approach for the management of HCC. Although currently not employed in the armamentarium of HCC management, autologous LT is a theoretically promising approach that could increase the number of patients receiving curative treatment. Data regarding autologous LT following immunotherapy are not yet available, but a hypothetical explanation of the mechanism behind this approach could ignite future discussions around this topic. Liver regeneration capabilities are well studied in the literature. The effects of immunotherapy in the TME have been extensively discussed above and generally promote an antitumoral immune response that aims to halt tumor progression and decrease tumor burden. As such, more liver parenchyma can be restored to its physiologic architecture. Such an occurrence can aid in the autologous LT process by increasing the available tissue for extraction and reimplantation following diseased liver removal. As ideal as this approach may sound, challenges along the way, such as remaining unidentified tumor burden, metastatic disease and recurrence of malignancy are all topics of concern that need further investigation. For the time being, autologous LT following immunotherapy requires more research in order to delineate the exact mechanisms that could result in positive outcomes.

Clinical trials and case reports assessing the use immunotherapy as a downstaging technique prior to LT in patients with HCC

Case reports: According to literature review, 20 cases involving patients with HCC receiving ICIs prior to LT have been published[13,73,74,81-83] (Table 2). The majority of the patients were male (85%) and the mean age was 58.4 years. The most common underlying liver disease was HBV-induced liver disease, while HCV infection, alcoholic liver disease and NAFLD were also observed. One patient had no underlying liver disease. The most commonly used ICI prior to LT was the PD1 inhibitor nivolumab (55% of cases). Other immunomodulating agents used were toripalimab, durvalumab, camrelizumab and pembrolizumab. The time interval between the last dose of ICI and LT varied significantly among the cases, with one patient receiving the last ICI dose 1 d prior to LT and another one almost 29 mo prior to the operation. No recurrence of the tumor occurred in patients that had a successful LT after ICI use. Nonfatal perioperative complications, excluding rejection, occurred in only one patient, who developed bile leak that was appropriately managed without further consequences. Out of the 20 cases described, two patients had fatal rejection and two others experienced mild rejection that was adequately treated. The first patient with fatal graft rejection, described by Chen *et al*[74], had chronic HBV infection. He underwent DDLT due to recurrent HCC that was previously treated with resection, RFA, TACE, MWA, sorafenib, lenvantinib and toripalimab. The last cycle of ICI therapy was administered 93 d prior to LT. Following the procedure, the patient's liver function status deteriorated rapidly, and a liver biopsy performed on the second postoperative day revealed massive liver tissue necrosis that was attributed to toripalimab. The patient expired 3 d after the procedure[73]. The second patient with fatal graft rejection, described by Nordness *et al*[81], had chronic HCV infection. He underwent DDLT due to recurrent HCC previously treated with resection, sorafenib, RAE, TACE and nivolumab. The last dose of nivolumab was administered 8 d prior to LT. On postoperative day 5, rapid elevation of liver enzymes was noted, and the patient deteriorated clinically to the point where he was transferred to the intensive care unit. A biopsy that was performed on the next day revealed acute hepatic necrosis with a dense lymphocytic infiltration, findings that point towards a diagnosis of ICI-induced graft rejection. Reversible graft rejection that was observed in two patients was due to low levels of immunosuppressive medications and was appropriately treated with dose escalation, without inflicting any major damage to the graft recipients.

Table 2 Summary of case reports assessing immune checkpoint inhibitors as a downstaging and/or bridging therapy prior to liver transplantation in patients with hepatocellular carcinoma

Sex	Age, yr	Underlying liver disease	ICI	Cycles (d)	Washout period	Post-LT outcome
M	66	ALD	Nivolumab	34	105	No rejection
M	65	HCV	Nivolumab	44	8	Fatal rejection
M	39	HBV	Toripalimab	10	93	Fatal rejection
M	69	None	Nivolumab	21	18	No rejection
F	56	HCV	Nivolumab	8	22	No rejection
M	58	HBV	Nivolumab	32	1	No rejection
M	63	HCV	Nivolumab	4	2	No rejection
M	30	HBV	Nivolumab	25	22	Mild rejection[1]
M	63	HBV	Nivolumab	4	13	No rejection
M	66	HBV	Nivolumab	9	253	No rejection
F	55	HBV	Nivolumab	12	7	No rejection
F	53	NASH	Nivolumab	2	30	No rejection
M	61	HBV	Durvalumab	NA	> 90	No rejection
M	53 ± 12.1	NA	Camrelizumab and/or Pembrolizumab	3 ± 2	870 on average	1 rejection in the cohort[1]

[1]The rejection was appropriately treated and the patient suffered no major adverse outcomes. ICI: Immune checkpoint inhibitor; HCC: Hepatocellular carcinoma; M: Male; F: Female; LT: Liver transplantation; ALD: Alcoholic liver disease; HCV: Hepatitis C virus; HBV: Hepatitis B virus; NASH: Non-alcoholic steatohepatitis; NA: Not available.

Clinical trials: Currently, there is a limited number of clinical trials assessing the use of ICIs prior to LT in patients with HCC. However, there are multiple studies evaluating neoadjuvant administration of immunotherapy prior to liver resection in patients with HCC[39] (Table 3). These are mainly phase I/II studies with no control arm that assess safety, efficacy, and tolerability of the immunomodulating agent, either alone or in combination with other therapies. Nivolumab is the most used ICI in these studies[84-88]. Other ICIs used include tislelizumab, cemiplimab, toripalimab and camrelizumab[89-92]. Most of these trials are ongoing, with most of them not having any published results. Analysis of completed studies, however, reveals satisfactory objective response rates and an acceptable rate of adverse events, setting the stage for the recommencement of phase III, randomized studies that will provide us with valuable information regarding the benefits of neoadjuvant immunotherapy before resection or LT.

To date, there are two clinical trials of neoadjuvant immunotherapy prior to LT in patients with HCC. The first trial (NCT04425226) is a randomized study that will assess the neoadjuvant use of pembrolizumab and lenvatinib as a downstaging and/or bridging therapy prior to LT in 192 patients with HCC. Participants will receive pembrolizumab 200 mg intravenously on day 1 of each 21-d cycle. Treatment will continue until unacceptable toxicity develops or until there are at least 42 d remaining to LT. Concurrently, study subjects will receive lenvatinib 8–12 mg orally at least 38 d every 6 wk and until there are at least 7 d prior to LT. The primary endpoint will be RFS, whereas secondary endpoints include the disease control rate, the percentage of patients who will experience adverse outcomes and who will discontinue study treatment due to an adverse event, and the ORR. Results of the study are expected in December 2024[93]. The second trial (NCT04035876) is a phase 1/II, single-arm study that evaluated the use of camrelizumab and apatinib as downstaging and/or bridging therapy prior to LT in 120 patients with HCC. Participants received camrelizumab 200 mg intravenously every 2 wk and apatinib 250 mg orally every day. Camrelizumab was discontinued 5 wk before and apatinib 1 wk before LT. Primary endpoints included objective remission rate and RFS, whereas secondary endpoints included OS, time to progress and rate of adverse events. Results of this study are not yet available[94].

CONCLUSION

LT is a curative treatment approach for HCC. With respect to the current transplant criteria, conventional LRT has been widely used as downstaging and/or bridging therapy to increase the pool of

Table 3 Clinical trials assessing immune checkpoint inhibitor use in the neoadjuvant setting prior to liver resection in patients with hepatocellular carcinoma

Trial name	Phase	Intervention	Status
NCT03510871	II	Nivolumab and ipilimumab (single-arm study)	Not yet completed; estimated completion date: December 2022
NCT03682276	I/II	Nivolumab and ipilimumab (single-arm study)	Not yet completed; estimated completion date: September 2022
NCT03299946	I	Nivolumab and cabozantinib (single-arm study)	Completed
NCT04615143	II	Tislelizumab or tislelizumab and Lenvatinib (sequential assignment)	Not yet completed; estimated completion date: December 2025
NCT03916627	II	Cemiplimab (parallel assignment)	Not yet completed; estimated completion date: September 2029
NCT03867370	I/II	Toripalimab or toripalimab and Lenvatinib (sequential assignment)	Not yet completed; estimated completion date: October 2022
NCT03630640	II	Nivolumab (single-arm study)	Not yet completed; estimated completion date: November 2023
NCT04123379	II	Nivolumab *vs* nivolumab and CCR2/5 inhibitor *vs* nivolumab and anti-IL-8 antibody (parallel assignment)	Not yet completed; estimated completion date: October 2024
NCT04297202	II	SHR-1210 (anti-PD1 inhibitor) and apatinib (single-arm study)	Completed

CCR2/5: Chemokine receptors type 2 and 5; IL-8: Interleukin-8; PD1: Programmed cell death receptor 1; NA: Not applicable.

potential LT candidates. Nevertheless, the benefits of immunotherapy in patients with advanced HCC have generated an extensive discussion whether ICIs could be used safely and effectively in the pretransplant process in order to yield favorable outcomes. When contemplating neoadjuvant immunotherapy, the risk of graft rejection after LT is a matter of concern. Results from a limited number of case reports, however, showed that the risk may not be as high, with fatal rejection presenting in only two out of 20 cases of LT after ICI administration. More studies need to be conducted to delineate the factors that could reliably predict outcomes after LT in patients receiving neoadjuvant immunotherapy. Determination of surface molecule expression, such as PD/PDL1, obtained *via* liver biopsy, is a tempting marker that could predict response to outcome, but, utilized alone, does not seem to accurately include all patients that would benefit from ICIs. More markers need to be taken into consideration, either alone or in conjunction with other aspects of disease treatment that focus on the pharmacokinetics of immunotherapy. Drug half-life could theoretically play an important role in determining the ideal time interval spanning from ICI discontinuation to LT. In practice, however, no fatal rejection was observed in patients with cessation of drug therapy even 1 d before surgery, emphasizing the fact that individualization of treatment regimen is a superior approach than strict adherence to the properties of the drug in order to allocate patients to the appropriate drug scheme. Patient comorbidities, availability of other neoadjuvant treatment options, and the ability to timely treat emerging ICI-related adverse effects are all remarks that should be explored prior to initiating immunotherapy. Clinical trials that assess neoadjuvant ICI therapy, either before liver resection or transplantation, show promising results, both in treatment safety and efficacy, with primary and secondary study endpoints being met successfully. Insights from future studies, which are currently underway, are necessary to better understand the impact of neoadjuvant immunotherapy in the perioperative period and beyond.

FOOTNOTES

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MINIREVIEWS

Challenges in liver transplantation in the context of a major pandemic

Eleni Theocharidou, Danielle Adebayo

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Abstract

Coronavirus disease-2019 (COVID-19) has led to a temporary suspension of liver transplant activity across the world and the remodeling of care for patients on the waiting list and transplant recipients with the increasing use of remote consultations. Emerging evidence shows that patients with more advanced liver disease are at increased risk of severe COVID-19 and death, whereas transplant recipients have similar risk with the general population which is mainly driven by age and metabolic comorbidities. Tacrolimus immunosuppression might have a protective role in the post-transplant population. Vaccines that have become rapidly available seem to be safe in liver patients, but the antibody response in transplant patients is likely suboptimal. Most transplant centers were gradually able to resume activity soon after the onset of the pandemic and after modifying their pathways to optimize safety for patients and workforce. Preliminary evidence regarding utilizing grafts from positive donors and/or transplanting recently recovered or infected recipients under certain circumstances is encouraging and may allow offering life-saving transplant to patients at the greatest need. This review summarizes the currently available data on liver transplantation in the context of a major pandemic and discusses areas of uncertainty and future challenges. Lessons learnt from the COVID-19 pandemic might provide invaluable guidance for future pandemics.

Key Words: COVID-19; Pandemic; Liver transplantation; Chronic liver disease; Immunosuppression; Vaccines

Core Tip: Coronavirus disease-2019 pandemic posed unprecedented challenges in terms of managing patients with advanced liver disease remotely, offering transplant for highly selected patients, managing immunosuppression, treating infected patients with chronic liver disease, transplanting infected patients, and utilizing grafts from infected donors. The transplant community responded rapidly to these challenges and many centers were able to resume activity soon after the first wave of the pandemic. Emerging data help shed light on areas of uncertainty and provide guidance for future challenges.

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INTRODUCTION

The rapid spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the severe disease precipitated by the coronavirus disease 2019 (COVID-19) has had a profound impact on healthcare systems worldwide. The challenges posed on liver transplantation (LT) programs were unprecedented, and can be summarized in the following: (1) Pre-transplant aspects (management of patients on the LT waiting list, impact of COVID-19 on patients with advanced liver disease); (2) peri-transplant aspects (temporary suspension of LT programs, testing of donors/recipients, LT after recovery from COVID-19, utilization of grafts from positive donors); and (3) post-transplant aspects (COVID-19 in LT recipients, management of immunosuppression, safety of vaccination against SARS-CoV-2). The aim of this review is to provide an outline of the unforeseen challenges that the COVID-19 pandemic posed on LT programs worldwide.

MANAGEMENT OF PATIENTS ON THE WAITING LIST

The declaration of COVID-19 pandemic by the World Health Organization in March 2020 precipitated significant changes in the delivery of healthcare in an effort to minimize patient and staff exposure to SARS-CoV-2. The traditional face-to-face consultations, which have been the basis of patient-doctor communication, ceased suddenly, and gave place to new virtual models of communication[1]. Patients were encouraged to have blood tests or other essential investigations performed locally (usually with help of their general practitioner) to avoid travelling. Telephone- and/or video-assisted consultations rapidly became the norm during the pandemic. Sending prescriptions and medications *via* post was another approach utilized to reduce risk of transmission/acquisition.

Patients with chronic liver disease (CLD) and particularly with decompensated cirrhosis (including those on the waiting list for LT) were classified as having high risk for severe COVID-19, and were, therefore, instructed to strictly self-isolate for prolonged periods of time. Their assessment and management were completed remotely to a significant extent, while maintaining very limited face-to-face consultations for highly selected patients who were considered at risk for CLD complications[2]. Procedures such as ultrasonography for hepatocellular carcinoma (HCC) surveillance or endoscopy for variceal surveillance, were deferred unless the patient was considered at high risk of HCC or variceal bleeding, respectively, and following individual risk-benefit assessment. The international hepatology associations [European Association for the Study of the Liver (EASL), American Association for the Study of Liver Diseases (AASLD), Asian Pacific Association for the Study of the Liver (APASL)] released promptly guidance for the management of patients with CLD, patients on the waiting lists and LT recipients[3-6]. The guidance included strict preventive measures (*i.e.*, vaccination against *Streptococcus pneumoniae* and influenza, prophylaxis against spontaneous bacterial peritonitis) to avoid hospital attendance and/or admission. The common denominator was avoidance of commuting and face-to-face contact unless it was considered essential. The caveats of no direct patient contact, in particular for patients on the waiting list, were acknowledged by clinicians, but it was felt that the risks of severe COVID-19 and death outweighed the risks associated with remote or virtual assessments[7]. An Austrian study that included patients with CLD admitted to hospital just before and after the outbreak of the pandemic, demonstrated the impact of the restrictions on patient satisfaction with regards to the quality of liver care[8]. The same study showed that CLD patients who were hospitalized during the pandemic were sicker indicating a higher threshold for hospital attendance and admission, and liver-related mortality was higher.

EVALUATION AND SELECTION OF CANDIDATES FOR LIVER TRANSPLANTATION

The same restrictions were applied to the evaluation and selection process of LT candidates. Many LT centers developed local policies for selecting patients and for prioritizing those who were already on the waiting list. Patients who were prioritized included those with acute liver failure, higher model for end-stage liver disease (MELD) score and those at risk for decompensation or HCC progression[4]. The evaluation process had to be remodeled taking into consideration travelling restrictions, distancing measures and minimization of exposure to SARS-CoV-2. LT assessments, *i.e.* patients and family education, social work and dietitian consultations, had to be performed either *via* video or telephone consultations. In several LT centers, the group education sessions were replaced by internet-based sessions with multiple participants.

The impact of COVID-19 on the waiting list for solid organ transplantation (SOT) was investigated in a study that used the Scientific Registry of Transplant Recipients (SRTR) data[9]. In March 2020 coinciding with the onset of the pandemic and in winter 2020/2021 coinciding with the second surge, there was a rapid decline in the length of the waiting list for SOT likely due to a reduced number of new listings, and a decline in the number of removals from the waiting lists due to reduced number of transplants performed. With regards to removals due to death, waiting list mortality remained constant for liver, but increased for kidney. The results of this study reflect the reduction in the activity (decreased transplant assessments/listings, decreased transplant activity) in many transplant centers not only in the US, but also worldwide.

TRANSPLANTATION ACTIVITY

The COVID-19 pandemic had a profound impact on SOT that was primarily driven by safety concerns regarding transmission (in the first phase when access to SARS-CoV-2 testing was very limited) and by limited resources (mainly intensive care beds). A web-based survey between September 7, 2020 and December 31, 2020 organized by three international societies (European Association for the Study of the Liver, European Society of Organ Transplantation- European Liver and Intestine Transplant Association, and International Liver Transplantation Society) compared transplant activity in the first six months of 2020 versus 2019[10]. Most transplant centers ceased activity for up to a month with the exception of patients with acute liver failure, high MELD score or acute-on-chronic liver failure, in which cases the decisions were made on a case-by-case basis. Out of 128 centers that responded to the survey, 30%-50% performed transplantations on patients with previous COVID-19. The majority reported lower transplant activity, fewer candidates being listed and higher waiting list mortality in 2020 compared to 2019. These differences were more profound in 'hit' countries (COVID-19 case fatality > 3.4%) than in 'non-hit' countries[10].

The analysis of the Global Observatory for Organ Donation and Transplantation data for 2019 and 2020 showed a global decrease in LT by 11.3%[11]. Almost all geographic regions were affected, but developed countries were able to subsequently recover transplant activity, whereas developing counties lagged. In the United States, 32 594 transplants were expected in 2020, and only 30 566 were performed (observed/expected (O/E) 0.94, confidence interval (CI): 0.88–0.99)[12]. A total of 58 152 waiting list registrations were expected and 50 241 transplants were performed (O/E 0.86, CI: 0.80–0.94). The observed/expected ratio for LT was 0.96 (0.89–1.04). There was a similar reduction in organ donation. The months with the lowest activity were April, May and December 2020. In Europe, there was a similar reduction in LT activity with areas with the highest incidence of COVID-19 showing the greatest reduction in activity.

The reduction in LT activity ranged from 25% (United States and France) to 80% (United Kingdom and India)[13]. Some countries/areas managed to maintain their LT activity (South Korea, some centers in Italy even in medium or high-incidence areas) by means of a rapid response to the pandemic and re-modeling of their pathways[13]. In the US, significant variability in LT activity was observed within regions of similar COVID-19 incidence[14]. This was presumably attributed to differences in resources, SARS-CoV-2 transmission among members of staff and leadership philosophy. The wider availability of SARS-CoV-2 testing might have been associated with the restoration of LT activity later in 2020.

COVID-19 IN TRANSPLANT CANDIDATES

Abnormal liver function tests are common in patients with COVID-19, and can be attributed to direct viral cytopathic effect, immune-mediated liver injury, hypoxia or drug-induced liver injury. Liver cells express SARS-CoV-2 entry receptors, including angiotensin-converting enzyme-2 receptors, and SARS-CoV-2 infection has been associated with strong upregulation of interferon responses in the liver, similar to other hepatotropic viruses[15]. These findings support SARS-CoV-2 hepatic tropism. Liver involvement in COVID-19 has been associated with higher mortality[16]. In patients with pre-existing chronic liver disease, COVID-19 can lead to exacerbation of the underlying disease, which in patients

with cirrhosis can result in acute decompensation[17]. Studies consistently show increased risk of mortality in patients with cirrhosis and COVID-19[18]. A study that included 305 SARS-CoV-2 positive patients with cirrhosis and compared them with SARS-CoV-2 positive patients without cirrhosis, and SARS-CoV-2 negative patients with and without cirrhosis, demonstrated a 3.5-fold increased mortality among patients with cirrhosis, and 1.7-fold increased mortality among SARS-CoV-2 positive patients [19]. Predictors of mortality in SARS-CoV-2 positive patients with cirrhosis were advanced age, decompensation, and higher MELD score.

The risk of death with COVID-19 is higher in patients with cirrhosis compared to patients with CLD without cirrhosis, and the risk increases with more advanced stages of liver disease. One of the largest international studies (29 countries) included 386 SARS-CoV-2 positive patients with cirrhosis, 359 SARS-CoV-2 positive patients with CLD without cirrhosis and 620 SARS-CoV-2 positive patients without CLD [20]. Mortality in patients with cirrhosis was significantly higher than in those with CLD without cirrhosis (32% *vs* 8%, $P < 0.001$). Mortality in Child-Pugh A cirrhosis was 19%, B 35% and C 51%. The main cause of death among patients with cirrhosis was respiratory failure in 71%. Acute decompensation occurred in 46%. Age and severity of liver disease were predictors of mortality.

In view of this data, international societies recommend testing for SARS-CoV-2 in every patient presenting with acute decompensation, and early admission for all patients with cirrhosis developing COVID-19.

An increasing number of cases of secondary sclerosing cholangitis following severe COVID-19 is being reported[21]. These patients had extensive intensive care unit (ICU) admission and developed prolonged cholestasis. Some of these cases improved with conservative management, but a case of LT has been reported[22].

SCREENING OF DONORS AND RECIPIENTS

International societies (AASLD, EASL and APASL) released guidance recommending screening of donors and recipients for SARS-CoV-2 with reverse transcription-polymerase chain reaction (RT-PCR) of upper respiratory tract secretions[3-5]. A negative RT-PCR is required within 48 hours from graft retrieval or LT[23]. In view of the high rates of false negative RT-PCR results, AASLD and APASL also recommend screening donors for recent exposure, fever or symptoms suggestive of COVID-19 and utilizing imaging of the chest (chest radiograph or computed tomography). Computed tomography of the chest is being increasingly used in the evaluation of COVID-19 patients, and is able to demonstrate lung changes even before RT-PCR becomes positive[23]. Screening of the recipient is similar and includes molecular testing, history of recent exposure, symptoms/signs and findings on imaging studies.

COVID-19 IN TRANSPLANT RECIPIENTS

It was initially hypothesized that LT recipients with SARS-CoV-2 infection might be at increased risk of death due to age, immunosuppression and metabolic comorbidities. Cohort studies published after the outbreak of the pandemic showed a case-fatality rate of 12%-25% which was not increased compared to the general population[24-32]. Tacrolimus immunosuppression was not found to be associated with the risk of death in the context of SARS-CoV-2 infection, on the contrary, it seemed to be protective as shown in some studies[31]. Age and comorbidities were the main predictors of outcome in most studies, similar to the general population[30]. The main findings of these studies are summarized in Table 1.

An analysis of the ELITA-ELTR COVID-19 registry between March 1 and June 27, 2020 included 243 adult LT recipients with COVID-19 across Europe[31]. Of them, 84% required hospital admission and 19% admission to the ICU. Overall mortality was 20%. Among those requiring ICU admission, the mortality rate was 25%. Respiratory failure was the main cause of death. Age > 70 years, diabetes mellitus and chronic kidney disease were independently associated with the risk of death. Tacrolimus was associated with lower probability of death.

A Spanish cohort study (SETH cohort) reported the outcomes of 111 LT recipients diagnosed with COVID-19. The incidence of SARS-CoV-2 infection in this cohort was almost double compared to the general population. Of them, 86.5% required hospital admission and 10.8% admission to the ICU[24]. Overall mortality rate was 18% and was lower than in the matched general population. Mycophenolate-containing immunosuppression was associated with increased risk of death, but not tacrolimus or everolimus. Immunosuppression withdrawal had no effect on outcome.

Similar results were reported by an international cohort study (18 countries) with 151 LT recipients with COVID-19 against 627 non-transplant COVID-19 patients[29]. Similar to previous reports, 82% of LT recipients required hospital admission. LT recipients were more likely to require ICU admission (28% *vs* 8%). Mortality rate was lower among LT recipients (19% *vs* 27%, $P = 0.046$). When the groups were matched for age, sex and comorbidities, LT was not associated with increased risk of death. Risk factors for death among LT recipients were age, creatinine and non-liver cancer.

Table 1 Severe acute respiratory syndrome coronavirus 2 infection in liver transplant recipients

Ref.	Origin of study population	Number of patients	Hospital admission (%)	ICU admission (%)	Mortality (%)	Risk factors for mortality
Belli *et al*[31]	Europe	243	84	19	20	Age > 70, diabetes mellitus, CKD
Colmenero *et al* [24]	Spain	111	86.5	10.8	18	MMF
Webb *et al*[29]	International (18 countries)	151	82	28	19	Age, creatinine, non-liver cancer
Kates *et al*[25]	United States	482 SOT (73 liver)	78	31	20.5	Age > 65, heart and lung comorbidities, obesity
Rabiee *et al*[26]	United States	112	72.3	26.8	22.3	Liver injury
Ravanan *et al* [28]	United Kingdom	597 SOT			25.8	Age
Becchetti *et al* [32]	Europe	57	72		12	Cancer
Becchetti *et al* [33]	Systematic review	1076	65	23	12.5	Middle-aged men, metabolic comorbidities

ICU: Intensive care unit; CKD: Chronic kidney disease; MMF: Mycophenolate mofetil; SOT: Solid organ transplant.

One study reported on the incidence of acute liver injury (defined by ALT 2-5x ULN) in LT recipients when compared to non-transplant CLD patients with COVID-19[26]. The incidence was lower in LT recipients (47.5% *vs* 34.6%, P = 0.037), but the presence of liver injury in the context of COVID-19 significantly increased the risk of mortality and ICU admission.

A systematic review of 1076 published cases provided more robust evidence on the outcomes of SARS-CoV-2 infection in LT recipients[33]. Majority of patients were male (67%). With regards to established risk factors for COVID-19, 39% had diabetes mellitus type 2, 44% had arterial hypertension, and 16% were obese. Overall, 65% required hospital admission, and 23% of the hospitalized patients required ICU admission. Death was reported in 135 cases. Infection was more common in middle-aged men with metabolic comorbidities. The mortality rate and case-fatality rate were not higher than in the general population. This finding does not confirm the initial concerns regarding COVID-19 course and outcomes in this presumably vulnerable population.

In summary, although the incidence of SARS-CoV-2 infection might be higher in LT recipients, the risk of death or ICU admission does not seem to be higher than in the general population. Age, metabolic comorbidities and cancer, which are established risk factors for severe COVID-19 and mortality, also increase the probability of worse outcomes in LT recipients similarly to the general population.

MANAGEMENT OF IMMUNOSUPPRESSION IN LT RECIPIENTS

Calcineurin inhibitors (CNIs), in particular tacrolimus, are the cornerstone of immunosuppression in LT. They inhibit calcineurin, thereby impairing the transcription of interleukin-2 and several other cytokines in T lymphocytes. CNIs form a complex with intracellular cyclophilin, which inhibits nuclear factor of activated T-cells (NFAT) resulting in inhibition of cytokine transcription and T-cell activation[34]. Tacrolimus is associated with increased susceptibility to infections, and risk of nephrotoxicity, neurotoxicity, diabetes mellitus and hypertension. Diabetes and hypertension are established risk factors for severe COVID-19. Renal dysfunction is not uncommon among patients with COVID-19, hence tacrolimus immunosuppression could theoretically increase this risk.

The initial concerns regarding the risk of severe COVID-19 and death in the context of immunosuppression in LT recipients were not confirmed by subsequent published evidence. Despite concerns, complete withdrawal of immunosuppression was rarely adopted and only in extremely severe cases. The ELITA-ELTR COVID-19 registry study demonstrated that tacrolimus was associated with lower risk of mortality [hazard ratio (HR) 0.55, 95%CI: 0.31–0.99] raising the possibility of a protective effect against SARS-CoV-2[31]. Tacrolimus dose was maintained in majority of patients who did not require hospitalization, whereas those with more severe disease that required hospital admission, and even more so those who required ICU admission, were more likely to have the dose adjusted or temporarily interrupted. This effect of calcineurin inhibitors might be mediated by inhibition of CoV growth *via* the cyclophilin pathway, and modulation of T-cell activation[35,36]. This potential protective effect was also demonstrated in the SETH cohort and the smaller COVID-LT study[24,33]. A systematic review and

meta-analysis of 11 cohort studies (published in the form of Letter to the Editor) showed that tacrolimus in SOT recipients was not associated with higher risk of severe COVID-19 (odds ratio (OR) 1.31, 95%CI 0.47–3.69) or increased mortality (OR 1.11, 95%CI 0.63–1.92)[37].

An important aspect raised in a small cohort study is monitoring of tacrolimus levels during SARS-CoV-2 infection. The latter might be associated with CYP3A4 suppression due to increased cytokine circulation. Tacrolimus is metabolized by CYP3A4. Out of 14 post-LT patients on stable tacrolimus immunosuppression, 13 experienced a significant increase in tacrolimus levels (up to 2-fold) during hospitalization for COVID-19 requiring a reduction in dose by nearly 50%[38]. The findings of this study raise awareness with regards to close drug level monitoring and dose adjustments in the context of SARS-CoV-2 infection.

Mycophenolate mofetil (MMF) inhibits lymphocyte proliferation. SARS-CoV-2 has a direct cytotoxic effect on CD8+ lymphocytes. SARS-CoV-2 infection in the context of MMF immunosuppression could have a synergistic effect on lymphocyte inhibition[34]. Data regarding the effect of MMF indicate a potential negative impact on the course of COVID-19. In the SETH cohort, patients receiving MMF had a more severe course of the disease, and this was more evident for doses higher than 1000 mg/d[24]. MMF was an independent predictor of mortality. This observation could be interpreted by the cytostatic effect that MMF exerts on activated lymphocytes, which alongside the cytotoxic effect of SARS-CoV-2 on the same target, might result in worse outcomes[39,40]. On the other hand, complete withdrawal of MMF at diagnosis ameliorated the risk of severe COVID-19. The most up-to-date EASL guidance recommends dose reduction or temporary discontinuation of antimetabolites (*e.g.*, azathioprine or MMF)[6] in patients with SARS-CoV-2 infection.

Complete withdrawal of immunosuppression does not seem to be associated with improved prognosis, hence is not encouraged[41]. However, immunosuppression might be associated with prolonged viral shedding following SARS-CoV-2 infection[42]. The currently available data indicate that comorbidities, which are not uncommon among LT recipients, rather than immunosuppression per se, increase the risk of severe COVID-19 and death. Although data are not extensive, CNI immunosuppression might reduce the risk of severe disease and fatal outcomes presumably by suppressing the augmented immune response precipitated by SARS-CoV-2. MMF at high doses might be associated with disease severity. It should be taken into consideration that reduction in immunosuppression is associated with risk of acute cellular rejection and graft loss. In this context, most international societies recommend against modifications of CNI immunosuppression. MMF reduction or temporary withdrawal is justified in the context of moderate-severe disease. Tacrolimus has numerous drug-to-drug interactions, and vigilance is required with drugs used in the context of COVID-19, such as tocilizumab and ritonavir-boosted nirmatrelvir[43].

IMMUNITY AND VACCINATION IN LT RECIPIENTS

The rapid spread of SARS-CoV-2 has led to the exceptionally fast development of vaccines with proven short-term safety and efficacy. In LT recipients, immunosuppressive therapy might be associated with impaired immune response to vaccination and lower immunogenicity than in immunocompetent individuals. Live attenuated vaccines are usually avoided after LT unless the benefit of vaccination outweighs the associated risks. Vaccines are also avoided in the first 3-6 mo after LT, which corresponds to the period of maximal immunosuppression, because of concerns regarding attenuated immune responses to vaccination[44]. Another theoretical concern is that immune responses to vaccines might trigger immune-mediated rejection, although this has not been confirmed in a meta-analysis[45]. EASL recommends that vaccination should be completed prior to LT whenever possible. Vaccines against SARS-CoV-2 are either mRNA or nonreplicating viral vector vaccines, which are safe in the context of immunosuppression.

With regards to COVID-19 vaccines, clinical trials have not included transplant patients receiving immunosuppressive therapy. Long-term safety and duration of protection in this population remains unclear. The ORCHESTRA SOT recipients cohort assessed antibody response after the first and second dose of mRNA vaccine[46]. The analysis included 1062 SOT patients (liver, 17.4%) and 5045 health care workers. The antibody response was significantly lower in SOT recipients (52.3% *vs* 99.4%), and the antibody levels were significantly lower in the same group. Predictors or better response were interval ≥ 3 years, liver transplant and azathioprine. A study of 35 LT recipients demonstrated partial antibody response to inactivated vaccines[47]. Interkeukin-2 receptor induction therapy and a shorter time after LT were associated with lower antibody response. These findings raise the possibility that booster vaccines might be required in LT recipients. These results were confirmed in a subsequent meta-analysis of 4191 CLD patients and LT recipients that showed antibody response rate after two doses of vaccine of 95% and 66%, respectively[48].

The suboptimal response to vaccination is associated with increased risk of breakthrough infections. A study that included 77 fully or partially vaccinated and 220 unvaccinated SOT recipients with SARS-CoV-2 infection, showed similar disease severity and mortality rates in the two groups[49]. A larger study of 1668 SOT recipients showed a 73% reduction in SARS-CoV-2 infection rate and 76% reduction

in mortality among fully vaccinated patients[49]. Fully vaccinated patients who acquired SARS-CoV-2 infection were less likely to have severe/critical COVID-19 or die compared to not fully vaccinated (22% *vs* 37%, and 0% *vs* 6.7%, respectively). Completion of vaccinations is likely to be critical in this population.

A third SARS-CoV-2 vaccine dose may confer additional benefit in SOT recipients, although still suboptimal compared to the healthy population. In a small cohort of 47 SOT recipients, a third dose increased median total anti-spike IgG (1.6-fold) and neutralizing antibodies (1.4-fold against delta)[50]. It is noteworthy that 32% had no detectable neutralizing antibodies against delta after third vaccination compared to 100% controls. Presence of neutralizing antibodies correlated with anti-spike IgG > 4 Log10 (AU/mL). The same researchers explored the effect of a fourth dose in the same population, and found that it increases anti-spike IgG and neutralizing capacity against many variants of concerns, with the exception of omicron against which neutralization remained poor[51].

A large meta-analysis including 11 713 SOT recipients demonstrated that the response for anti-spike antibodies after mRNA vaccine was 10.4% for 1 dose, 44.9% for 2 doses, and 63.1% for 3 doses[52]. Factors associated with poor antibody response were older age, deceased donor status, antimetabolite use, recent rituximab exposure and recent antithymocyte globulin exposure. The role of MMF as a negative predictor for antibody response has been demonstrated in further studies[53,54].

In summary, vaccination against SARS-CoV-2 confers some protection in SOT recipients, which is lower compared to the healthy population. Booster doses can improve neutralizing capacity, however, this remains suboptimal[55]. In this context, additional protective measures beyond vaccination are necessary in SOT recipients. EASL recommends vaccination against SARS-CoV-2 after the first 3-6 mo following LT, because vaccination in the context of high immunosuppression might not be effective[44]. In this setting, vaccination of household members is highly recommended. In the first phases of the pandemic, priority for vaccination was given to healthcare professionals caring for transplant patients in an effort to protect this vulnerable population.

TRANSPLANT FROM SARS-COV-2 POSITIVE DONORS

The initial response of transplant societies to the challenges posed by COVID-19 pandemic was to recommend testing for SARS-CoV-2 RNA in donors/recipients before transplant, and to recommend against LT in cases of positivity. In the course of the pandemic, some centers started performing life-saving LT for high-risk patients utilizing grafts from SARS-CoV-2 positive donors to recipients with active or resolved infection[56]. A multicenter Italian study included 10 LTs from donors with active COVID-19[56]. Two recipients were SARS-CoV-2 RNA positive at the time of LT. None of the remaining 8 recipients developed SARS-CoV-2 RNA positivity. Eight recipients had IgG antibodies against SARS-CoV-2. SARS-CoV-2 RNA was not detected in donor liver tissue at the time of LT. This study introduced the concept that using grafts from SARS-CoV-2 positive donors might be a safe practice, particularly in patients who are the highest need for LT.

The safety of this practice was confirmed in smaller case series. A series from the US with 5 SOTs (2 livers, 1 simultaneous liver-kidney, 1 kidney and 1 simultaneous kidney-pancreas) from SARS-CoV-2 positive donors to negative recipients showed no risk of transmission to recipients[57]. SARS-CoV-2 RNA was not detected in allograft biopsies.

A systematic review of all SOT from past or active SARS-CoV-2 infected donors until December 2021, included 69 recipients who received 48 kidneys, 18 livers and 3 hearts from 57 donors, and 6 additional lung transplants[58]. Ten of 57 (17.5%) donors had active COVID-19 and 18 had detectable SARS-CoV-2 RNA. Viral transmission was not documented among non-lung SOT recipients. However, viral transmission occurred in three lung recipients, who developed COVID-19 symptoms, and one of them subsequently died. Strategies to mitigate the risk of donor/graft-recipient transmission potentially include SARS-CoV-2-directed monoclonal antibody therapy and/or pre-emptive remdesivir administration, although the efficacy of this approach needs to be confirmed[59].

Decision-making regarding SOT from SARS-CoV-2 positive donors should take into consideration the risk of transmission/acquisition and the sequelae of developing COVID-19, as well as the risk of disease progression and death associated with the underlying disease[60]. Patients with cirrhosis, and particularly those with decompensated disease, who develop COVID-19 are at high risk of death. On the other hand, patients on the waiting list are at risk of death unless they are offered life-shaving LT, and the suspension of LT activity has led to increased mortality on the waiting list. Utilizing non-lung grafts from carefully selected infected donors might benefit patients who are at the highest risk of death without immediate transplant. Although this practice seems to be safe based on limited currently available data, patients and their families should be informed and actively involved in shared decision-making.

TRANSPLANT OF SARS-COV-2 POSITIVE RECIPIENTS

LT following recovery from COVID-19 has been a challenge as the appropriate time interval is not well defined as yet. Several cases of recipients with previous or active SARS-CoV-2 infection have been reported[61-63]. The decision to proceed to LT was made on a case-by-case basis taking into consideration the risk of death without immediate LT. The largest case series included 14 patients who received LT following symptomatic SARS-CoV-2 infection, 4 of whom had detectable RNA at the time of LT[64]. One recipient who was negative at the time of LT became positive 9 days post-LT. None of the patients developed SARS-CoV-2-related complications. In another case series, 4 patients received LT 2 weeks after SARS-CoV-2 positivity and 2 patients 4 weeks after a positive test[65]. One recipient died secondary to sepsis. Despite the encouraging results, there have been two reports of portal vein thrombosis and hepatic artery thrombosis in SARS-CoV-2 positive recipients of LT[66,67].

SARS-CoV-2 RNA negativity has been proposed as a prerequisite for proceeding safely with LT, and a time interval of 2-4 wk between resolution of symptoms and LT has been also proposed[14]. However, prolonged SARS-CoV-2 RNA shedding can have an impact on decisions to proceed and delay life-saving LT. Therefore, the absence of severe COVID-19 symptoms, in particular respiratory complications, might be a more important parameter in decision-making than RNA negativity per se. More evidence is required to form more specific guidance in that direction.

CONCLUSION

Since March 2020, the transplant community has faced unprecedented challenges derived from very limited resources and risk of transmission among patients and healthcare workers. The immediate response was suspension of activities that required face-to-face contact, conversion to technology-assisted remote consultations and suspension of transplant activity for most LT centers. Published evidence demonstrated that patients with CLD, especially those with more advanced stages of the disease, were at higher risk for severe COVID-19 and death. In-person consultations and LT were reserved for selected patients when the risk associated with the underlying liver disease outweighed the risk associated with SARS-CoV-2 transmission/acquisition. In the course of the pandemic, SARS-CoV-2 testing, antiviral treatments and vaccines became available and changed outcomes and practices. Many LT centers resumed transplant activity, though at different paces. Increasing evidence did not show that LT recipients are at increased risk of severe COVID-19 or death, and immunosuppression not only does not increase the risk, but might be protective against the immune-mediated sequalae of the virus. Our understanding of utilizing grafts from SARS-CoV-2 positive donors or transplanting SARS-CoV-2 positive recipients has increased dramatically and allowed a life-saving procedure to be performed for patients who might otherwise have died due to their liver disease. Preliminary data confirm the short-term safety of vaccines, but also showed a partial antibody response in LT recipients. There is no doubt that we need more data to form evidence-based guidance in areas such as: (1) Optimal and appropriate use of novel telemedicine technologies; (2) Balancing the risk from the underlying CLD and the rapidly spreading virus; (3) Continuing transplant activity without compromising safety for patients and workforce; (4) Utilizing grafts from infected donors to address shortage of grafts; (5) Transplanting actively or recently infected recipients who might otherwise die; (6) Managing immunosuppression in patients who acquire the infection; (7) Safety of antiviral therapies in patients with CLD and transplant recipients; (8) Schedule for vaccination and the need for booster doses; and (9) Long-term safety of vaccines.

The COVID-19 pandemic has provided lessons with regards to rapid remodeling of care in the context of a pandemic with a view to reducing the risk for vulnerable patient groups such as transplant candidates and recipients.

FOOTNOTES

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Abstract

Liver transplantation is a major abdominal operation and the intimate anatomic relation of the liver with the right hemidiaphragm predisposes the patient to various manifestations in the chest cavity. Furthermore, chronic liver disease affects pulmonary function before and after liver transplantation resulting in a considerable percentage of patients presenting with morbidity related to chest complications. This review aims to identify the potential chest complications of surgical interest during or after liver transplantation. Complications of surgical interest are defined as those conditions that necessitate an invasive procedure (such as thoracocentesis or a chest tube placement) in the chest or a surgical intervention performed by a thoracic surgeon. These complications will be classified as perioperative and postoperative; the latter will be categorized as early and late. Although thoracocentesis or a chest tube placement is usually sufficient when invasive measures are deemed necessary, in some patients, thoracic surgical interventions are warranted. A high index of suspicion is needed to recognize and treat these conditions promptly. A close collaboration between abdominal surgeons, intensive care unit physicians and thoracic surgeons is of paramount importance.

Key Words: Surgical chest complications; Liver transplantation; Chest related morbidity; Multidisciplinary treatment; Surgery

Core Tip: Chest complications during and after liver transplantation significantly affects the surgical and hospitalization outcomes. This minireview focuses on surgical chest complications for transplant patients and categorizes them by time of appearance. This paper may be a helpful guide and tool for medical students, members of the transplantation team and all the collaborative specialties to recognize early chest complications and plan the appropriate treatment.

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INTRODUCTION

The diaphragm is the boundary between the thoracic and abdominal cavities. Yet, it is common in everyday clinical practice to observe pathologies that originate in one cavity impacting the other[1]. Liver transplantation is a major abdominal operation and the proximity of the operating field with the right hemidiaphragm predisposes it to various manifestations in the chest cavity. Furthermore, chronic liver disease affects pulmonary function before and after liver transplantation resulting in a considerable percentage of patients presenting with morbidity related to chest complications. Age, model for end stage liver disease (MELD) score, preexisting lung disorders and perioperative events, particularly transfusion, contribute to these complications[2]. Indeed, pulmonary complications constitute a significant problem after liver transplantation[3-5]. In one retrospective study enrolling 135 patients, the first postoperative chest roentgenogram was within normal limits in less than half of the cases[6]. In another cohort of adult-to-adult living donor liver transplantation, chest complications were observed in 19.8% of recipients[7]. In the retrospective study by Panfili *et al*[8], pulmonary complications were frequently revealed on imaging during the first postoperative week.

This review aims to identify the potential chest complications of surgical interest during or after liver transplantation. Complications of surgical interest are defined as those conditions that necessitate an invasive procedure (such as thoracocentesis or a chest tube placement) in the chest or a surgical intervention performed by a thoracic surgeon. These complications will be classified as perioperative and postoperative; the latter will be categorized as early and late.

PERIOPERATIVE COMPLICATIONS

Intraoperative pneumothorax is a well described complication of surgery with liver transplantation not being an exception and should be promptly recognized and treated as it can result in life-threatening tension pneumothorax. Pneumothorax can occur because of a bleb rupture, a tracheobronchial trauma during orotracheal intubation, an accidental lung puncture during central venous catheter placement or diaphragm perforation during dissection and barotrauma. Bozbas *et al*[9] described another mechanism during liver transplantation. After the extraction of a voluminous native liver, the rapid expansion of the right lower lobe resulted in a massive air leak, probably due to the development of important shear forces that damaged the pulmonary parenchyma. The insertion of a chest tube is the first therapeutic measure, while persistent air leaks or tracheobronchial lacerations should be treated accordingly.

POSTOPERATIVE COMPLICATIONS

Early postoperative complications

The most typical early postoperative complication is pleural effusion with an estimated incidence of 32%-47%[9-11]. It occurs more frequently on the right side, with left-sided occurrence being rare. Its pathogenesis is multifactorial. Ritschl *et al*[12] identified the following mechanisms responsible for the occurrence of pleural effusion: (1) Low serum albumin levels and postoperative hypoproteinemia; (2) High rates of intraoperative blood and fluid transfusions; and (3) Local mechanisms at the right side of the diaphragm. More specifically, the diaphragmatic defects allow fluid migration towards the chest cavity. Moreover, right hemi diaphragmatic paralysis caused by perioperative right phrenic nerve injury results in the right lower lobe atelectasis, favoring the development of pleural effusion.

There is no consensus concerning indications for chest tube placement and the choice of treatment modality depends mostly on clinical experience and individual appreciation. Similarly, there is no recommendation concerning the type and size of the chest tube. Chest tube placement is necessary for

22%-52% of liver recipients. In a large retrospective study analyzing 597 liver recipients,12 patients with effusion were treated by a chest tube and had a higher MELD score. Other significant risk factors are recipient body mass index (BMI), hospitalization status before liver transplantation [home, hospital, intensive care unit (ICU)], number of intraoperative red blood cell transfusions and donor BMI[5]. There are emerging recommendations advocating for preventive right chest tube placement in the early postoperative period since a decrease in infectious pulmonary complications and ICU stay has been observed[12]. However, the potential complications of invasive percutaneous pleural procedures (thoracocentesis and chest tube placement) should also be considered. The more frequent complications are pneumothorax due to accidental lung puncture and hemothorax due to coagulopathy or technical pitfalls causing minor (pleural) or significant (vascular injury most of the time involving an intercostal artery) hemorrhage. In a large retrospective multicentric study, the incidence of hemothorax was 0.42%, and it was more frequent among patients who underwent thoracocentesis[13]. Nearly half of these patients underwent thoracic surgery (thoracotomy or thoracoscopy). This condition was associated with a high (50%) mortality rate. Postoperative hemothorax can also occur after central venous catheter introduction, especially in patients with coagulopathy[13]. Diaphragmatic lacerations or resection during liver transplantation can also result in postoperative hemothorax. The mispositioning of the chest tube (in the subcutaneous tissues or a subdiaphragmatic location) must also be cited. Another complication is re-expansion pulmonary edema, which occurs during the rapid evacuation of massive pleural effusions[14].

Bacterial pneumonia is a common postoperative complication in liver recipients. In the retrospective study of Ma *et al*[15], one-third of patients enrolled developed bacterial pneumonia[15]. This group of patients had an extended hospital stay and more frequent pleural effusions than patients without pneumonia. Without prompt treatment, a parapneumonic pleural effusion can evolve into a pleural empyema, a significant source of morbimortality[16].

Mid-term and chronic postoperative complications

Liver recipients are prone to opportunistic infections because of immunosuppression. Some conditions may affect the lung and cause lung necrosis and cavitation[17]. Consequently, air leaks may result in pneumothorax, pneumomediastinum and subcutaneous emphysema[18,19]. A common pathogen is *Pneumocystis jirovecii,* and treatment is no different than in the general population; watchful waiting, chest tube placement or exploratory thoracoscopy. Pneumocystis pneumonia is a relatively late complication after liver transplantation; however, it can occur at an earlier setting (within 1 to 3 wk postoperatively). Its incidence is very low (inferior to 1% during the 1st year) in patients receiving prophylaxis, while it is estimated to be between 3% and 11% in the absence of prevention[19,20].

Invasive aspergillosis is the second most common fungal infection after liver transplantation and is associated with high mortality rates[21,22]. A high clinical suspicion is warranted, especially in the early postoperative period. A computed tomography scan is beneficial in identifying the characteristic lesions caused by invasive aspergillosis. Antifungal drugs are the mainstay of treatment, but lung resection can be curative in selected cases as in the case reported by Abe *et al*[23].

The diaphragm itself can be injured during liver transplantation and result in substantial morbidity, as in the case reported by Rosat *et al*[24]. Their patient experienced a left diaphragmatic herniation 5 years after orthotopic liver transplantation. This complication is more common in pediatric patients but rare in adult patients. A traumatic dissection and the excessive use of cautery during liver transplantation are factors responsible for the devitalization of the diaphragmatic muscle. The immunosuppression hinders the healing process. The negative intrathoracic pressure combined with the positive intraabdominal pressure results in the defect's enlargement and the migration of the abdominal viscera into the thorax. The clinical spectrum may vary from totally asymptomatic patients or the presence of non-specific digestive symptomatology to life-threatening visceral strangulation. Once a diaphragmatic hernia is detected, elective repair is warranted, and the abdominal approach is privileged over the thoracic, although there is still debate concerning optimal surgical access.

Chronic pleural effusions constitute a significant source of morbidity among liver recipients. A thick visceral fibrous peel develops if a pleural effusion is untreated, resulting in a trapped lung and restrictive respiratory syndrome. Cuk *et al*[25] provides an overview of this entity. In their retrospective study, the incidence of the trapped lung in patients with persistent pleural effusion was 21.4%. These patients present increased mortality, extended hospital stay and more surgical interventions in the chest. In this cohort, nearly all pleural effusions were exudates, which support the hypothesis that a chronic inflammatory process occurs in the pleural cavity resulting in the migration of fibroblasts and the development of the pleural peel. Parapneumonic pleural effusions, especially pleural empyema, are a major cause of trapped lung occurrence. Intraabdominal sepsis is a predisposing factor for developing pleural empyema[1]. A frequent pitfall while treating these patients is the false diagnosis of pneumothorax after a thoracentesis for pleural effusion. It is instead a suboptimal lung expansion rather than a true pneumothorax. Sometimes the thickened visceral pleura is visualized in the chest roentgenogram and the correct diagnosis can be established, avoiding thus unnecessary additional pleural interventions such as chest tube placement and elevated suction levels that can result in a lung tear. Shirali *et al*[16] analyzed the outcomes of 33 liver recipients with pleural space complications who necessitated a thoracic surgical intervention due to chronic pleural effusion and empyema. The most common thoracic

Table 1 List of complications and prevention measures

Timing of complication	Type of complication	Prevention measures
Intraoperative	Pneumothorax	High level of suspicion
		Cautious OT intubation
		CVC placement under echography guidance
		Low airway pressures during mechanic ventilation
		Closure of diaphragmatic defects encountered during LTx
Early postoperative	Pleural effusion	Correction of hypoproteinemia
		Limited perioperative blood transfusions
		Proper surgical technique
		Preventive chest tube placement
	Pneumothorax	Echographic guidance for percutaneous pleural procedures
	Hemothorax	Correction of coagulopathy
		Echographic guidance for percutaneous pleural procedures
		Proper surgical technique during LTx
	Atelectasis	Pain management
		Chest physiotherapy
		Drainage of pleural effusions
	Chest tube misplacement	Proper surgical technique
	Re-expansion pulmonary edema	Staged evacuation of massive pleural effusions
	Bacterial pneumonia	Chest physiotherapy
		Early extubation and weaning from mechanical ventilation
		Prevention and treatment of atelectasis
	Pleural empyema	Drainage of parapneumonic pleural effusions
Mid-term and chronic	Opportunistic infections causing lung necrosis and cavitation	Proper prophylaxis
	Invasive aspergillosis	High clinical suspicion
		Prompt imaging (CT scan)
	Diaphragmatic herniation	Proper surgical technique during LTx
	Trapped lung	Prompt treatment of pleural effusion before chronicity
		Radical treatment of pleural empyema

CT: Computed tomography; CVC: Central venous catheter; LTx: Liver transplantation; OT: Orotracheal.

operations were decortication and empyema evacuation. The 30-d morbidity was 69.7%. The authors concluded that developing pleural space complications requiring surgery in orthotopic liver transplant recipients suggests a poor prognosis.

CONCLUSION

Surgical chest complications following liver transplantation are prevalent and constitute a significant source of morbidity and mortality (Table 1). Most of these complications in liver recipients do not differ from the formal population, whilst others are specific to the transplanted patients primarily because of the immunosuppression. A thoracocentesis or a chest tube placement is usually sufficient when invasive measures are deemed necessary. Nevertheless, in some patients, thoracic surgical interventions are warranted. A high index of suspicion is necessary to recognize and treat these conditions promptly. A close collaboration between abdominal surgeons, ICU physicians and thoracic surgeons is of paramount importance.

FOOTNOTES

Author contributions: Agrafiotis AC, Poras M and Katsanos G were involved in the conception and design; Karakasi KE and Neiros S were administrative support; Poras M, Karakasi KE and Neiros S contributed to the provision of the study material; Poras M, Karakasi KE and Neiros S were involved in the collection and assembly of data; Agrafiotis AC, Vasileiadou S and Katsanos G were involved in the data analysis and interpretation; and all authors wrote the manuscript and approved the final manuscript.

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ORIGINAL ARTICLE

Observational Study

Effects of an active lifestyle on the physical frailty of liver transplant candidates

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Abstract

BACKGROUND

Liver transplantation is the most important therapeutic intervention for end-stage liver disease (ELD). The prioritization of these patients is based on the model for end-stage liver disease (MELD), which can successfully predict short-term mortality. However, despite its great validity and value, it cannot fully incorporate several comorbidities of liver disease, such as sarcopenia and physical frailty, variables that can sufficiently influence the survival of such patients. Subsequently, there is growing interest in the importance of physical frailty in regard to mortality in liver transplant candidates and recipients, as well as its role in improving their survival rates.

AIM

To evaluate the effects of an active lifestyle on physical frailty on liver transplant candidates.

METHODS

An observational study was performed within the facilities of the Department of Transplant Surgery of Aristotle University of Thessaloniki. Twenty liver transplant candidate patients from the waiting list of the department were included in

the study. Patients that were bedridden, had recent cardiovascular incidents, or had required inpatient treatment for more than 5 d in the last 6 mo were excluded from the study. The following variables were evaluated: Activity level *via* the International Physical Activity Questionnaire (IPAQ); functional capacity *via* the 6-min walking test (6MWT) and cardiopulmonary exercise testing; and physical frailty *via* the Liver Frailty Index (LFI).

RESULTS

According to their responses in the IPAQ, patients were divided into the following two groups based on their activity level: Active group (A, 10 patients); and sedentary group (S, 10 patients). Comparing mean values of the recorded variables showed the following results: MELD (A: 12.05 ± 5.63 *vs* S: 13.99 ± 3.60; $P > 0.05$); peak oxygen uptake (A: 29.78 ± 6.07 mL/kg/min *vs* S: 18.11 ± 3.39 mL/kg/min; $P < 0.001$); anaerobic threshold (A: 16.71 ± 2.17 mL/kg/min *vs* S: 13.96 ± 1.45 mL/kg/min; $P < 0.01$); 6MWT (A: 458.2 ± 57.5 m *vs* S: 324.7 ± 55.8 m; $P < 0.001$); and LFI (A: 3.75 ± 0.31 *vs* S: 4.42 ± 0.32; $P < 0.001$).

CONCLUSION

An active lifestyle can be associated with better musculoskeletal and functional capacity, while simultaneously preventing the evolution of physical frailty in liver transplant candidates. This effect appears to be independent of the liver disease severity.

Key Words: Liver transplantation; Frailty; Six-minute walk test; Cardiopulmonary exercise testing; Exercise therapy; Observational study

Core Tip: This study highlights the importance of regular physical activity and exercise of low and medium intensities in the routine of liver transplant candidates. As liver transplantation is a highly demanding procedure, imposing a significant amount of stress across every system, physical frailty is steadily proving to be a factor of great importance, not only due to its role in mortality prediction but also due to its potential improvement *via* preoperative interventions.

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INTRODUCTION

Liver transplantation is the greatest tool for the management and treatment of end-stage liver disease (ELD)[1]. Nevertheless, there is a worldwide gap between the demand for liver transplants and the availability of organ donations[2], increasing the need for optimization of candidate prioritization and organ distribution[3]. It is well established in the literature that the model for end-stage liver disease (MELD) score is a unique tool in this direction[4]. Nevertheless, there are further clinical parameters that may play a substantial role in the waiting list mortality, especially in patients with lower MELD scores [5].

Sarcopenia is related to waiting list mortality and survival after liver transplantation[6-9]. Furthermore, sarcopenic candidates require longer inpatient care, not only on the intensive care unit level but also in ward-based care[10,11]. Functional capacity has also been described as a useful predictive tool, as it is related to better postoperative survival rates and required length of stay[12,13]. It is worth noting that cardiopulmonary exercise testing (CPET) is used quite extensively in other transplant candidates; nevertheless, it is not equally popular in the prelisting assessment of a liver transplant candidate[14,15]. One of the main disadvantages of CPET is the need for expensive equipment within a laboratory setting with equally trained healthcare professionals. The 6-min walking test (6MWT) is mentioned as an alternative assessor of functional capacity in the literature[16], the lower values of which are associated with increased mortality both in the waiting list and after transplantation[17,18].

Furthermore, physical frailty has been gaining growing attention due to its correlation with mortality prediction in liver transplantation. Physical frailty is a clinical syndrome that is correlated with both sarcopenia and functional capacity and is characterized by reduced strength and stamina, as well as increased mortality risk and postoperative dependence[19-21]. The Liver Frailty Index™ (LFI™) is an

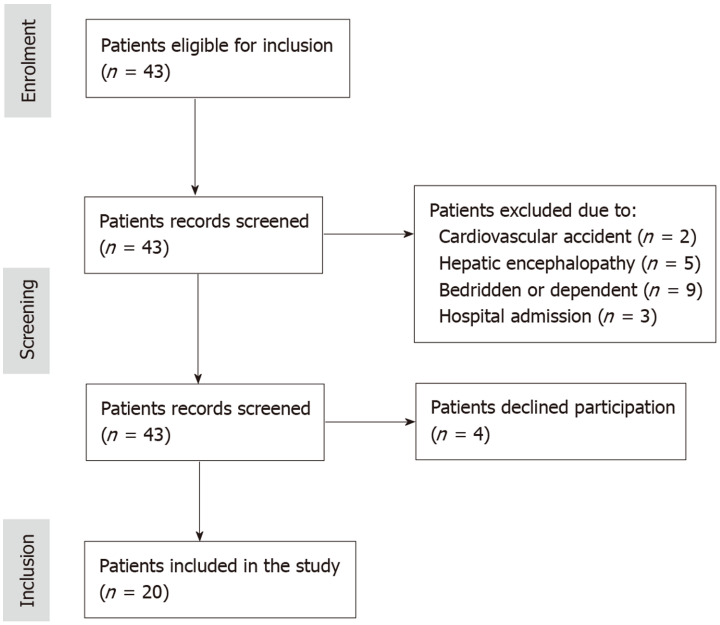

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Figure 1 Recruitment of patients for the observational study.

innovative tool, developed by Lai *et al*[22], which appears to significantly improve mortality prediction when combined with MELD, especially in patients with low MELD scores[22,23].

The course of liver disease is well correlated with a gradual diminishment of both functional capacity and musculoskeletal robustness. Taking the importance of the above clinical tools into consideration, not only on mortality prediction but also on patient prioritization, this observational study evaluated the effects of an active lifestyle on indices of physical functioning, in order to identify the effects of physical activity on physical frailty and cardiovascular capacity on liver transplant candidates.

MATERIALS AND METHODS

Study population

Liver transplant candidates from the Department of Transplant Surgery of the Aristotle University of Thessaloniki in the Hippokration General Hospital of Thessaloniki were recruited for the study. Patients enlisted in the liver transplantation waiting list registry, according to criteria of the Hellenic Transplantation Organization, were deemed eligible for enrollment. The observational study design excluded patients with other comorbidities hindering their activity level or the ones having received instructions from their physicians to limit it, due to a recent acute deterioration of their condition.

Therefore, patients were deemed ineligible if one of the following was true: Recent cardiovascular incident in the preceding 12 mo; grade 2 or higher hepatic encephalopathy; bedridden patients with complete dependence; and recent hospital admission requiring longer than 72 h of inpatient care due to condition deterioration.

A total of 43 patients had their records screened to be included in the observational study. Following the exclusion criteria described above, 19 patients were excluded. In particular, 2 patients were recovering from a recent cardiovascular incident, 5 were classified with hepatic encephalopathy of grade 2 or higher, 9 were completely bedridden and unable to self-accommodate everyday needs, and finally 3 required long inpatient care within the past 3 mo. The remaining 24 patients were contacted and informed about the study; four declined participation. The recruitment process diagram is presented in Figure 1. All patients participating in the study were informed about the purpose and methodology of the study and provided written informed consent. The study protocol was approved by the Department's Ethics Committee of Aristotle University of Thessaloniki (Protocol No. 65/2021). The study was performed from February 16 to June 21, 2021.

Activity level evaluation

The self-administered, short form of the International Physical Activity Questionnaire (IPAQ) was used to evaluate the activity level of the participants. The IPAQ questionnaire was completed by the participants independently, without any guidance from the study investigators. It includes seven questions, collecting self-reported information for the number of days and time spent doing vigorous

Table 1 Study participants' age, sex, and primary cause of end-stage liver disease

No.	Age	Sex	Primary cause
1	32	Female	Primary biliary cholangitis
2	53	Female	Liver hemangioma
3	38	Female	Liver hemangioma
4	53	Male	Hepatitis B virus
5	38	Male	Autoimmune hepatitis
6	51	Female	Hepatocellular carcinoma
7	32	Male	Hepatocellular carcinoma
8	61	Female	Hepatitis B virus
9	63	Male	Non-alcoholic fatty liver disease
10	47	Female	Hepatic cystadenomas
11	62	Female	Primary biliary cholangitis
12	54	Male	Hepatitis C virus
13	52	Male	Alcohol-related liver disease
14	63	Male	Alcohol-related liver disease
15	49	Female	Hepatitis B virus
16	52	Male	Hepatitis B virus
17	50	Male	Hepatitis B virus
18	52	Female	Non-alcoholic fatty liver disease
19	50	Male	Non-alcoholic fatty liver disease
20	50	Female	Primary biliary cholangitis

activity, moderate physical activity, walking, and sitting each day during the course of 1 wk[24,25]. The participants completed the Greek version of the questionnaire[26]. Questions 1 and 2 were about the days and time spent on vigorous activities, questions 3 and 4 referred to activities of moderate intensity, questions 5 and 6 referred to walking, and question 7 asked about the time spent sitting. This tool classifies respondents into three categories of physical activity, namely low, moderate, and high, according to the following criteria[27]: (1) Category 1 - low, consisting of individuals failing to meet any of the criteria detailed below; (2) Category 2 - moderate, consisting of individuals that fulfill any of the following three criteria: At least 3 d of vigorous activity, lasting more than 20 min daily; at least 5 d of moderate activity or walking, lasting more than 30 min daily; and at least 5 d of exercise comprising of a combination of walking, moderate, and vigorous activities, equal to 600 metabolic equivalent of task (MET) minutes or more; and (3) Category 3 - high, consisting of individuals that fulfill either of the following: At least 3 d of vigorous activity, reaching at least 1500 MET minutes weekly; and daily exercise comprising of a combination of walking, moderate, and vigorous activities, reaching at least 3000 MET minutes weekly.

Functional capacity evaluation

Two different methods were used to evaluate the functional capacity of participants, namely CPET and the 6MWT. CPET was performed on the Trackmaster Treadmill (Full Vision Inc., Newton, KS, United States), using the Bruce protocol, whereas gas exchange was measured by the MedGraphics Breeze Suite CPX Ultima (Medical Graphics Corp., St. Paul, MN, United States). The test was performed under the supervision of trained personnel and a cardiologist, within the facilities of the Laboratory of Sports Medicine of the Aristotle University of Thessaloniki. Maximal effort was achieved by all participants, upon reaching a respiratory exchange ratio larger than 1.10. Peak oxygen uptake (VO_{2peak}) and anaerobic threshold (AT) were assessed to evaluate the functional capacity of the participants.

Furthermore, a 6MWT was performed indoors by all participants. The testing design included a 30-m long, flat, and circular track, which was clearly marked for every meter. Patients performed the test twice and the longest distance achieved was recorded as their result. They were also instructed to immediately abandon their attempt if they felt unwell or had uncontrollable fatigue. During the 6MWT, patients received verbal encouragement on the 2nd and 4th min of every attempt and a notification when 60 s were left. Pulse oximetry was used to measure the oxygen saturation and heart rate during the test,

Table 2 International Physical Activity Questionnaire responses

No.	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Result
1	0 d	-	2 d	0 h 15 min	5 d	1 h 0 min	8 h 0 min	Moderate
2	2 d	0 h 15 min	4 d	30 min	5 d	1 h 0 min	4 h 30 min	Moderate
3	0 d	-	2 d	0 h 20 min	7 d	1 h 30 min	6 h 0 min	Moderate
4	0 d	-	0 d	-	3 d	0 h 30 min	8 h 0 min	Low
5	0 d	-	3 d	0 h 30 min	3 d	1 h 0 min	6 h 0 min	Moderate
6	0 d	-	2 d	0 h 20 min	4 d	0 h 45 min	6 h 30 min	Moderate
7	0 d	-	3 d	0 h 45 min	4 d	1 h 15 min	4 h 30 min	Moderate
8	0 d	-	2 d	0 h 15 min	2 d	0 h 30 min	7 h 30 min	Low
9	0 d	-	0 d	-	3 d	0 h 15 min	9 h 30 min	Low
10	0 d	-	3 d	0 h 30 min	3 d	0 h 45 min	6 h 15 min	Moderate
11	0 d	-	0 d	-	3 d	0 h 15 min	9 h 15 min	Low
12	0 d	-	2 d	0 h 20 min	3 d	0 h 30 min	6 h 45 min	Low
13	0 d	-	2 d	0 h 15 min	4 d	0 h 20 min	7 h 0 min	Low
14	0 d	-	0 d	-	5 d	0 h 15 min	8 h 0 min	Low
15	0 d	-	0 d	-	3 d	0 h 40 min	7 h 30 min	Low
16	0 d	-	2 d	0 h 20 min	3 d	0 h 30 min	6 h 0 min	Low
17	0 d	-	3 d	0 h 30 min	4 d	1 h 30 min	4 h 0 min	Moderate
18	0 d	-	3 d	0 h 20 min	4 d	1 h 0 min	6 h 0 min	Moderate
19	0 d	-	0 d	-	7 d	1 h 15 min	5 h 30 min	Moderate
20	0 d	-	0 d	-	3 d	0 h 30 min	8 h 0 min	Low

whereas the Borg scale Rating of Perceived Exertion was used to monitor exercise intensity.

Physical frailty evaluation

The LFI was used to evaluate the physical frailty of the study participants[28]. This clinical tool, developed by Lai *et al*[29], includes three tests that assess balance, neuromuscular coordination, and sarcopenia. The three tests are as follows: (1) Hand grip strength (using a dynamometer in the standard position, the participant squeezes the grip three times while the dynamometer rests on no surface); (2) Sit-to-stand test (from sitting position and keeping both arms folded in front of their chest, the participant is timed while standing up and sitting down five consecutive times); and (3) Balance test (the participant is timed standing up in three different balance positions, with feet side-by-side, semi tandem and tandem, while receiving no further support, for a maximum of 10 s).

Statistical analysis

IBM SPSS Statistics, version 25.0 (IBM Corp., Armonk, NY, United States) was used for the statistical analyses. Continuous parameters were compared using the independent samples *t*-test. The values of the parameters of the sample were tested for normal distribution with the Shapiro-Wilk test. Point biserial correlation analysis was used to determine the relationship between activity level and the frailty and functional capacity variables. Difference between values was considered to be of statistical significance for *P* values less than 0.01. All data are presented as the mean ± standard deviation.

RESULTS

General characteristics of patients

Twenty patients were included in the study, all of whom are listed in the waiting list of the Department of Transplant Surgery in the Hippokration General Hospital of Thessaloniki. The majority of patients came from the city of Thessaloniki (n = 9, 45%), whereas the rest were distributed across the Greek mainland and islands. There were 10 male and 10 female patients included in the study, with a median age of 50.1 years. The primary causes of ELD of the participants were hepatitis B (n = 5, 25%), non-

Table 3 Peak oxygen uptake and anaerobic threshold results

No.	Group	VO_{2peak} in mL/kg/min	AT in mL/kg/min
1	Active	29.9	15.8
2	Active	40.8	21.1
3	Active	27.1	18.0
4	Sedentary	18.9	14.8
5	Active	25.7	14.1
6	Active	24.2	15.0
7	Active	39.6	18.8
8	Sedentary	18.4	14.2
9	Sedentary	13.8	12.8
10	Active	22.2	14.2
11	Sedentary	13.2	11.6
12	Sedentary	25.3	17.0
13	Sedentary	20.0	14.7
14	Sedentary	16.9	12.8
15	Sedentary	17.0	13.8
16	Sedentary	19.5	14.0
17	Active	30.0	16.9
18	Active	28.5	16.5
19	Active	29.8	16.7
20	Sedentary	18.1	13.9

AT: Anaerobic threshold; VO_{2peak}: Peak oxygen uptake.

alcoholic fatty liver disease (n = 3, 15%), primary biliary cholangitis (n = 3, 15%), alcohol-related liver disease (n = 2, 10%), liver hemangioma (n = 2, 10%), hepatocellular carcinoma (n = 2, 10%), hepatitis C (n = 1, 5%), autoimmune hepatitis (n = 1, 5%), and hepatic cystadenomas (n = 1, 5%). The mean MELD score for the patients in the study was 13.02 ± 4.71. Demographic details for each patient are listed in Table 1, including the primary cause of ELD per participant.

Activity level

All responses collected *via* the IPAQ can be seen in Table 2. Ten patients were classified as having a moderate physical activity level (category 2), whereas ten patients were found to be in the low physical activity level category (category 1). Using these responses, the sample was divided into two groups; patients with a moderate activity level were characterized as active (A), and patients with low activity level were allocated in the sedentary group (S). The active and sedentary groups were found to be similar regarding their MELD scores (A: 12.05 ± 5.63 *vs* S: 13.99 ± 3.60, respectively; $P > 0.05$).

Functional capacity

All participants successfully completed their CPET, successfully reaching a respiratory exchange ratio equal to 1.10 or higher. No patient had to abandon their examination due to excess fatigue or the presentation of adverse effects. No patient was instructed to terminate the exercise stress test due to changes to their electrocardiogram.

The mean VO_{2peak} achieved by active participants was higher compared to the mean value recorded by the sedentary group (A: 29.78 ± 6.07 mL/kg/min *vs* S: 18.11 ± 3.39 mL/kg/min, respectively; $P < 0.001$). Similarly, the AT in active subjects was higher than that in their sedentary counterparts (A: 16.71 ± 2.17 mL/kg/min *vs* S: 13.96 ± 1.45 mL/kg/min, respectively; $P < 0.01$). All results for VO_{2peak} and AT are presented in Table 3.

Regarding the 6MWT, all participants successfully completed two attempts, with the longest distance considered the test result. No complication was recorded, and no effort was abandoned due to fatigue or exhaustion. Detailed results per participant are presented in Table 4. The active group covered a larger mean distance on the test compared to the sedentary group (A: 324.7 ± 55.8 m *vs* S: 458.2 ± 57.5 m,

Table 4 Six-minute walking test results

No.	Group	6-min walking test in m
1	Active	396
2	Active	456
3	Active	595
4	Sedentary	250
5	Active	433
6	Active	397
7	Active	429
8	Sedentary	347
9	Sedentary	264
10	Active	502
11	Sedentary	259
12	Sedentary	360
13	Sedentary	431
14	Sedentary	362
15	Sedentary	320
16	Sedentary	330
17	Active	460
18	Active	456
19	Active	458
20	Sedentary	324

respectively; $P < 0.001$).

Physical frailty evaluation

The LFI was used to assess the robustness or frailty of the study participants. Patients successfully completed all exercises after first witnessing a demonstration. The sedentary group was more likely to score a greater LFI score and to be frail, whereas its mean value was above the limit for patient classification as frail compared to the active group, which was more likely to score smaller values (S: 4.42 ± 0.32 *vs* A: 3.75 ± 0.31, respectively; $P < 0.001$). The detailed performance per test is described in Table 5. Patients with a LFI greater than 4.4 were classified as frail[23,29]. No patient from the active group was classified as frail (LFI < 4.4, $n = 10$), whereas 6 patients were found to be frail according to the LFI in the sedentary group (LFI > 4.4, $n = 6$). Mean value comparisons are presented for all variables in Table 6.

Correlation analysis

Pearson correlation analysis was used to determine if disease severity was associated with worse functional capacity or higher frailty scores. Correlation was tested between MELD scores and LFI, VO_{2max}, AT, and 6MWT. No significant correlation was found between MELD and LFI ($r_p = 0.29$, $P > 0.05$), VO_{2max} ($r_p = -0.10$, $P > 0.05$), AT ($r_p = -0.25$, $P > 0.05$) or 6MWT ($r_p = -0.36$, $P > 0.05$).

Point-biserial correlation was run to determine the relationship between the activity level and functional capacity and physical frailty markers. MELD and activity level was not significantly correlated ($r_{pb} = -0.212$, $P > 0.05$), whereas there was significant correlation between activity level and LFI ($r_{pb} = -0.747$, $P < 0.001$), VO_{2peak} ($r_{pb} = 0.781$, $P < 0.001$), AT ($r_{pb} = 0.618$, $P < 0.01$), and 6MWT ($r_{pb} = 0.779$, $P < 0.001$). This relationship is presented in Table 7.

DISCUSSION

According to the results of this observational study, physical activity appears to prevent physical frailty and retain cardiovascular capacity in liver transplant candidates, independent of their MELD score. This can be potentially used as a tool for prehabilitation in listed patients for a liver transplant. Availability of liver transplants has always been well below demand, especially in Greece, with the coronavirus disease

Table 5 Liver Frailty Index test results

No.	Hand grip strength in kg			Sit-to-stand in s	Balance test in s			LFI
	Att. 1	Att. 2	Att. 3		Side-by-side	Semi-tandem	Tandem	
1	18	19	19	12.4	10.0	10.0	10.0	3.95
2	26	26	25	8.5	10.0	10.0	10.0	3.11
3	25	24	24	10.1	10.0	10.0	10.0	3.42
4	19	18	18	16.8	7.9	9.1	8.2	4.76
5	26	27	27	11.0	10.0	10.0	10.0	3.9
6	19	18	19	13.1	9.1	10.0	8.9	4.08
7	30	28	29	10.0	10.0	10.0	10.0	3.71
8	14	14	13	17.2	8.5	9.2	8.1	4.66
9	13	14	14	17.6	8.5	9.4	8.0	4.92
10	18	17	18	13.3	9.0	10.0	9.0	4.15
11	12	11	12	16.1	9.3	10.0	9.0	4.62
12	20	19	19	11.9	10.0	10.0	10.0	4.23
13	26	27	28	12.2	10.0	10.0	10.0	4.00
14	22	21	21	11.8	10.0	10.0	10.0	4.15
15	18	18	17	12.8	10.0	10.0	10.0	4.03
16	18	19	18	13.0	9.5	9.8	8.9	4.42
17	27	27	26	9.4	10.0	10.0	10.0	3.70
18	19	20	20	11.3	10.0	10.0	10.0	3.80
19	27	28	27	9.8	10.0	10.0	10.0	3.74
20	15	14	14	14.2	9.0	9.4	8.4	4.43

Att: Attempt; LFI: Liver Frailty Index.

Table 6 Mean values of peak oxygen uptake, anaerobic threshold, 6-min walking test and, Liver Frailty Index

Value	Active group	Sedentary group
VO_{2peak} in mL/kg/min	29.78 ± 6.07[a]	18.11 ± 3.39[a]
AT in mL/kg/min	16.71 ± 2.17[b]	13.96 ± 1.45[b]
6MWT in m	458.2 ± 57.5[a]	324.7 ± 55.8[a]
LFI	3.75 ± 0.31[a]	4.42 ± 0.32[a]

[a]$P < 0.001$.
[b]$P < 0.01$.
6MWT: 6-min walking test; AT: Anaerobic threshold; LFI: Liver Frailty Index; VO_{2peak}: Peak oxygen uptake.

2019 pandemic posing an even greater challenge. This study was driven by the need to identify possible important and potentially modifiable clinical parameters, which, when used in concordance with the MELD score, would be able to optimize the capacity of a medium-size transplant center[3,6].

According to the LFI, 30% (n = 6) of the study participants are classified as frail (LFI > 4.4)[23,29], a percentage that is concordant with the results of a previous review study[30]. Physical frailty has been associated with increased waiting list mortality, independently of the MELD score, presence of ascites or hepatic encephalopathy[31]. Furthermore, in the postoperative spectrum, frailty has been associated with increased 30-d mortality, extended inpatient and intensive unit care[32], increased rates of acute cellular rejection[33], increased dependency[34,35], and vertebrae fractures[36]. Constructed, the home-based exercise program appears to positively influence frailty indexes and partially restore musculo-skeletal robustness[37-40]. Our study compared each patient's physical activity level with their physical

Table 7 Correlation analysis between activity level and model for end-stage liver disease score peak oxygen uptake, anaerobic threshold, 6-min walking test, and Liver Frailty Index

Value	r_{pb}	*P* value
MELD	-0.212	> 0.05
VO_{2peak} in mL/kg/min	0.781	< 0.001
AT in mL/kg/min	0.618	< 0.01
6MWT in m	0.779	< 0.001
LFI	-0.747	< 0.001

6MWT: 6-min walking test; AT: Anaerobic threshold; LFI: Liver Frailty Index; MELD: Model for end-stage liver disease; r_{pb}: Point-biserial correlation coefficient; VO_{2peak}: Peak oxygen uptake.

frailty. Although patients were not under professional trainer guidance, frequent activity such as walking and gardening, appeared to have a preventive effect on the evolvement of physical frailty. This could potentially provide clinicians with an important tool in the preoperative treatment of candidates, while on the waiting list for a transplant, being a tool that could potentially improve transplantation outcomes.

Functional capacity has also been associated with postoperative dependency and mortality. Epstein *et al*[12] described an increased 100-d mortality in patients with lower peak oxygen uptake, whereas other studies have associated a smaller VO_{2peak} with extended intensive care unit stay and mechanical ventilation dependency[41]. Similarly, smaller distances in the preoperative 6MWT have been associated with increased mortality after liver transplantation[42,43]. In 2021, Henrique *et al*[18] identified a statistically significant increased risk of cirrhosis decompensation in patients with values smaller than 401.8 m in the 6MWT, whereas Bhanji *et al*[44] described a double risk of waiting list mortality in patients with values smaller than 250 m and its statistically significant reduction for every 100 m improvement. In our study, active participants were much more likely to record values above 401.8 m (80% *vs* 10%; $P < 0.01$), consistent with the findings of the effects of exercise in liver patients in other studies[45,46].

The inclusion of indexes of frailty and functional capacity in the clinical practice of liver transplantation appears to be a valuable aid in patient prioritization, especially in candidates with low MELD scores[47]. Furthermore, regular physical activity appears to be a valuable tool to improve these modifiable factors. Physical frailty has been reported as reduced in liver transplant candidates through the adoption of an active lifestyle in several studies[48,49], while functional capacity has been reported as similarly improved[45,50]. This can potentially lead to improved survival rates and reduced hospitalization length and readmission rates[51,52]. Our study shares similar results, further supporting the notion that physical activity can have a significant role in preoperative preparation for candidates, potentially achieving improved outcomes. Furthermore, our data suggests that home-based, patient-controlled exercise can have an adequate impact.

The active participants of our study, although not following an organized and formal exercise protocol, had substantially better musculoskeletal and functional status, appeared to be more robust, and could potentially have great tolerance to stressors. This suggests evidence that exercise interventions could have a positive impact on liver transplant candidates, without the need for formal and difficult exercise regimes that bear a higher risk of lower compliance. However, this study had limitations, namely the small sample size and no prospective results. Further data collection and follow-up could confirm the effects of this lifestyle on pretransplantation and posttransplantation survival, dependency, and complications.

CONCLUSION

In conclusion, an active lifestyle can potentially be a tool of preoperative preparation of liver transplant candidates to reduce mortality, hospitalization, and dependencies. Physical frailty and functional capacity can be improved with exercise training interventions. Clinical tools such as the 6MWT and the LFI could be used for better mortality prediction and patient prioritization, which is of significant importance in smaller and medium-sized transplant centers, where organ donation is unable to meet the existing high demand.

ARTICLE HIGHLIGHTS

Research background

Liver transplantation forces a substantial stress on the human physiology, which is even more significant considered the deconditioning that accompanies end-stage liver disease (ELD). Physical frailty has emerged as an important factor both pre- and postoperatively, aiming to improve results and outcomes.

Research motivation

The limited amount of available organ donations in addition to the high demand in liver transplants, highlight the need for proper planning and prioritization, while at the same time working towards further outcome improvement.

Research objectives

The main objective was to identify if an active lifestyle can significantly improve physical frailty and functional capacity in patients with ELD.

Research methods

An International Physical Activity Questionnaire, a functional capacity assessment, and a physical frailty evaluation were utilized.

Research results

There was a statistically significant difference and statistically significant correlation between the activity level and the Liver Frailty Index, the peak oxygen uptake, the anaerobic threshold, and the 6-min walking distance.

Research conclusions

Physical activity can potentially improve functional capacity and frailty in liver transplant candidates.

Research perspectives

Future research should focus on the regimen of the exercise that would be more suitable, or better quantify the amount of physical exercise needed for these patients. Furthermore, the potential use of these markers in survival and outcomes should be evaluated.

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FOOTNOTES

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ORIGINAL ARTICLE

Observational Study

Parvovirus B19 status in liver, kidney and pancreas transplant candidates: A single center experience

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Abstract

BACKGROUND

Parvovirus B19 (B19V) is associated with a wide range of clinical manifestations. The major presentation is erythema infectiosum. However, a persistent infection may cause pure red cell aplasia and chronic anemia in immunocompromized patients. The B19V seroprevalence varies with age and geographical location.

AIM

To determine the B19V serological status and DNAemia in kidney, liver, and pancreas transplant candidates.

METHODS

Patients who underwent kidney, liver, or simultaneous kidney and pancreas/liver

transplantation between January 2021 and May 2022 were included in the study. The serum samples were collected before transplantation. For detection of B19V DNA, a LightMix Kit B19V EC (TIB MOLBIOL, Berlin, Germany) was used. B19V IgM and IgG antibodies were detected using a commercial ELISA test (Euroimmun, Lübeck, Germany).

RESULTS

One hundred and thirty-one transplant candidates were included in the study, 71.0% male, with an average age of 53.27 years ± 12.71 years. There were 68.7% liver, 27.5% kidney, 3.0% simultaneous pancreas/kidney transplant (SPKT), and 0.8% simultaneous liver/kidney transplant recipients. No patients had detectable B19V DNA. B19V IgG seroprevalence was 77.1%. No acute or recent infections were detected (IgM antibodies). There was no difference in the mean age of seronegative and seropositive patients (51.8 years ± 12.9 years *vs* 53.7 years ± 12.7 years, t = -0.603; P = 0.548). Although seropositivity was lower in patients aged less than 30 years (66.6%) compared to the patients aged 30-59 years and > 60 years (80.4% and 78.1%, respectively), this difference was not significant. In addition, there was no difference in seropositivity between male and female transplant candidates, 76.3% and 78.9% (χ^2 = 0.104; P = 0.748). The seroprevalence did not differ among organ recipients, with 77.8%, 80.6%, and 50.0% for liver, kidney, and SPKT, respectively, (χ^2 = 5.297; P = 0.151). No significant difference was found in the seroprevalence in kidney transplant patients according to dialysis modality. Seroprevalence was 71.1% in hemodialysis patients, and 100% in peritoneal dialysis patients (χ^2 = 0.799; P = 0.372).

CONCLUSION

The B19V seroprevalence is expectedly high among kidney, liver, and pancreas transplant candidates, but there are still 22.9% of seronegative individuals who remain at risk for primary disease and severe manifestations. Further research should elucidate the necessity of B19V screening in peri-transplant management.

Key Words: Parvovirus B19; Seroprevalence; DNA; Kidney transplantation; Liver transplantation; Pancreas transplantation

Core Tip: Many liver, kidney, or pancreas transplant recipients are parvovirus B19 seronegative and at risk for primary disease and severe manifestations. Serological studies on pretransplant could simplify the diagnostic work-up of anemia after transplantation in these complex patients.

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INTRODUCTION

Parvovirus B19 (B19V) is a small non-enveloped single-stranded DNA virus of the family *Parvoviridae*, genus *Erythroparvovirus*[1]. It was first discovered in a healthy blood donor[2] and then linked to aplastic crises in children with sickle cell anemia[3]. Subsequently, the major presentation, erythema infectiosum (fifth disease), was described[4]. B19V mainly infects the human erythroid progenitor cells [5]. The cellular receptor is globoside (erythrocyte P antigen), found on erythroid cells, erythroid precursors and red cells of the placenta and fetal myocardium, fetal liver, and some megakaryocytes and endothelial cells[6]. Rarely, individuals may lack blood group P antigen, which confers resistance to B19V infection[7].

In healthy individuals, the disease is often asymptomatic or occurs as a two-phase illness: Fever and non-specific influenza-like symptoms during the early phase of viremia, followed by erythema, arthralgia, or both, at the time of appearance of specific antiviral antibodies[8,9]. The cutaneous manifestations of B19V infection vary. Four basic patterns have been reported: exanthema, gloves-and-socks, periflexural, and palpable purpura[10]. A robust humoral immune response is required to control B19V infection and clear DNAemia. Neutralizing antibodies to B19V structural proteins appear to confer life-long protective immunity[11]. Therefore, in immunocompromized patients unable to mount

sufficient antibody response, the infection may persist and cause pure red cell aplasia and chronic anemia[12,13]. More recently, other disease manifestations have been reported, ranging from hepatitis and myocarditis to meningoencephalitis[14-17].

In the transplant setting, B19V is long known to cause persistent anemia and pure red cell aplasia due to the inability of the immunosuppressed host to clear the virus[18-20]. The epidemiology of B19V infection in solid organ transplant (SOT) recipients is unknown, with wide variances of rates reported in different studies, from 0% to 58%[21-24]. Some recent studies report a much lower rate, under 15%[23, 25]. It is noteworthy that the immune response mediates non-hematological manifestations of B19V infection; thus immune-mediated symptoms may be absent or blunted in transplant recipients. Therefore, a high level of suspicion should be present to diagnose the infection.

Serology may not reliably establish the diagnosis in the transplant population due to the inability to produce a sufficient antibody response, and polymerase chain reaction (PCR) should be used to detect viral DNA in this population[11]. High-level viremia is more likely associated with symptomatic disease [11]. Conversely, if detected at low levels, persistent DNAemia after infection may not be clinically significant[11]. Despite the lack of robust data, intravenous administration of immunoglobulins (IVIg) and decrease of immunosuppression levels are the mainstay of treatment of SOT recipients with symptomatic B19V infection[11,19]. Although IVIg's optimal dosage and duration are unknown, most patients respond well to treatment. Unfortunately, recurrence of anemia is common[26-28]. There are preliminary reports of foscarnet being used for treatment[29]. Cidofovir has shown *in vitro* efficacy, but further research is needed[30]. Also, the conversion from calcineurin inhibitor-based immunosuppression to everolimus has been described[31].

Currently, routine screening of donor and recipient serostatus for B19V is not recommended; there have been research efforts[24,32]. There is also a lack of epidemiologic data, including the seroprevalence in transplant candidates, depending on the region or organ type[11,33].

This study aimed to determine the B19V serological status and active viral replication by B19V DNA quantification in kidney, liver, and pancreas transplant candidates at a large national transplant center.

MATERIALS AND METHODS

Patients who were transplanted (kidney, liver, or simultaneous kidney and pancreas/liver) at Merkur University Hospital from January 2021 to May 2022 were included in the analysis. The hospital is a high-volume transplant center with approximately 110 liver and 50 kidney transplants performed yearly, representing over 90% of the liver transplantation program in the country and the only institution performing simultaneous transplantations. This was a single-center, prospective study.

The serum samples were collected before the transplantation. Data about the patients were collected prospectively using the hospital's electronic medical record.

Viral DNA was extracted from blood samples using a High Pure Viral Nucleic Acid Kit (Roche Applied Science, Penzberg, Germany). For quantification of B19V DNA in nucleic acid extracts, a LightMix Kit Parvovirus B19 EC (TIB MOLBIOL, Berlin, Germany) was used.

B19V IgG and IgM antibodies were detected using a commercial enzyme-linked immunosorbent assay (ELISA; Euroimmun, Lübeck, Germany). Results were interpreted according to the manufacturer's recommendations as follows: IgM ratio < 0.8 negative, 8.8-1.1 borderline, > 1.1 positive; IgG RU/mL < 4 negative, 4.0-5.5 borderline, > 5.5 positive.

Statistical analysis

Statistical analysis was performed using SPSS version 25 (Armonk, NY, United States, IBM Corp). A $P < 0.05$ was considered to be significant. The data are expressed as the median and interquartile range (IQR), or mean ± SD, as appropriate. Categorical variables are presented as frequency counts and percentages. The normality of the data distribution was tested using the Shapiro-Wilks test. The categorical values were compared using the χ^2 test. In cases with less than 5 outcomes, Fisher's exact test was used. For continuous variables, a parametric (Student's *t*-test, ANOVA) or nonparametric test (Mann-Whitney *U*, Wilcoxon, Kruskal-Wallis) was used, depending on the distribution.

RESULTS

A total of 131 transplant candidates were included in the study, with 70.9% being male. The average age was 53.27 years ± 12.71 years. The median age was 57 years, IQR 43-63 years. The age distribution of patients is presented in Figure 1.

There were 68.7% liver, 27.5% kidney, 3.0% simultaneous pancreas-kidney transplant (SPKT) and 0.8% simultaneous liver-kidney transplant (SLKT) recipients (Table 1).

None of the tested patients had detectable B19V DNA. IgG seroprevalence was 77.1%. No recent infections (IgM antibodies) were detected.

Table 1 Study population characteristics (*n* = 131)

Item	Value
Age, yr (mean ± SD)	53.27 ± 12.71
Gender	
Male	93 (70.9%)
Female	38 (29.1%)
Transplant type	
Liver	90 (68.7%)
Kidney	36 (27.5%)
SPKT	4 (3.0%)
SLKT	1 (0.8%)
Virology results	
B19V DNA positive	0 (0%; one-sided 97.5% CI: 0-2.8)
B19V IgM positive	0 (0%; one-sided 97.5% CI: 0-2.8)
IgG B19V positive	101 (77.1%; 95% CI: 68.9-83.9)

SPKT: Simultaneous pancreas/kidney transplantation; SLKT: Simultaneous liver/kidney transplantation; CI: Confidence interval.

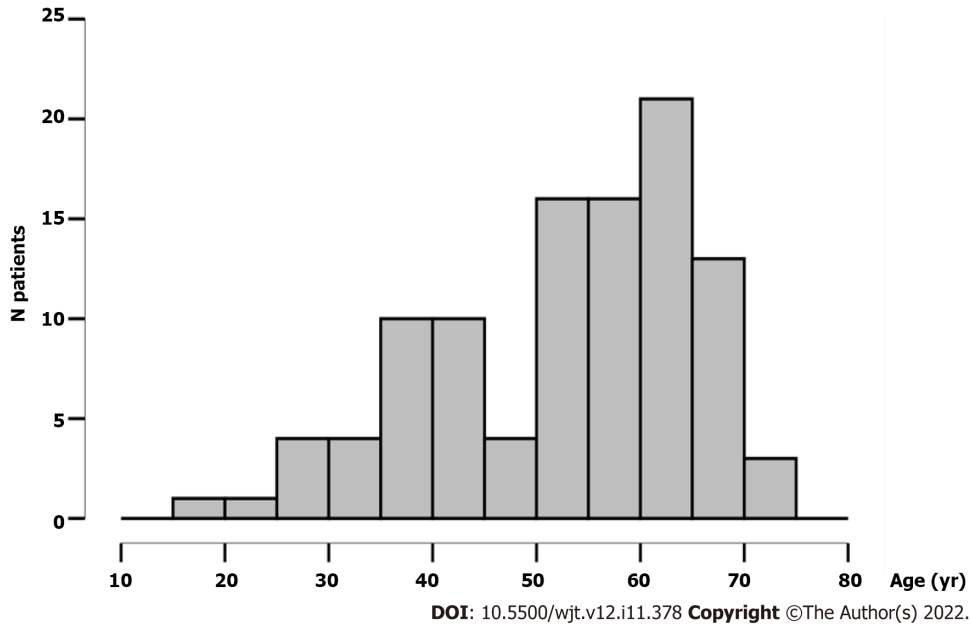

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Figure 1 Distribution of transplant candidates according to age.

There was no difference in the mean age of seronegative and seropositive patients (51.8 years ± 12.9 years *vs* 53.7 years ± 12.7 years, t = -0.603; P = 0.548). In addition, there was no difference in seropositivity between male and female transplant candidates, 76.3% *vs* 78.9%, respectively (χ^2 = 0.104; P = 0.748). When divided into age groups, the seroprevalence was 66.7% in those under 30 years, 80.4% in those aged 30 to 59 years, and 78.1% in patients over 60 (χ^2 = 0.619; P = 0.734) (Table 2).

The seroprevalence did not differ significantly among different organ recipients, with 77.8%, 80.6%, and 50% for liver, kidney, and SPKT, respectively, (χ^2 = 5.297; P = 0.151). There was only one SLKT recipient who was seronegative. The recipients of SPKT were significantly younger than kidney or liver recipients (36.0 years ± 6.8 years, 52.6 years ± 11.6 years and 54.8 years ± 12.9 years, respectively, P = 0.014).

There was no association between immunosuppression prior to transplantation and seropositivity. B19V seroprevalence was 81.3% in the subgroup which received immunosuppression prior to transplantation and 76.4% in the subgroup that did not (χ^2 = 0.176; P = 0.675).

Table 2 Parvovirus B19 IgG seroprevalence rates in transplant candidates

Characteristics	Tested, *n* (%)	IgG positive, *n* (%)	χ^2	*P* value
Gender			0.104	0.748
Male	93 (71.0)	71 (76.3)		
Female	38 (29.0)	30 (78.9)		
Age, yr			0.619	0.734
< 30	6 (5.8)	4 (66.6)		
30-59	56 (54.4)	45 (80.4)		
> 60	41 (39.8)	32 (78.1)		
Transplant type			5.297	0.151
Liver	90 (68.7)	70 (77.8)		
Kidney	36 (27.5)	29 (80.6)		
SPKT	4 (3.0)	2 (50.0)		
SLKT	1 (0.8)	0 (0)		
IS before transplantation			0.498	0.780
Yes	16 (18.2)	13 (81.3)		
No	72 (81.8)	55 (76.4)		
Dialysis modality				0.372[1]
HD	38 (95)	27 (71.1)		
PD	2 (5)	2 (100)		

[1]Fisher's exact test. SPKT: Simultaneous pancreas/kidney transplantation; SLKT: Simultaneous liver/kidney transplantation; IS: Immunosuppression; HD: Hemodialysis; PD: Peritoneal dialysis.

No significant difference was found in the seroprevalence in kidney transplant candidates according to the dialysis modality. Seroprevalence was 71.1% in hemodialysis patients, and 100% in peritoneal dialysis patients (χ^2 = 0.799; *P* = 0.372). In addition, there was no association with dialysis duration (40.1 mo ± 25.4 mo in seropositive *vs* 37.4 mo ± 17.6 mo in seronegative, *t* = -0.288, *P* = 0.775).

DISCUSSION

Our results show a high seroprevalence of B19V among transplant candidates. The seroprevalence of 77.1% was higher compared to a large previous study in the general Croatian population, where a seroprevalence of 64.1% was found[34]. Surprisingly, the seroprevalence did not differ with age, which is commonly reported. However, although not significantly, seropositivity was lower in patients aged less than 30 years (66.6%) compared to patients aged 30-59 and 60 years (80.4% and 78.1%, respectively). The transplant population tested in this study was skewed to slightly older recipients, as shown in the age distribution. This could partly explain the inability to detect the expected difference in seroprevalence with age. In the Croatian general population, seroprevalence in the matching age group 50-59 years was 69.1%[34], which is concordant to our findings. However, it is important to note that the seroprevalence in transplant patients younger than 30 years was higher (66.6%) compared to the same age group in the general population (53.2%)[34].

Additionally, it is important to emphasize that our study investigated transplant candidates, not recipients. The candidates, contrary to the recipients, have not yet received immunosuppression. The data on transplant candidates is even scarcer in literature than on SOT recipients[11]. A German study reported a similar seroprevalence rate of 82% in transplant candidates (kidney, liver, heart, and bone marrow)[35]. Moreover, no difference was found in seroprevalence between various organ recipients, but with a trend toward lower seroprevalence among simultaneous kidney and pancreas candidates. All kidney transplant candidates in our study were patients on dialysis. Few studies analyzed the B19V seroprevalence in hemodialysis or peritoneal dialysis patients. Prevalence rates of 67.5% and 54% were reported from Brazil and Iran, respectively[36,37], which is similar to our result of 71.1% in hemodialysis patients. In our study, we found no association of seroprevalence with the duration of hemodialysis (40.1 mo ± 25.4 mo in seropositive *vs* 37.4 mo ± 17.6 mo in seronegative, *t* = -0.288, *P* =

0.775). Due to better treatment of anemia today, most dialysis patients do not receive transfusions. Therefore, the duration of dialysis does not appear to be a risk factor. The lower prevalence in SPKT candidates was not statistically significant. The SPKT candidates were significantly younger than other transplant candidates, which could explain the trend. Moreover, although there is a paucity of data in the literature on B19V infection in SPKT recipients, the cases presented[38-40] imply a more severe course. We hypothesize that pancreas candidates may be at higher risk for infection given a larger proportion of seronegative recipients due to the immunosuppressive nature of diabetes[41] and the younger age of the recipients. The possible difference among various organ type recipients includes not only age as seen in SPKT recipients but also different numbers of blood transfusions due to bleeding events in cirrhotic patients. Interestingly there was no association between immunosuppression prior to transplantation (*e.g.*, for glomerulonephritis or autoimmune liver disease) and seropositivity.

Following acute infection in immunocompetent individuals, viral genomes may persist in various tissues for life. However, acute B19V infection can lead to severe complications in immunocompromized patients. In our study, no B19V DNA was found. In a German study, B19V DNA was detected in 4.0% of patients. Whereas DNAemia was found in 5.5%, 6.7%, and 5.7% of liver, heart, and bone marrow recipients, and viral genomes were found in only 1.4% of kidney recipients[35]. In a large recent Chinese study, a B19V DNA positive rate of 1.9% was reported in transplant candidates[25].

In addition, a large proportion of patients are still seronegative at the time of transplant and remain at risk for severe disease manifestations. Currently, there is no specific prevention of B19V disease. There is also no routine screening of donor and recipient serostatus for B19V. The true incidence of parvovirus infection in SOT recipients is unknown, with rates varying considerably across different studies[21-25]. There have been efforts in prospective routine monitoring of B19V in the first 6 mo after transplantation in seronegative SOT recipients. The findings showed low incidence rates (1.2% recipients per month) and even lower clinically significant events[24]. In another recent study, prospective monitoring revealed a higher incidence of B19V (10.17%), all infections occurred in seronegative recipients and were deemed clinically significant[42]. To conclude, large prospective data series on B19V disease in transplant recipients are lacking, but in our opinion, at the moment there is no rationale for routine B19V testing. However, pretransplant serostatus could be cost-efficient given the lower cost of a serological test than PCR testing and could potentially reveal patients at high risk. Post-transplant anemia is prevalent and often multifactorial. Serostatus could potentially hasten the diagnosis of B19V infection in selected patients and thus help avoid diagnostic delay and unnecessarily broad testing.

Moreover, B19V has also been implicated as a trigger for thrombotic microangiopathy[43,44], especially in the transplant setting[45-48]. These implications warrant additional research, but the information on serostatus could be beneficial during thrombotic microangiopathy workup, which is expensive and usually long-lasting. A large number of post-transplant thrombotic microangiopathies are regarded as secondary, either to immunosuppressive drugs or transplant itself; thus, B19V infection as a possible causative agent is probably underdiagnosed[49]. Identifying high-risk individuals pretransplant could be beneficial and help elucidate this pathophysiologically complex state[50].

Our study has limitations. Firstly, it is a single-center study with low numbers of rare transplantations, *e.g.*, SPKT and SLKT. Secondly, the incidence of clinical B19V infection was not reported in the post-transplant follow-up of these patients, reflecting the clinical significance of the serological status detected pretransplant. We plan to prospectively evaluate DNAemia and serostatus post-transplant as well as clinical manifestations to establish the clinical significance and epidemiology of B19V disease post-transplant. In addition, blood samples from control subjects were unavailable; therefore, it was not possible to compare the prevalence of B19V DNA in healthy individuals.

CONCLUSION

The B19V seroprevalence is expectedly high among kidney, liver, and pancreas transplant candidates, but 22.9% of seronegative individuals remain at risk for primary disease and severe manifestations. Further research should elucidate the utility of B19V screening in peri-transplant management.

ARTICLE HIGHLIGHTS

Research background

Parvovirus B19 (B19V) is an important pathogen in transplant settings. The epidemiology of B19V infection in solid organ transplant (SOT) recipients is not well studied, and reported prevalence rates vary greatly.

Research motivation

Data on B19V infection in transplant settings are scarce.

Research objectives
To analyze the prevalence of B19V antibodies and DNA in SOT candidates (kidney, liver, or simultaneous kidney and pancreas/liver) at a large national transplant center.

Research methods
Serum samples collected before transplantation were tested for the presence of B19V IgM and IgG antibodies and B19V DNA. Patients' data were collected using the electronic medical record.

Research results
A total of 131 transplant candidates were included in the study, with 70.9% being male. The average age was 53.27 years ± 12.71 years. None of the tested patients had detectable B19V DNA and IgM, while IgG seroprevalence was 77.1%. There was no difference in seropositivity between males and females (76.3% *vs* 78.9%). According to age, the seroprevalence was 66.7% in those under 30 years, 80.4% in those aged 30-59 years, and 78.1% in patients over 60. The seroprevalence did not differ significantly among different organ recipients, with 77.8%, 80.6%, and 50% for liver, kidney, and simultaneous pancreas-kidney transplant, respectively. There was no association between immunosuppression prior to transplantation and B19V IgG seropositivity.

Research conclusions
The B19V seroprevalence is high in transplant candidates, but 22.9% of seronegative individuals remain at risk for primary disease and severe manifestations.

Research perspectives
Further studies on large samples as well the B19V prevalence during the post-transplant period are needed to determine the clinical significance of B19V infection in transplant patients.

FOOTNOTES

Author contributions: Simunov B contributed to the concept of the study, collected and analyzed the data, and wrote the original draft; Jurekovic Z, Zidovec Lepej S, Bainaruch A, Pavicic Saric J, Hruskar Z, and Radmanic L analyzed the data; Mrzljak A and Vilibic-Cavlek T made contributions to the concept of the study, and revised the manuscript critically; all authors approved the final version of the manuscript.

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