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Review article

Immunosuppression for older liver transplant recipients

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ABSTRACT

Older liver transplant recipients have a lower risk of acute rejection than younger patients (9% for patients aged ≥65 years versus 23% for those aged 18–34 years) and are more vulnerable to immunosuppression-related complications. The number of liver transplant recipients ≥65 years has risen to 22% in Europe and the US, but limited information is available on the optimal immunosuppressive regimen for these patients. In this review, we discuss the appropriate management of immunosuppressive agents in older adults to minimize adverse events while avoiding acute rejection. The way the body processes drugs greatly depends on age. In the case of calcineurin inhibitor drugs, aging reduces hepatic metabolism, leading to changes in their pharmacokinetics. Corticosteroids also show decreased clearance as the patient ages. In severe cases of hypoalbuminemia, dose adjustment of mycophenolate acid derivatives may be necessary. However, the pharmacokinetic profiles of the mammalian target of rapamycin inhibitors, basiliximab, and rabbit anti-thymocyte globulin remain unaffected by age. Furthermore, age-related frailty may impact drug metabolism and require tailored interventions and closer follow-up. Although there is limited research, elderly liver transplant recipients require less immunosuppression with double or triple-agent regimens, lower exposure to calcineurin inhibitors, and a shorter course of corticosteroids. The usage of mammalian target of rapamycin inhibitors in older transplant populations has not been specifically investigated, and thus their usage should align with indications for younger patient groups.

1. Introduction

The number of older adults waiting for liver transplantation (LT) is increasing globally [1]. In Europe and the US, about 22% of transplants are performed in patients ≥65 years [1,2]. This trend is due to the changing demographics of patients with end-stage liver disease, the success of LT, and the development of new methods for increasing access to transplantation. Some of these methods include using expanded criteria donor (ECD) organs [3], elderly grafts [4,5], donors after cardiocirculatory death [6], and machine perfusion (MP) technology [7,8].

International data suggests that LT is feasible for elderly patients and yields early outcomes comparable to younger patients due to stringent pre-transplant screening criteria [9–16]. Increased early mortality is typically observed in older patients with a high model for end-stage liver disease (MELD) score (>25–28) [9–16]. As a result, international guidelines recommend against using advanced age as an absolute

Abbreviations: 6-MWD, 6-min walk distance; ACR, acute cellular rejection; ADL, Activity of Daily Living test; ADME, absorption, distribution, metabolism, and excretion; BS, Braden Scale; CBG, corticosteroid-binding globulin; CFS, Clinical Frailty Scale; CKD, chronic kidney dysfunction/disease; CNI, calcineurin inhibitors; CPET, cardiopulmonary exercise testing; CYA, cyclosporine A; DGF, delayed graft function; ECD, extended criterion donors; EVR, everolimus; FFI, Fried Frailty Index; GS, Gait Speed test; ICU, intensive care unit; IRI, ischemia/reperfusion injury; LFI, Liver Frailty Index; LFT, liver function test; LT, liver transplantation; LTL, Leukocyte telomere length; KPS, Karnofsky performance score; KT, kidney transplantation; LBM, lean body mass; MASLD, metabolic dysfunction-associated steatotic liver disease; MELD, model for end-stage liver disease; MetALD, metabolic and alcohol-related/associated liver disease; MMF, mycophenolate mofetil; MP, machine perfusion; MPA, mycophenolic acid; mTOR, mammalian target of rapamycin; mTORi, mTOR inhibitors; rATG, rabbit antithymocyte globulin; SPPB, Short Physical Performance Battery; SRTR, Scientific Registry of Transplant Recipients; TAC, tacrolimus; UNOS, United Network for Organ Sharing; Vd, volume of distribution.

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exclusion criterion for LT [9]. However, long-term survival is inevitably affected by older age at the time of transplantation [10].

In the medical literature, two types of predictors of early survival in elderly transplant recipients have been identified. The first category is related to characteristics of the donor graft, such as age and post-transplant function recovery [17,18]. The second category is related to pre-transplant recipient conditions, such as sarcopenia [19], the model for end-stage liver disease (MELD) score [20], and organ failure at the time of transplant [21]. Remarkably, the recipient's age did not predict early survival, and studies that compared the early outcomes of young versus elderly recipients did not report higher rates of mortality [12] or vascular or biliary complications [22]. Notably, three studies [22–24] reported a higher incidence of neuropsychiatric complications in elderly recipients. A recent meta-analysis found no difference in the risk of early complications between young and older recipients, possibly because of the stringent selection criteria for elderly recipients. Despite the increasing prevalence of cardiovascular comorbidities and diabetes with age, not all studies included in this meta-analysis reported higher proportions of comorbidities in elderly recipients [25].

On the other hand, recipients aged ≥60–70 years have a 10–20% lower five-year survival rate than younger recipients despite similar transplant benefits [9,10,16]. This survival gap increases over time post-transplantation [16]. The five-year survival probability declines by a similar degree in older transplant recipients compared to the general population for similar age groups [16]. For United Network for Organ Sharing (UNOS) recipients over 70 years, the actuarial 5-year patient survival rate is 55%, whereas for younger patients, it is 73% [10]. In Europe, 5-year survival rates are 66% for recipients aged over 60 years compared with 73% for those aged between 46 and 60 years [1]. The most significant factors that lead to long-term morbidity and mortality in elderly LT recipients are cardiovascular issues (25%), the development of new cancers (25%), chronic kidney dysfunction/disease (CKD) (15%), a recurrent liver disease (15%), a recurrent malignancy (5%), rejection of the transplanted organ (5%), metabolic disease (5%), and other diseases (5%) [16].

Although the number of older recipients has been increasing, there are no established guidelines for managing immunosuppression in older recipients [26,27]. Current consensus reports concentrate solely on preventing acute graft rejection (ACR) [28]. Prospective, multicenter, randomized controlled trials are needed to evaluate immunosuppressive agents in older recipients. Currently, limited data can be derived from case series and retrospective analyses. A recent retrospective, single-center study comparing 78 older (≥60 years) versus 65 younger [18–59] recipients receiving methylprednisolone, tacrolimus (TAC), and mycophenolate mofetil (MMF) did not found differences in acute cellular rejection (ACR) (19.2% versus 23.1%, respectively for older and younger patients; $p = 0.57$), infection (43.6% versus 33.8%; $p = 0.23$), malignancy (3.8% versus 1.5%; $p = 0.40$), and mortality rates (3.8% versus 3.1%; $p = 0.80$) within one year post-transplantation [29]. The limited number of cases in the series limits its generalizability to current clinical practice.

Because of limited data, this review assists clinicians in minimizing immunosuppression-related complications in older LT recipients.

2. Older patients require less immunosuppression: the role of immunosenescence

"Old age" is not a specific biological stage. Still, immunosenescence refers to various changes in the immune system that lead to a dysfunctional immune response and increased inflammation throughout the body, known as inflamm-aging [30]. The functions of both the innate and adaptive immune systems are affected by aging [31,32], and age-related immune dysfunction involves decreased production of mast cells, increased mast cell degranulation, decreased macrophage activity, increased production of inflammatory cytokines, decreased NK cytotoxicity and IL-2 production, and decreased neutrophil chemotaxis, apoptosis, and free radical production (Table 1) [32]. The adaptive immune compartment is also affected by changes in CD4 and CD8 T-cell repertoires, increased frequency of memory T-cells, and decreased B-cell production [30]. Thymic involution plays a crucial role in T-cell immunosenescence [33], and patients aged >60 years show decreased T-cell populations and diversity [34]. In addition, the chronic activation of T cells reported in older individuals results in downregulation of the co-stimulatory CD28-based metabolic pathway, and subsets of CD4+/CD28− and CD8+/CD28− T-cells have been reported [34]. This downregulation of CD28 expression in human T-cells is a signature of replicative immunosenescence and has been associated with impaired vaccine responses in non-transplant adults [35,36]. As a result, older adults have an increased incidence of malignancies, higher rates of infection, autoimmune dysfunction, and related mortality [37,38].

In transplant populations, immunosenescence-related dysfunctions in T-cell and B-cell compartments have been explored mainly in kidney transplantation (KT). Schaenman et al. assessed the T-cell phenotype in 60 kidney transplant recipients by comparing 23 older (≥60 years) and 37 matched younger patients (<60 years) in the first year after transplantation. Older recipients showed a decrease in the frequency of naïve CD4+ and CD8+ T cells and an increase in the frequency of terminally differentiated and senescent CD8+ T cells [39]. Notably, older patients with infection after transplantation also showed a significantly increased frequency of T-cell immune senescence [39].

Antibody responses are also affected by aging, resulting in an increased frequency and severity of infectious diseases, and reduced protective effects of vaccination [36,40]. Older age affects the production of high-affinity protective antibodies and shortens the duration of protective immunity following immunization [40].

After lymphocyte-depleting treatments, the process of immune reconstitution is affected by aging, and the use of rabbit anti-thymocyte globulin (rATG) carries a higher risk of impaired CD4+ T cell reconstitution in KT recipients [41]. *This risk is dependent on the age of the individual and is characterized by a decline in the capacity to regenerate CD4+ T-cells after rATG treatment* [42]. *Age-related chronic immune dysfunction or inflammaging* results in systemic inflammation characterized by a shift in the production of pro-inflammatory cytokines, including IL-6, IL-1β, TNF-α, and IFN-γ [30]. Inflammation contributes to metabolic dysfunction and insulin resistance and is enhanced by malnutrition [43]. *Inflammaging* has been implicated in the pathogenesis of several debilitating chronic diseases, from type 2 diabetes mellitus to osteoporosis, Alzheimer's disease, rheumatoid arthritis, and coronary heart disease, most of which are further enhanced by CNI-related toxicity [26].

Table 1
Immunosenescence-related changes in the adaptive and innate immune functions.

Innate immunity
• Decreased mast cell production
• Increased mast cell degranulation
• Decreased macrophage activity
• Increased production of inflammatory cytokines (IL-6, IL-1β, TNF-α, and IFN-γ, aka *inflamm-aging*)
• Decreased NK cytotoxicity
• Decreased IL-2
• Decreased neutrophil chemotaxis
• Decreased neutrophil apoptosis
• Decreased free radical production
Adaptive immunity
• Thymic involution
• Reduction of naïve CD4+ and CD8+ T-cell repertoires
• Increase in the frequency of terminally differentiated and senescent CD8+ T-cells
• Impaired CD4+ T-cell reconstitution after induction
• Increased frequency of memory T-cells
• Downregulation of T-cell CD28 expression
• Decreased B-cell production
• Reduced production of high-affinity protective antibodies
• Shorter duration of protective immunity following immunization

Age-related thymic involution and shrinkage of the T-cell repertoire account for the decreased rate of graft rejection and increased risk of infection and malignancy in older LT recipients. According to the Scientific Registry of Transplant Recipients (SRTR) estimates, the incidence of acute rejection in patients aged ≤34 years is >50% higher than that in patients aged ≥65 years [38]. Accordingly, although post-transplant infections are estimated to occur in more than half of LT recipients, 89% of elderly LT patients (average age, 71 years) develop infectious complications within the first year post-transplant with urinary tract infections, and cytomegalovirus viremia is the most common infection [38]. Older LT recipients show higher infection-related mortality, and sepsis accounts for 50% of deaths in the early post-transplant period [44].

3. Age-related changes in drug metabolism and pharmacokinetics

Aging alters drug metabolism through changes in absorption (A), distribution (D), metabolism (M), and excretion (E) [45] (Table 2). Oral absorption can be reduced by a decrease in gastrointestinal motility, reduced splanchnic blood flow, reduced gastric acid secretion, and smaller intestinal surface area [45]. However, the effects of aging on P-glycoprotein (P-gp) expression are unknown, and no correlation has been reported between P-gp expression in intestinal tissue and patient age [45]. In addition, aging is associated with an increase in the relative fat content of the body and a decrease in muscle mass [46], resulting in a larger volume of distribution (Vd) of lipophilic drugs [47–49].

Owing to a reduction in protein production in older individuals, protein binding decreases by up to 15%–25% compared with younger adults, resulting in increased free drug concentrations [50]. TAC (99%), mTORis (91%), and mycophenolic acid (MPA) (up to 97%) are albumin-bound compounds [51], and age-related hypoalbuminemia may lead to higher pharmacological exposure to immunosuppressive medications, especially MPA derivatives [52]. Aging is also associated with reduced renal and hepatic drug clearance [52–55]. Drug metabolism via the hepatic cytochrome P450 (CYP450) enzyme decreases with age, resulting in higher plasma levels of CNIs, mTORis, and corticosteroids [56–58]. With the expanding use of older liver donors [4], these modifications may be observed more frequently in clinical practice and require appropriate monitoring during patient follow-up.

Because of the increasing proportion of patients referred to LT for metabolic dysfunction-associated steatotic liver disease (MASLD) and metabolic and alcohol-related/associated liver disease (MetALD) [59], special considerations are necessary for obese patients. Obesity affects all ADME phases because of its multisystem characteristics; however, the most relevant change is the modification in the Vd of different drugs and immunosuppressants. Notably, the Vd of CNIs decreases in obese patients despite their lipophilic characteristics [60]. This effect is due to drug binding to lipoprotein or additional tissue distribution, resulting in a prolonged elimination half-life of TAC and CyA [60]. Given that patients with MASLD/MetALD also have a higher amount of body fat, these results are likely to apply to this group of patients and require close monitoring of drug trough levels versus non-obese patients [60].

Donor and recipient co-morbidities may have profound effects on drug metabolism. Diabetes mellitus (DM) is associated with a reduction in hepatic CYP3A activity, resulting in an increase in free drug concentration [61]. Given the prevalence of DM in the deceased donor population and the incidence of post-transplant de novo DM in LT recipients receiving CNIs, these effects must be considered when administering immunosuppressants to elderly recipients [60].

Our drug-metabolizing systems undergo constant modifications throughout our lifespan [62]. Aging is followed by significant modifications in the liver CYP isoenzyme expression pattern, thus affecting the oxidative (Phase I) transformation of the majority of immunosuppressants [63]. Various studies have shown that the content and the expression of liver genes responsible for drug metabolism (CYPs) can vary in elderly individuals leading to an age-related decline in drug clearance [62]. However, the extent of variation in CYP-mediated drug metabolism among people of different ages also depends on exposure to environmental pollutants, dietary habits, gender, and genetic variations that are distinctive of different ethnic groups [64]. Changes in the expression and activity of hepatic CYP enzymes that occur with age are believed to be caused by alterations in the levels of hormones such as growth hormone, gonadal hormones, prolactin, thyroid hormone, insulin, glucagon, and glucocorticoids [64]. These hormones play important roles in regulating CYP enzymes at a post-transcriptional level [64]. The age-related alterations in the hepatic CYP expression may also occur at the transcriptional level and are often associated with oxidative stress. [62] Additionally, CYP inducibility can be modified by age, resulting in decreased drug metabolism, and increased free-drug circulating levels in elderly individuals [62].

The apical villi-associated *MDR1*-encoded P-glycoprotein (Pgp) is pivotal in regulating the efflux of most immunosuppressants in the intestinal lumen [65–67]. Various polymorphisms (single nucleotide polymorphisms; SNPs) in the *MDR1* gene have been identified, and a silent mutation in exon 26 (C3435T) has been correlated with duodenal expression of Pgp, which might affect the disposition of certain drugs, such as immunosuppressants [68]. The function of Pgp might be altered in advanced age, but current evidence about the impact of aging on Pgp expression is quite controversial [69] In a study on a validated, leukocyte-based model, Pgp expression and polymorphism were assessed with rhodamine fluorescence in 18 healthy elderly subjects (mean age 69 years) and 20 geriatric frail patients (mean age 78 years) compared with 21 healthy Caucasian individuals (mean age 33 years). In both elderly populations, no significant difference could be observed in Pgp-mediated efflux pump activity, and only frail elderly demonstrated some reduced Pgp function [69].

Table 2
Age-related modifications of drug absorption, distribution, metabolism, and excretion.

Absorption
Decreased oral absorption of medication due to:
• decreased gastrointestinal motility
• reduced splanchnic blood flow
• reduced gastric acid secretion
• diminished intestinal surface area
• impact of age on intestinal p-glycoprotein is largely unknown
Distribution
Increased volume of distribution:
• increase in relative fat content
• decreased muscle mass
• larger volume of distribution (Vd) for lipophilic immunosuppressive drugs
• reduced protein/albumin binding and higher free drug exposure
Metabolism
• Reduced expression/activity of hepatic/intestinal CYP450 enzyme
• Increased free drug exposure
Excretion
• Reduced hepatic and renal clearance
• Increased free drug exposure

4. Immunosuppressant categories

The effect of aging on the PK profile of the immunosuppressants currently available is shown in Table 3.

4.1. Calcineurin inhibitors

The pharmacokinetic profile of CNIs has been extensively investigated, and studies in KT populations have shown that total weight normalized CNI trough concentrations are 50% higher in older recipients, irrespective of the CNI category [70]. In their 2016 study,

Table 3
Age and impact of immunosuppressants in older liver transplant recipients.

Immunosuppressant	Impact of aging	Suggestions
CNI	• Higher Cmax • Higher AUC • Prolonged half-life • Decreased clearance	• Reduced oral dosages can attain similar exposure levels versus younger patients • Older recipients are more vulnerable to neurologic complications
MPA	• Generally, MPA PK is not affected by aging • Hypoalbuminemia may increase the unbound MPA fraction and its clearance	• No adjustments are suggested in older recipients • In case of hypoalbuminemia evaluate dosage reduction due to the risk of increased infections (CMV)
Corticosteroids	• Aging is associated with decreased drug clearance • Hypoalbuminemia may increase the unbound fraction	• Reduce dosages especially considering co-morbidities (DM, osteoporosis, hallucinations, etc.…)
mTORi	• Stable PK in older patients	• No adjustments
rATG	• Stable PK in older patients	• Adjustments to be considered based on safety risk (infections)
BAX	• Stable PK in older patients	• No adjustments

NOTE: AUC, area under the curve; BAX, basiliximab; CMV, cytomegalovirus; CNI, calcineurin inhibitor; MPA, mycophenolic acid; mTORi, mammalian target of rapamycin inhibitor; PK, pharmacokinetics; rATG, rabbit anti-thymocyte globulin.

David-Neto et al. assessed the TAC PK profile in 44 older KT patients versus 31 younger recipients [71]. Despite comparable tacrolimus trough levels, older recipients showed higher maximum concentration (Cmax) and area under the curve (AUC), a longer time to achieve the maximum concentration, and decreased total body clearance [71]. Similarly, in a study of CyA PK, the required daily dose to maintain comparable target CyA concentrations was significantly lower among KT patients aged >65 years than in younger recipients, CyA clearance was decreased, and intracellular concentrations of CyA in T lymphocytes were higher in older patients [72].

4.2. Mycophenolate acid derivatives

In their study of the PK and pharmacodynamic profile of MPA in KT recipients, Tang et al. compared 26 elderly and 54 younger recipients treated with mycophenolate mofetil and tacrolimus [73]. While inosine monophosphate dehydrogenase (IMPDH) activity pre-transplantation did not differ between elderly and younger patients, the area under the MPA plasma concentration–time curve ($AUC_{0\text{-}12h}$) was not significantly different between the two groups. Based on their experience, the authors concluded that age did not significantly affect the PK or PD of MPA [73]. Notably, MPA undergoes enterohepatic circulation, and conditions affecting intestinal motility and absorption surface area (i.e., co-administration with CyA) may reduce MPA-free plasma concentration and require dose strength adjustments [74].

4.3. rATG

The PK profile of rabbit anti-thymocyte globulin (rATG) has been investigated in recipients of liver, kidney, or blood hematopoietic progenitor cell transplantation, but no age-dependent alterations have been observed in these populations [75–77].

4.4. Basiliximab

Although not approved for use in LT, basiliximab (BAX) is used in some countries because of the provisions introduced by regulatory authorities. The PK profile of BAX (12 mg/m^2 or 10 mg for patients weighing <40 kg or 20 mg for those weighing ≥40 kg) is independent of age, weight, or body surface area [78].

4.5. mTORi

The PK profile of mTORis has been extensively studied, and no significant difference in drug clearance across age groups has been observed [79–83]. Notably, older KT patients show stable everolimus PK parameters without significant changes in dose or exposure during the first six months after transplantation [83].

4.6. Corticosteroids

Corticosteroids are bound to albumin and corticosteroid-binding globulin (CBG), and hypoalbuminemia may affect drug concentrations and exposure levels [84]. The clearance of corticosteroids decreases with age, resulting in enhanced exposure; however, the clinical impact of this finding is limited due to the temporary use of steroids in most LT recipients [85].

5. Frailty, biological age, and immunosuppression

In the elderly transplant population, the recipient's response to immunosuppression can vary greatly because of multiple factors, including genetic predisposition. Biological age is a more accurate predictor of the post-transplantation course, which includes the efficacy and side effects of certain immunosuppressive regimens, specifically of older recipients.

One surrogate of biological age is frailty and its contributing factors, such as sarcopenia, malnutrition, immobility, and reduced energy expenditure [86]. Frailty is a multisystem aging syndrome that affects approximately 20% of end-stage liver disease patients [86]. Clinical experience and literature data suggest that frailty is a distinct phenotype accompanied by immune dysfunction [87,88].

Grading the degree of frailty and measuring biomarkers are distinct methods for assessing biological age [89]. Grading of frailty is a clinically relevant proxy of biological age. In this regard, different tools have been suggested to determine frailty during the pre-transplant workup of patients with liver disease. Some of these, such as the eyeball test, the Activities of Daily Living (ADL), the Clinical Frailty Scale (CFS), and the Karnofsky Performance Score, are entirely subjective [32]. Other tests include subjective and objective measures such as the Braden Scale (BS), Fried Frailty Index (FFI), 6-Minute Walk-Distance (6-MWD), Gait Speed (GS), and Short Physical Performance Battery (SPPB) [32]. Two tests, the Liver Frailty Index (LFI) and Cardiopulmonary Exercise Testing (CPET), have been developed with a focus on liver disease-associated frailty and the evaluation of cardiopulmonary reserve [32,88].

Biomarkers can be used to detect age-related changes before they become evident and could be used to reduce the impact of aging [89]. Those that have been recently suggested include the mean leukocyte telomere length (LTL) [90], epigenetics (i.e., DNA modifications that do not alter the DNA sequence such as DNA methylation) [91], transcriptomics [92], circulating proteins (i.e., proteomics) [93], and metabonomics [94]. A quantitative approach based on frailty indices may offer information that is immediately transferable for implementing treatment strategies (i.e., immunosuppression) and prognosis. On the other hand, biomarkers hold the promise of measuring aging before clinically detectable dysfunction ensue and might help tailor care in transplant populations. However, to date, no information is available on the superiority of these tests in predicting immunosenescence in patients, and a thorough evaluation requires a comprehensive approach

and sound clinical experience [88]. Large-scale studies using frailty to determine biological age as a tool to guide immunosuppression have yet to be performed but are urgently needed to assess the benefits of these tools.

The impact of frailty components on the drug PK profile is illustrated in Fig. 1. Studies on cancer patients have revealed that loss of skeletal muscle (sarcopenia) and increased adiposity lead to a lower lean body mass (LBM), resulting in a higher drug concentration after each dose (Cmax), lower Vd, and shorter drug half-life [95]. These changes may increase the risk of drug-induced toxicity. Therefore, it is essential to maintain a lower threshold of suspicion of adverse events and perform more frequent laboratory controls of drug exposure levels and liver function tests (LFT).

In contradiction to this rule, in obese patients, lipophilic CNIs binding to circulating lipoproteins and/or fatty tissue show a prolonged half-life and longer intervals to achieve target trough levels [60]. Transplant clinicians should be aware of this altered PK profile and avoid drug overload by repeat drug dose strengthening. Additionally, hepatic steatosis is variably associated with the reduction of CYP3A4 activity, with resulting free drug circulating levels for immunosuppressants undergoing phase I (i.e., oxidization) liver clearance (both CNI and mTORi) [96,97]. Similarly, in protein-calorie malnourished patients, drugs metabolized in the liver may be more likely to cause toxic effects due to the decreased rate of hepatic metabolism [97]. Studies in malnourished human subjects indicate that dietary factors and nutritional status influence all ADME phases, from absorption to plasma protein binding, distribution, biotransformation, and excretion of drugs. Malnutrition-associated hypoalbuminemia leads to increased free drug plasma levels, resulting in a higher risk of associated toxicity [97].

Finally, recent evidence shows that older and frail patients are more exposed to polypharmacy because of co-existing morbidities [98]. In this setting, inappropriate drug prescription, drug-to-drug interactions, and drug-related adverse events may precipitate some features of frailty, such as cognitive decline, falls, and incontinence, and worsen their reduced functional reserve [98]. Medication management in these patients may be extremely challenging, and tailored interventions should be encouraged to optimize adherence to drug administration, reduce adverse events, and improve outcomes [99].

Despite all the above considerations on frailty and immune dysfunction, a recent single-center series on 241 LT recipients has reported an increased rate of ACR in frail versus non-frail patients (15% versus 5%, $p = 0.02$) within 3 months after surgery [100]. However, these data should be interpreted with caution because of flaws in the research design, differences in the timing of frailty assessment between

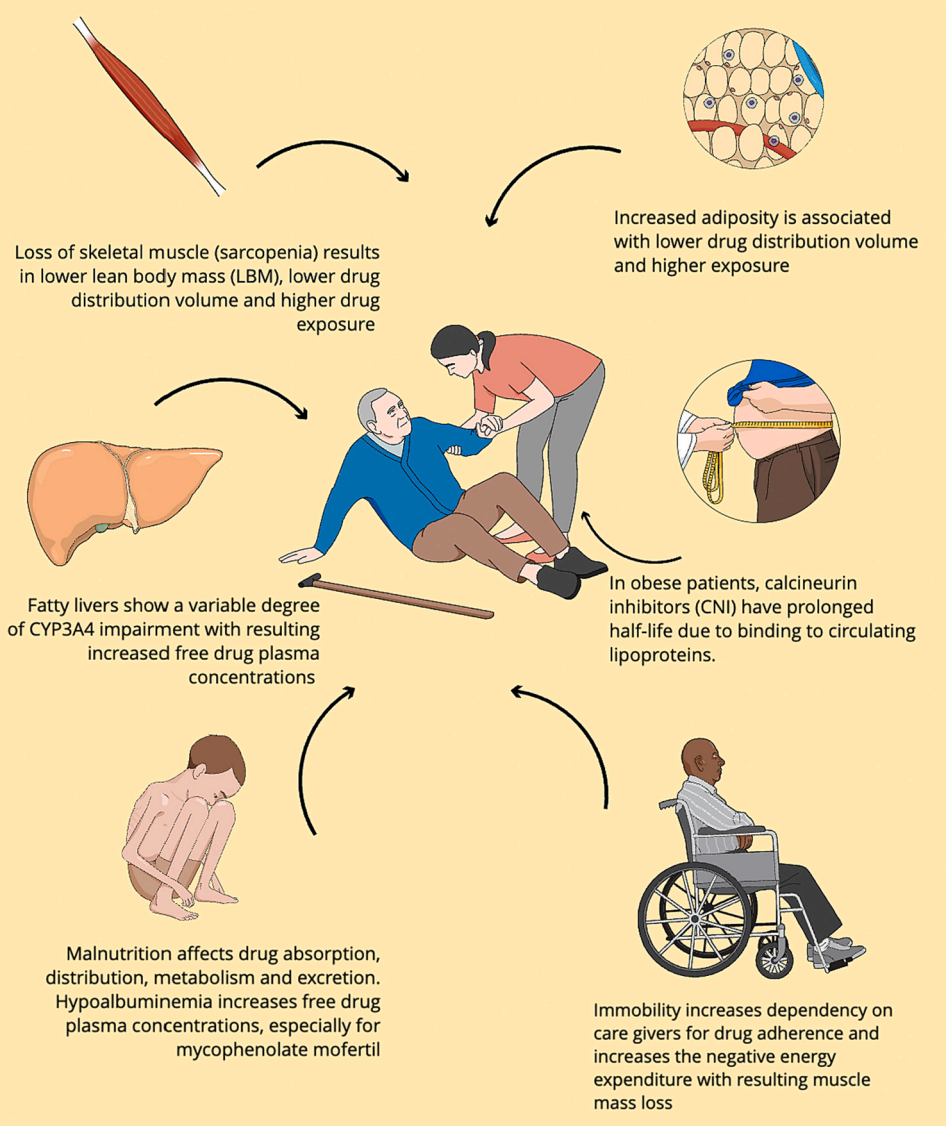

Fig. 1. The implications of frailty and its components on immunosuppressive drug metabolism.

frail and non-frail patients, and lack of information regarding the immunosuppression regimens of patients who experienced ACR [101].

6. Immunosuppression for older recipients in clinical practice

Older liver disease patients cannot be excluded from transplantation based only on chronologic considerations, but a comprehensive biologic assessment is needed to avoid transplant futility. Based on existing literature on older kidney transplant recipients and the pharmacokinetic (PK) profile of currently available immunosuppressants, the most appropriate immunosuppressive strategy for older liver transplant recipients is a personalized approach that balances the need for adequate immunosuppression (i.e., absence of rejection) and minimization of complications [26,45,102]. This approach should be dynamic and requires constant monitoring of liver function tests (LFTs), drug trough levels, and the patient's clinical conditions (triangulation) [26]. In general, older recipients appear to be at a lower risk of ACR than younger patients [30] and may require less intense immunosuppression; however, the consequences of rejection treatment (i.e., steroid boluses or increased CNI exposure) are likely to be more severe in older graft recipients. It is crucial to choose the right immunosuppressive treatment for a transplant patient based on the specific stage of the transplant journey, starting from before the transplant to the late post-transplant phase. It is necessary to implement medical interventions as early as possible, including at the initial patient's referral to the transplant center, to enhance the outcome.

6.1. Pre-transplant

When considering immunosuppression treatment for elderly recipients, it is important to consider their age and specific health concerns. This involves assessing their native disease, overall health (including frailty and other health issues [32]), adherence level [99,102], and expected post-transplant survival rate (102,10,394,95). To gather this information, it is necessary to consult with referring clinicians and caregivers [103]. Additionally, pre-transplant interventions should be considered to improve the patient's nutritional status because sarcopenia and malnutrition can impact immunosuppressant drug metabolism and toxicity [95,97]. For patients with lower motility, cognitive deficits, and low literacy, it is advisable to select a caregiver from within the family because family members are the primary support for patients with chronic illness and disability [104]. Finally, it is essential to provide patients with a clear understanding of the post-transplant process to increase their empowerment and awareness. Patients with hepatocellular carcinoma (HCC) or advanced malignancies are more likely to receive higher-risk liver grafts (i.e., ECD, DCD, and MP-rescued organs), which are at a greater risk of delayed graft function (DGF). Pre-transplant diabetes mellitus (DM) should be targeted and corrected due to its significant prediction of post-transplant cardiovascular and end-stage renal disease [105]. Pre-transplant encephalopathy must be promptly treated as it is associated with higher mortality risk, post-transplant delirium, and longer stay in ICU [106].

6.2. Transplantation

The second step involves assessing the characteristics of the donor. Older liver grafts and fatty livers may have varying degrees of impaired CYP3A4 function, which can lead to decreased drug clearance and increased risk of toxicity [30,32]. Longer cold ischemia time (CIT) is also associated with an increased risk of ischemia/reperfusion injury (I/RI) and delayed graft function (DGF), which in turn may contribute to a higher risk of (ACR) [107,108]. Complex surgeries and unstable intraoperative hemodynamics can result in decreased tissue perfusion, which increases the risk of acute kidney injury and postoperative infections. Therefore, it is highly recommended to introduce calcineurin inhibitors (CNI) gradually in this setting and use induction agents such as BAX, which allows for delayed (5–8 days) TAC introduction and reduced trough levels [26].

The use of induction agents (BAX, rATG, corticosteroids) can potentially reduce and stagger CNI exposure in the early post-transplant phases. rATG should be used with care in the elderly population because of a higher risk of infectious adverse events despite unaltered PK in older recipients [75–77–69]. BAX and corticosteroids should be administered without shifting the net immunologic balance to over-immunosuppression, and concomitant CNI and MPA exposure reduction can achieve this. While BAX PK is not affected by age, corticosteroids may have increased free plasma levels [84], especially in patients with a negative protein–calorie net expenditure, and MPA may require dose strengthening in patients with hypoalbuminemia (51.52,73) (Table 4).

6.3. Post-transplantation

Finally, older patients are also more likely to experience adverse effects from maintenance immunosuppression, including infection, cancer, post-transplant diabetes, and CNI-related nephrotoxicity [16,30]. All these donor- and recipient-derived risk factors should be considered when individualizing immunosuppressive regimens (Table 4).

During post-transplant follow-up, maintenance immunosuppressive regimens may need further adjustment when efficacy or side effects arise. An upfront approach to immunosuppression-related complications is preferred [26] because older recipients are more vulnerable to metabolic, neurologic, and oncologic complications. It is possible to switch from CNIs to mTORi in elderly recipients because the PK profile of mTORi is not affected by aging. The benefits of the mTORi introduction align with the recommendations provided for younger patient groups [27]. on the renal and oncologic risk of transplant recipients [27]. Older recipients also require the implementation of a chronic care model with closer post-transplant follow-up visits, more frequent drug monitoring because of the increased incidence of drug-related adverse events, and lower levels of medication adherence, along with tailored

Table 4
Planning of immunosuppression regimen for older LT recipients.

Phase	Risk factors	Suggestions
Early (0–30 days)	Donor-derived: • Age, co-morbidities (DM) and risk of DGF (ECD, long CIT, MP) Recipient-derived: • Biological age, severity of liver dysfunction at transplantation, malignancy (i.e. HCC), co-morbidities (DM, encephalopathy)	• Stagger CNI introduction and reduce CNI exposure • Assess need for induction (BAX) • Hypoalbuminemia may lead to overexposure of corticosteroids and MPA • Avoid CNI overload in obese patients due to prolonged CNI half-life
Maintenance (>30 days)	Donor-derived: • Older liver grafts have reduced metabolic activity • DM reduces CYP3A4 liver activity Recipient-derived: • Biological age, co-morbidities (DM, CKD, neurologic, oncologic) and infection risk	• Monitor immunosuppressants trough levels more frequently than in younger recipients due to the increased risk of adverse events and higher nonadherence to medication • Consider rapid steroid taper • Consider mTORi introduction to protect against renal, cardiovascular, and oncologic complications

NOTE: BAX, basiliximab; CIT, cold ischemia time; CKD, chronic kidney function; CNI, calcineurin inhibitor; DGF, delayed graft function; DM, diabetes mellitus; ECD, extended criteria donors; HCC, hepatocellular carcinoma; MP, machine perfusion; MPA, mycophenolic acid; mTORi, mammalian target of rapamycin inhibitor.

interventions to improve medication use [99,104].

7. Conclusions

In older LT recipients, the choice of immunosuppression should be based on a biological rather than a chronologic definition of aging, combining quantitative assessments (i.e., frailty indices) and biological markers. A less intense regimen tailored to donor-derived characteristics and recipients' co-morbidities is warranted, along with a closer follow-up protocol to allow for constant monitoring of drug-related adverse events and a higher risk of nonadherence to medication in elderly patients.

Declaration of Competing Interest

PDS serves as an advisory board member for Novartis, Astellas, and Chiesi. The other authors declare no conflicts of interest.

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