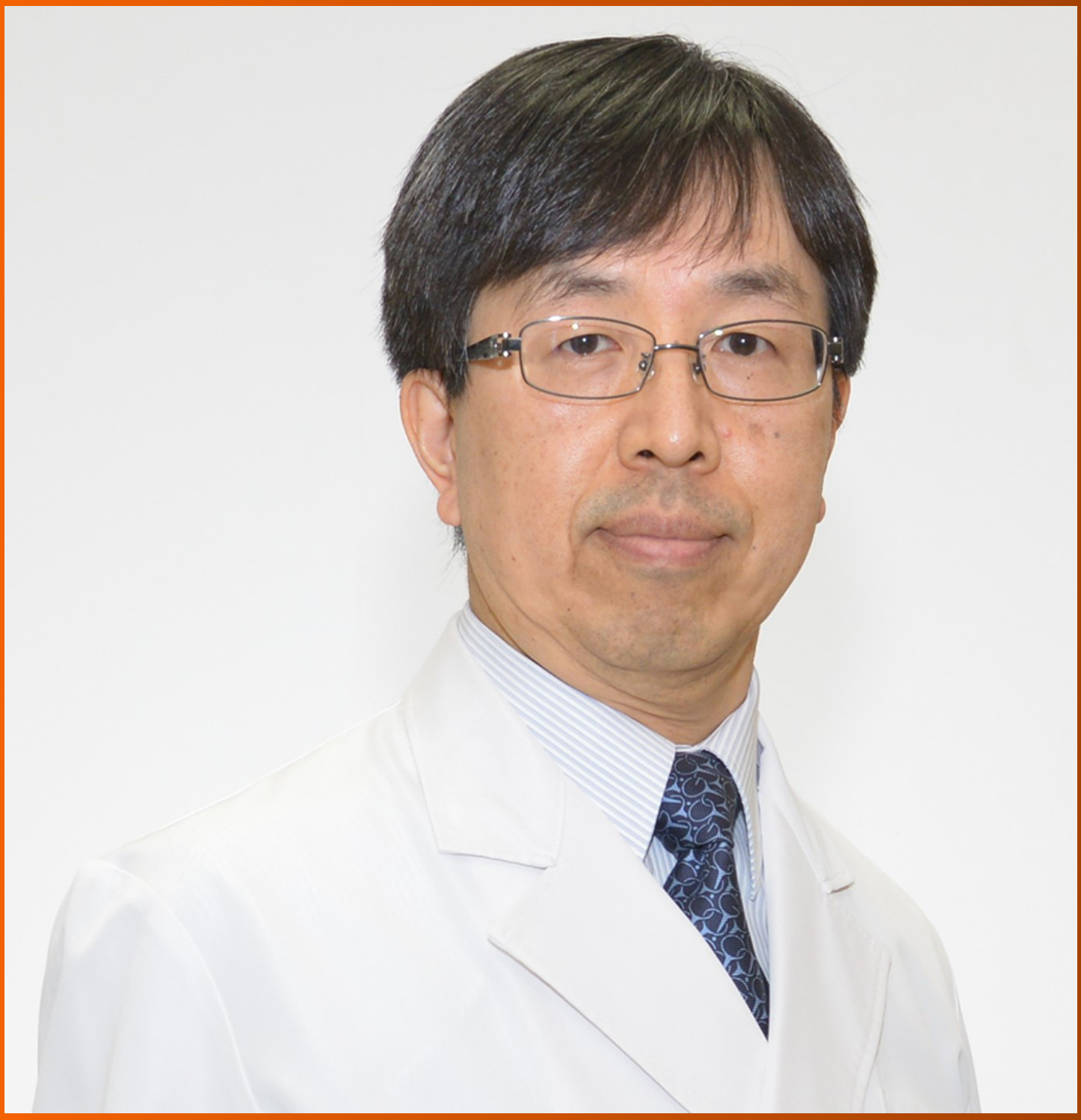
ISSN 2220-3230 (online)

World Journal of *Transplantation*

World J Transplant 2021 October 18; 11(10): 410-442



Published by Baishideng Publishing Group Inc

World Journal of Transplantation

Contents

Monthly Volume 11 Number 10 October 18, 2021

MINIREVIEWS

ORIGINAL ARTICLE

Retrospective Study

META-ANALYSIS

World Journal of Transplantation

Monthly Volume 11 Number 10 October 18, 2021

Contents

ABOUT COVER

Peer Reviewer of *World Journal of Transplantation*, Masayuki Nagasawa, MD, PhD, Chief Doctor, Professor, Department of Pediatrics, Musashino Red Cross Hospital, Musashino City 180-8610, Tokyo, Japan. mnagasawa.ped@tmd.ac.jp

AIMS AND SCOPE

The primary aim of *World Journal of Transplantation* (*WJT*, *World J Transplant*) is to provide scholars and readers from various fields of transplantation with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJT mainly publishes articles reporting research results obtained in the field of transplantation and covering a wide range of topics including bone transplantation, brain tissue transplantation, corneal transplantation, descemet stripping endothelial keratoplasty, fetal tissue transplantation, heart transplantation, kidney transplantation, liver transplantation, lung transplantation, pancreas transplantation, skin transplantation, *etc.*.

INDEXING/ABSTRACTING

The *WJT* is now abstracted and indexed in PubMed, PubMed Central, Scopus, China National Knowledge Infrastructure (CNKI), and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

NAME OF JOURNAL
World Journal of Transplantation

ISSN
ISSN 2220-3230 (online)

LAUNCH DATE
December 24, 2011

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Maurizio Salvadori, Sami Akbulut, Vassilios Papalois

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2220-3230/editorialboard.htm

PUBLICATION DATE
October 18, 2021

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION ETHICS
https://www.wjgnet.com/bpg/GerInfo/288

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

World Journal of Transplantation

Submit a Manuscript: https://www.f6publishing.com

World J Transplant 2021 October 18; 11(10): 410-420

DOI: 10.5500/wjt.v11.i10.410

ISSN 2220-3230 (online)

MINIREVIEWS

Hemodynamic management in brain dead donors

Chiara Lazzeri, Manuela Bonizzoli, Cristiana Guetti, Giorgio Enzo Fulceri, Adriano Peris

ORCID number: Chiara Lazzeri 0000-0003-0131-4450; Manuela Bonizzoli 0000-0002-6435-5754; Cristiana Guetti 0000-0002-4006-5023; Giorgio Enzo Fulceri 0000-0002-4289-241X; Adriano Peris 0000-0003-0724-4422.

Author contributions: Lazzeri C, Peris A, Bonizzoli M performed the majority of the writing, prepared the tables; Guetti C performed data accusation and writing; Fulceri GE provided the input in writing the paper.

Conflict-of-interest statement: No conflict of interest.

Manuscript source: Invited manuscript

Specialty type: Transplantation

Country/Territory of origin: Italy

Chiara Lazzeri, Manuela Bonizzoli, Cristiana Guetti, Giorgio Enzo Fulceri, Adriano Peris, Intensive Care Unit and Regional ECMO Referral Centre, Azienda Ospedaliero Universitaria Careggi, Florence 50134, Italy

Corresponding author: Chiara Lazzeri, MD, Senior Researcher, Intensive Care Unit and Regional ECMO Referral Centre, Azienda Ospedaliero Universitaria Careggi, Viale Morgagni 85, Florenze 50134, Italy. lazzeri.ch@gmail.com

Abstract

Donor management is the key in the complex donation process, since up to 20% of organs of brain death donors (DBD) are lost due to hemodynamic instability. This challenge is made more difficult due to the lack of strong recommendations on therapies for hemodynamic management in DBDs and more importantly to the epidemiologic changes in these donors who are becoming older and with more comorbidities (marginal donors). In the present manuscript we aimed at summarizing the available evidence on therapeutic strategies for hemodynamic management (focusing on vasoactive drugs) and monitoring (therapeutic goals). Evidence on management in elderly DBDs is also summarized. Donor management continues critical care but with different and specific therapeutic goals since the number of donor goals met is related to the number of organs retrieved and transplanted. Careful monitoring of selected parameters (possibly including serial echocardiography) is the clinical tool able to guarantee the achievement and maintaining of therapeutic goals. Despide worldwide differences, norepinephrine is the vasoactive of choice in most countries but, whenever higher doses (> 0.2 mcg/kg/min) are needed, a second vasoactive drug (vasopressin) is advisable. Hormonal therapy (desmopressin, corticosteroid and thyroid hormone) are suggested in all DBDs independently of hemodynamic instability. In the single patient, therapeutic regimen (imprimis vasoactive drugs) should be chosen also according to the potential organs retrievable (*i.e.* heart *vs* liver and kidneys).

Key Words: Brain-dead donors; Hemodynamic; Management; Vasoactive drugs; Hormanal therapy; Echocardiography

Core Tip: Donor management continues critical care but with different and specific therapeutic goals since the number of donor goals met is related to the number of

Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

Received: March 20, 2021
Peer-review started: March 20, 2021
First decision: July 18, 2021
Revised: July 22, 2021
Accepted: September 10, 2021
Article in press: September 10, 2021
Published online: October 18, 2021

P-Reviewer: Gomes A
S-Editor: Fan JR
L-Editor: A
P-Editor: Yuan YY

organs retrieved and transplanted. Careful monitoring of selected parameters (possibly including serial echocardiography) is the clinical tool able to guarantee the achievement and maintaining of therapeutic goals. In the single patient, therapeutic regimen (imprimis vasoactive drugs) should be chosen also according to the potential organs retrievable (*i.e.* heart *vs* liver and kidneys).

Citation: Lazzeri C, Bonizzoli M, Guetti C, Fulceri GE, Peris A. Hemodynamic management in brain dead donors. *World J Transplant* 2021; 11(10): 410-420
URL: https://www.wjgnet.com/2220-3230/full/v11/i10/410.htm
DOI: https://dx.doi.org/10.5500/wjt.v11.i10.410

INTRODUCTION

The number of patients on waiting list for transplant is increasing with a still high mortality rate and greater efforts should be made to maximize the organ pool and optimize organ quality from donors.

Donor management is key in the complex donation process, since up to 20% of organs of brain death donors (DBD) are lost due to hemodynamic instability[1-3]. This challenge is made more difficult due to the lack of strong recommendations on therapies for hemodynamic management in DBDs and more importantly to the epidemiologic changes in these donors who are becoming older and with more comorbidities (marginal donors)[4].

In the present manuscript we aimed at summarizing the available evidence on therapeutic strategies for hemodynamic management (focusing on vasoactive drugs) and monitoring (therapeutic goals). Evidence on management in elderly DBDs is also summarized.

A "PubMed" search was made using the words "Brain death donors and hemodynamics and adults". Only articles in English language were included referring to adults, while case reports and investigations on children were not comprised.

RATIONALE

A consistent number of donors are unfortunately lost because not properly treated[5], underscoring the pivotal role of active critical care to mitigate the imbalance between demand and supply of organs for transplantation. Though complex, intensive care management of potential donors, by the achievement of therapeutic goals, was associated with a 2-fold increase in transplanted organs[6]. This concept is further proved by the analysis of outcomes of two renal recipients from the same donor and of failure of multiorgan transplantation from the same donor[7,8].

THERAPEUTIC GOALS

In essence, donor management continues critical care but with different and specific therapeutic goals.

A checklist of nine therapeutic donor goals (DG) was proposed by eight organ procurement organization in United Network for Organ Sharing region[9]. The number of met DGs was reported to progressively increase from the time to diagnosis of brain death to organ recovery (from 15% to 38%). DG met at the time of consent were related to the number of transplanted organs, since if more four DGs were met at the time of cosent, an odd ratio of 2.03 was reported for at least four organs transplanted. Moreover, if more than 7 DGs were met after consent a reduced need of dialysis in the first week after transplant was observed[10].

A key question was whether the time of donor treatment could influence the number and quality of transplanted organs. According the results of prospective studies, a longer period of donor treatment was associated with a higher number of organs transplanted in the lack of differences in the number of DGs achieved. This phenomenon was more evident for heart and lung transplantation probably thanks to

an efficacious treatment of potential reversible cardiac diseases such as stress cardiomyopathy[11-14]. In the United States longer periods of management are common and a "relax and repair approach" was proposed in opposition to a "rush and retrieve" one (that is, in presence of donor stability a risk of deterioration can be avoided since little can be achieved).

Due to the frequently encountered hemodynamic instability, historically DG were developed in order to maintain physiologic homeostasis. An early series of goals, the so-called series of 100: Systolic pressure > 100 mmHg, urine output > 100 mL/h, partial pressure of O_2 (PaO_2) > 100 mg and hemoglobin concentration > 100 mg/dL [15].

In the subsequent years, guidelines for donor treatments and other goals were introduced, even if there is great worldwide variations in management strategies[16, 17].

DG is shown in Table 1. Despite disparities in guidelines[18], these goals are based on clinical practice and their clinical significance comes from serial measurements during donor management and subsequent adaptation of therapies. Each parameter should be clinically and critically interpreted in the single patient. For instance, high values of central venous pressure can be observed in patients with chronic cor pulmonare and moderate tricuspid regurgitation, independently of the volemic status; in this clinical condition, dynamic changes of central venous pressure should be considered.

HEMODYNAMIC MANAGEMENT

Hemodynamic management is considered really a challenge due to the quite high frequency of donor instability. The severity of circulatory changes have been related to the speed of brain death. More severe hemodynamic alterations were described when brain death develops in a shorter time[19].

Two are the main physiopathologic steps in hemodynamic derangements: (1) The sympathetic storm (following the increase in intracranial cerebral pressure and progressive brainstem ischemia) causes compensatory arterial hypertension and raised systemic vascular resistance, associated with central redistribution of blood volume. It follows an increased after load and eventually visceral ischemia; and (2) Peripheral vasodilation due to the abrupt loss of sympathetic tone. Endocrine changes may worsen this phenomenon mainly by volume depletion.

In these patients, as brain death develops, treatment for hemodynamic imbalance shifts from preventing injuries from increased sympathetic tone (ischemic injury) to counterbalancing systemic injuries due to magnified vasodilation (ineluctably leading to reperfusion injury).

Despite no major studies specifically addressed which monitoring tools should be applied in DBDs, the following monitoring sets could be suggested according to clinical practice: (1) Invasive arterial pressure (mean arteria pressure ≥ 65 mmHg); (2) Urine output (≥ 1 mL/kg/h); (3) Central venous pressure (8-10 cm H_2O); (4) Lactate values; (5) Mixed venous oxygen saturation; and (6) Echocardiography (mainly to assess left and right ventricular functions and to exclude previous or newly developed cardiac alterations).

Echocardiography has emerged as a clinical useful tool in intensive care unit (ICU) every day clinical practice. In patients with severe neurologic injury, serial echocardiographic assessments give the opportunity to provide useful information to tailor hemodynamic regimen in the single patient and, moreover, to identify potential reversible clinical conditions (*i.e.* stress cardiomyopathy) whose early treatment could lead to an increased number of trapiantable hearts and, even in the older donor, to an hemodynamic stabilization.

The reversibility in left ventricle (LV) dysfunction in patients with severe brain injury has been described as "neurogenic stunned myocardium"[20], mainly on the basis of data obtained in experimental models[21-23] and on a few investigations performed in humans[24,25]. Several papers documented that aggressive treatment in BD donors was associated with improvement in myocardial function and with an increased number of transplanted hearts, previously considered not suitable for transplantation[26-28]. In 49 patients with severe brain injury (potential heart donors), our group observed that echocardiography performed after ICU admission led to the identification of LV abnormalities potentially reversible after tempestive aggressive treatment. Indeed, in our series, two patients were considered eligible for heart donation, resulting in 20% increase in donor retrieval rate[14].

Table 1 Donor management goals

Goals	Monitoring
MAP ≥ 65 mmHg	Invasive arterial pressure
CVP ≥ 10	Central venous catheter
Hemoglobin ≥ 10 g/dL	Blood gas analysis
Diuresis ≥ 1 mL/kg/h	
Na 135-155 meq/L	

MAP: Mean arterial pressure; CVP: Central venous pressure.

In a large analysis[12] (United Network of Organ Sharing database, 2007-2015) of 472 donor hearts with left ventricular ejection fraction < 40%, on initial transthoracic echocardiography which recovered during donor treatment, it was reported successful transplantation of these hearts with no increase in adverse outcomes (cardiac allograph outcome, primary graft failure) when compared to hearts which did not experienced LV dysfunction. Similarly, in Sweden (dataset 2006-2016) 45 hearts (of 338 donor hearts) with LV dysfunction were transplanted, and after transplantation LV ejection fraction normalized in all recipients. Short-term outcomes or the composite end point of death or retransplantation over time were comparable between recipients of donor hearts with *vs* without LV dysfunction[29].

All these findings underscore the utility of serial echocardiographic examinations in severe neurologic acute injury for the identification of potential reversible cardiac conditions, eligible for early aggressive treatments. Thanks to this clinical and methodologic approach, some hearts considered not suitable for transplantation could be successfully transplanted.

VASOACTIVE DRUGS

Dopamine

A retrospective-case control study, performed in Germany in 1999, reported that dopamine use in DBDs resulted in improved graft survival after kidney transplantation[30-34]. These results were confirmed in a large cohort study of 2704 DBD kidney grafts (Eurotransplant Registry)[31] and in 254 recipients of kidney transplantation [33]. The beneficial effects of dopamine on kidney grafts were related not only to the hemodynamic effects of dopamine but mainly to its ability to scavance reactive oxygen species (by preventing the depletion of glutathione)[34]. In a randomized controlled trial including 264 DBDs, the use of low dose dopamine (4 mcg/kg/min) was associated with a reduced requirement for dialysis in recipients of the dopamine group [35]. However, the percentage of patients also on norepinephrine was quite high both in the dopamine and in the control groups (78.4% and 85.6%, respectively).

According to the follow-up trial, an improved survival was observed only if dopamine treatment was longer that 7 h till cross clamp. In the same trial, an improved outcome of heart grafts was observed in dopamine treated patients[36].

Regarding the effects of dopamine use on the outcomes of other organs, data are more conflicting. Dopamine pretreatment has no effect on liver transplantation probably because it is rapidly degraded in hepatocytes[34]. Concerning the heart, high dose of dopamine donor treatment (> 10mcg/kg/min) showed no association with mortality in 568 heart transplants[37]. In the study by von Ziegler *et al*[38] donor pretreatment with norepinephrine was compared with dopamine pre-treatment in heart transplants and no differences were observed in survival between the two subgroups. However, in a subset population of long term (5-year) follow-up, norepinefrine was associated with better survival.

In recent years, dopamine was eliminated from routine use in ICU due to large individual variation in dopamine clearance (with unpredictable adrenergic stimulation [34,39,40]). Regarding DBD management and based on growing evidence, dopamine use cannot be advised due to the lack of evidence of beneficial effects in the multiorgan donor and the scarce vasoconstrictor effect of dopamine at low doses. Indeed, its use has been progressively replaced by norepinephrine in most countries worldwide[18].

Vasopressin

Vasopressin can be used to treat both diabetes insipidus and hypotension thanks to its action on V2 renal receptors and on V1 receptors on smooth muscle cells. Due to its short half life, it should be administered by infusion with an usual dosage range of 0.5 to 2.4 units *per* hour. Higher doses may cause deleterious vasoconstritor effects in several districts (renal, splachnic, pulmonary and coronary districts[41]). In a large cohort of 10431 DBDs, donor vasopressor use was an independent predictor of a high number (≥ 4 organs) of procured organs. However, this study focuses on donor hemodynamic parameters and not on allograft outcomes[42]. To date, no data are consistent with the potential advantage of vasopressin over other vasoactive agents, even if vasopressin is the drug of choice for hypotension in DBDs in some countries such as Canada, Ireland and India[18].

Norepinephrine

Norepinephrine is the vasoactive drug of choice in several countries including Europe [4,18] with an increasing use in the last years, despite not univocal literature data. A beneficial effect of norepinephrine use was reported in 270 kidney recipients, since decreased rates of graft rejection and loss followed increased number of norepinephrine infusion days[43].

In regard to heart transplantation, conflicting results are reported on norepinephrine dosage and graft outcomes[44,45]. According to a survey, in potential heart donors, most heart transplant centers in United Sttaes are reluctant to accept donors under moderate dose of catecholamine[46]. High dose norepinephrine was correlated with right ventricular impairment and adverse 1-year outcome in a prospective investigation[47]. Conversely no differences in short term mortality was observed in a German Registry between different norepinephrine doses[48].

Based on this conflicting evidence, in potential heart donors we suggest to add vasopressin (continuous infusion) when a dose of norepinephrine > 0.2 mcg/kg/min is needed.

Hormonal therapy

The rationale for hormonal supportive therapy in BD donors comes from the physiopathology of brain death. Insulin and glucose management can be considered part of the intensive care management.

In human brain death, posterior pituitary dysfunction is commonly encountered (as documented by the frequency of diabetes insipidus), while anterior pituitary function may be only partially affected, probably thanks to the preserved pituitary blood flow. Thus, the hormones usually affected are antidiuretic hormone (ADH), thyroid hormones and cortisol[41].

Deficient levels of vasopressin (also known as ADH) were reported in up to the 80% of brain dead donors[49] and diabetes insipidus was described in the 77% of donors in Australia[50]. Low free T3 are frequently encountered in human donors, while variable concentrations of TSH and T4 are reported. The changes in thyroid hormones in brain death seem to resemble the euthyroid sick syndrome, commonly seen in critically ill patients[22,51,52].

Growing evidence does support the use of hormonal replacement therapy in DB donors, independently of hemodynamic instability[52-55]. In 1995, in an United Kingdom center, most donors were initiated on hormone replacement therapy by infusion, which led to the conversion of many of donors initially considered to be unacceptable, based on hemodynamic parameters, to acceptable donors[56]. In a cohort of 47 DBDs (2006 to 2011), hormonal replacement therapy initiated in the lack of hemodynamic instability was independently associated with highly-yield (≥ 4 organs) procurement[29]. A shorter duration of norepinephrine administration was also observed in this subgroup.

Treatment of diabetes insipidus is essential for donor stability. If untreated, diabetes insipidus causes hypovolemia, and marked hypernatremia which may be detrimental to organ outcome, especially for liver and kidney graft outcomes[57,58]. Diabetes insipidus should be suspected in presence of polyuria of ≥ 3 mL/kg/h and/or rising serum sodium levels) and the synthetic vasopressin analogue 1-deamino-8-D-arginine vasopressin (DDVAP) should be used. It selectively acts on V2 renal receptors and it does not have vasoconstrictor activity. DDVAP can be given as an intravenous bolus of between 2 and 6 mcg since it has a much longer half-life than vasopressin. At higher doses (0.3 mcg/kg) DDVAP exerts procoagulant effects (Table 2).

Administration of thyroid hormone has been highly suggested in guidelines and reviews[54,59-62]. According to animal and humans studies[63,64], replacement of

Table 2 Vasoactive drugs and hormonal therapy in brain death donors–proposed regimen

	Dosage	Comments
Vasoactive		
Norepinephrine (mcg/kg/min)	≤ 0.2 mcg/kg/min, if higher dosage needed add vasopressin	In potential heart donors, the lowest dosage is preferable
Vasopressin (U/h)	Up to 2.5 U/h	
Hormonal replacement therapy		
Idrocorticosteroid	100 mg bolus, 200 mg/24 h infusion	
T3	4 mcg intravenous bolus, followed by infusion of 3 mcg *per* hour	T3 could be preferred since it is immediately available to tissues
Desmopressin (DDVAP)	4 mcg intravenous bolus eventually repeat every 6 to 8 h as needed	

DDVAP: 1-deamino-8-D-arginine vasopressin.

thyroid hormone is able to restore and reactivate mitochondrial energy metabolism. At the cardiac level, it induces an increase alpha heavy chain formation and a decrease in beta heavy chain formation, and an improvement in calcium handling, up regulation of beta adrenergic receptors, leading to a positive inotropic effect[65].

In an interesting review[66], it was reported that all retrospective analyses documented that thyroid hormone administration was beneficial. Recent evidence[64,67] does support the notion that thyroid administration in brain death is associated with an increased number of organ transplanted and improved survival of heart recipients. A 5-year recipient survival improvement was documented in heart recipients when thyroid hormone had been administered[68].

T3 may be initiated with a 4 mg intravenous bolus followed by infusion of 3 mg *per* hour alternatively, T4 may be given initially with a 20 mg intravenous bolus followed by infusion of 10 mg *per* hour.

The rationale for the administration of cortisols, the third component of hormal replacement therapy, relies on replacing steroid in pituitary-adrenal dysfunction, on supplementing steroid because of a "functional" or "relative" adrenal insufficiency, and on the immunomodulatory and anti-inflammatory beneficial effects of steroids.

Evidence supports this notion. Weaning of norepinephrine was more frequent in the 80 BD donors who received steroids than the 128 ones who did not, although no benefit was observed in primary functional recovery of transplanted grafts[69]. Recipients of donor livers who had received steroids showed less ischemia-reperfusion injury and acute rejection[70]. Low-dose of steroids is preferred since high dose did not show differences in number of retrieved and transplanted organs[52,71-73].

Different regimens of steroids were described with no documented benefit of one over the other[18]. Based on our experience, we suggest the use of hydrocortisone 100 mg bolus followed by 200 mg/d (continuous infusion).

AGE AND BRAIN DEAD DONORS

The characteristics of the pool of BD donors have deeply changed over the past years especially in developed Western countries. While DBDs were once largely young and declared dead due to traumatic brain injury, they are now older, with more comorbidities and declared dead due to cerebrovascular injury[74,75]. This phenomenon was confirmed in Italy (Tuscany Region) in a cohort of 1286 potential heart donor (aged ≤ 60) over a 15-year period in whom we observed an age increase and a change in brain dead causes (mainly a reduction in the incidence of traumatic brain injury)[4].

After BD development, the only variation observed with advancing age is lower values of diastolic blood pressure, which is most likely related to arterial changes due to aging[76]. Diastolic blood pressure is known to increase up to the age of about 50 years due to the rise in arteriolar resistance, but, later in life, the large artery stiffening contributes a wider pulse pressure including a decreased diastolic blood pressure. In the BD donor, this phenomenon may affect perfusion pressure, highlighting potential difficulties in hemodynamic management in older donors, and it may be worsened by the age-related reduction in β-receptor function[77]. In 92 consecutive DBDs[78],

advancing age was associated with a more pronounced vasodilatation (lower values of diastolic blood pressure) probably due to age-related reduction in arterial stiffness and beta-receptor function (conditioning a reduced response to endogenous and/or exogenous norepinephrine stimulation).

Older DBDs usually donate liver and/or kidney. Though the monitoring set and hemodynamic goals do not differ from younger DBDs, clinical peculiarities in management may apply to older DBDs. Due to the coexistence of atherosclerotic age-related disease (involving also small vessels), the lowest dosage of vasoactive drugs should be used, able to achieve and grantee the best perfusion of abdominal organs, as mainly indicated by urine output and dynamic lactate values. Though fluid restriction is not required, close monitoring of sodium is needed in potential liver donors. In older DBDs, the possibility of *ex vivo* perfusion should be considered, mainly in presence of comorbidities (in primis diabetes and hypertension) and not optimal indices of organ perfusion (*i.e.* Transaminases values).

TIMING FOR AN OPTIMAL MANAGEMENT

The main target of "an early management" is the achievement of good systemic perfusion since ICU admission in a patient with severe neurologic injury, despite his/her potential non favorable outcome. According to our experience, three steps can be identified for an efficacious treatment. The first one starts with ICU admission of a patient with severe neurologic injury and it is strictly part of critical care, consisting of hemodynamic, metabolic and infectious monitoring. In this phase, an echocardiographic assessment allows the detection of previous (eventually unknown) heart disease as well as new-onset cardiac conditions, such as stress cardiomyopathy, which deserve targeted therapies. Dosages of vasoactive drugs should be tailored in order to avoid excessive organs' vasoconstriction, possibly by means of close monitoring of hemodynamic targets (in primis central venous pressure and lactate values). The second step is represented by treatments during brain death development and it mainly consists in the management of hemodynamic and metabolic deragements. Finally the third step, that is properly "DBD management", since brain death diagnosis to the operating theatre.

KEY MESSAGES

Intensive care management should begin on ICU admission of a patient with severe acute neurologic injury at risk of developing brain death. With the aim to reach optimal systemic organ perfusion and identify all reversible clinical conditions (*i.e.* stress cardiomyopathy) elegible for efficaceous treatment.

In the single patient, therapeutic regimen (imprimis vasoactive drugs) should be chosen also according to the potential organs retrievable (*i.e.* heart *vs* liver and kidneys).

Donor age may affect management due to peculiarities of brain death in older donors.

The utility of serial echocardiographic examinations in severe neurologic acute injury for the identification of potential reversible cardiac conditions, eligible for early aggressive treatments. Thanks to this clinical and methodological approach, some hearts considered not suitable for transplantation could be successfully transplanted.

Hormal replacement therapy should be initiated in DBDs independently of hemodynamic instability.

CONCLUSION

Donor management continues critical care but with different and specific therapeutic goals since the number of DG met is related to the number of organs retrieved and transplanted. Careful monitoring of selected parameters (possibly including serial echocardiography) is the clinical tool able to guarantee the achievement and maintaining of therapeutic goals. In the single patient, therapeutic regimen (imprimis vasoactive drugs) should be chosen also according to the potential organs retrievable (*i.e.* heart *vs* liver and kidneys).

REFERENCES

1 **Martin-Loeches I**, Sandiumenge A, Charpentier J, Kellum JA, Gaffney AM, Procaccio F, Westphal GA. Management of donation after brain death (DBD) in the ICU: the potential donor is identified, what's next? *Intensive Care Med* 2019; **45**: 322-330 [PMID: 30820584 DOI: 10.1007/s00134-019-05574-5]

2 **Patel MS**, De La Cruz S, Sally MB, Groat T, Malinoski DJ. Active Donor Management During the Hospital Phase of Care Is Associated with More Organs Transplanted per Donor. *J Am Coll Surg* 2017; **225**: 525-531 [PMID: 28739153 DOI: 10.1016/j.jamcollsurg.2017.06.014]

3 **Patel MS**, Zatarain J, De La Cruz S, Sally MB, Ewing T, Crutchfield M, Enestvedt CK, Malinoski DJ. The impact of meeting donor management goals on the number of organs transplanted per expanded criteria donor: a prospective study from the UNOS Region 5 Donor Management Goals Workgroup. *JAMA Surg* 2014; **149**: 969-975 [PMID: 25054379 DOI: 10.1001/jamasurg.2014.967]

4 **Peris A**, Lazzeri C, D'Antonio L, Bombardi M, Bonizzoli M, Guetti C, Maccherini M, Migliaccio ML. Epidemiological changes in potential heart donors after brain death: a retrospective 15 year cohort study. *Intern Emerg Med* 2019; **14**: 371-375 [PMID: 29943077 DOI: 10.1007/s11739-018-1897-8]

5 **Salim A**, Velmahos GC, Brown C, Belzberg H, Demetriades D. Aggressive organ donor management significantly increases the number of organs available for transplantation. *J Trauma* 2005; **58**: 991-994 [PMID: 15920414 DOI: 10.1097/01.ta.0000168708.78049.32]

6 **McKeown DW**, Ball J. Treating the donor. *Curr Opin Organ Transplant* 2014; **19**: 85-91 [PMID: 24553498 DOI: 10.1097/MOT.0000000000000059]

7 **Robert R**, Guilhot J, Pinsard M, Longeard PL, Jacob JP, Gissot V, Hauet T, Seguin F. A pair analysis of the delayed graft function in kidney recipient: the critical role of the donor. *J Crit Care* 2010; **25**: 582-590 [PMID: 20381298 DOI: 10.1016/j.jcrc.2010.02.011]

8 **Oto T**, Excell L, Griffiths AP, Levvey BJ, Bailey M, Marasco S, Macdonald P, Snell GI. Association between primary graft dysfunction among lung, kidney and heart recipients from the same multiorgan donor. *Am J Transplant* 2008; **8**: 2132-2139 [PMID: 18727699 DOI: 10.1111/j.1600-6143.2008.02357.x]

9 **Malinoski DJ**, Patel MS, Daly MC, Oley-Graybill C, Salim A; UNOS Region 5 DMG workgroup. The impact of meeting donor management goals on the number of organs transplanted per donor: results from the United Network for Organ Sharing Region 5 prospective donor management goals study. *Crit Care Med* 2012; **40**: 2773-2780 [PMID: 22846779 DOI: 10.1097/CCM.0b013e31825b252a]

10 **Malinoski DJ**, Patel MS, Ahmed O, Daly MC, Mooney S, Graybill CO, Foster CE, Salim A; United Network for Organ Sharing (UNOS) Region 5 Donor Management Goals (DMG) Workgroup. The impact of meeting donor management goals on the development of delayed graft function in kidney transplant recipients. *Am J Transplant* 2013; **13**: 993-1000 [PMID: 23406284 DOI: 10.1111/ajt.12090]

11 **Berman M**, Ali A, Ashley E, Freed D, Clarke K, Tsui S, Parameshwar J, Large S. Is stress cardiomyopathy the underlying cause of ventricular dysfunction associated with brain death? *J Heart Lung Transplant* 2010; **29**: 957-965 [PMID: 20627624 DOI: 10.1016/j.healun.2010.04.008]

12 **Casartelli M**, Bombardini T, Simion D, Gaspari MG, Procaccio F. Wait, treat and see: echocardiographic monitoring of brain-dead potential donors with stunned heart. *Cardiovasc Ultrasound* 2012; **10**: 25 [PMID: 22721412 DOI: 10.1186/1476-7120-10-25]

13 **Munshi L**, Keshavjee S, Cypel M. Donor management and lung preservation for lung transplantation. *Lancet Respir Med* 2013; **1**: 318-328 [PMID: 24429157 DOI: 10.1016/S2213-2600(12)70064-4]

14 **Lazzeri C**, Guetti C, Migliaccio ML, Ciapetti M, Peris A. The utility of serial echocardiograms for organ procurement in brain death. *Clin Transplant* 2017; **31** [PMID: 28836706 DOI: 10.1111/ctr.13094]

15 **Gelb AW**, Robertson KM. Anaesthetic management of the brain dead for organ donation. *Can J Anaesth* 1990; **37**: 806-812 [PMID: 2225301 DOI: 10.1007/BF03006543]

16 **Selck FW**, Deb P, Grossman EB. Deceased organ donor characteristics and clinical interventions associated with organ yield. *Am J Transplant* 2008; **8**: 965-974 [PMID: 18341685 DOI: 10.1111/j.1600-6143.2008.02205.x]

17 **Franklin GA**, Santos AP, Smith JW, Galbraith S, Harbrecht BG, Garrison RN. Optimization of donor management goals yields increased organ use. *Am Surg* 2010; **76**: 587-594 [PMID: 20583513 DOI: 10.1177/000313481007600621]

18 **Turner AJ**, Hick PE. Inhibition of aldehyde reductase by acidic metabolites of the biogenic amines. *Biochem Pharmacol* 1975; **24**: 1731-1733 [PMID: 16 DOI: 10.1016/0006-2952(75)90016-7]

19 **Frenette AJ**, Williamson D, Weiss MJ, Rochwerg B, Ball I, Brindamour D, Serri K, D'Aragon F, Meade MO, Charbonney E. Worldwide management of donors after neurological death: a systematic review and narrative synthesis of guidelines. *Can J Anaesth* 2020; **67**: 1839-1857 [PMID: 32949008 DOI: 10.1007/s12630-020-01815-0]

20 **McKeown DW**, Bonser RS, Kellum JA. Management of the heartbeating brain-dead organ donor. *Br J Anaesth* 2012; **108** Suppl 1: i96-107 [PMID: 22194439 DOI: 10.1093/bja/aer351]

21 **Kenigsberg BB**, Barnett CF, Mai JC, Chang JJ. Neurogenic Stunned Myocardium in Severe Neurological Injury. *Curr Neurol Neurosci Rep* 2019; **19**: 90 [PMID: 31720870 DOI: 10.1007/s11910-019-0999-7]

22 **Pandalai PK**, McLean KM, Bulcao CF, Duffy JY, D'Souza KM, Merrill WH, Pearl JM, Akhter SA. Acute beta-blockade prevents myocardial beta-adrenergic receptor desensitization and preserves early ventricular function after brain death. *J Thorac Cardiovasc Surg* 2008; **135**: 792-798 [PMID: 18374758 DOI: 10.1016/j.jtcvs.2007.09.038]

23 **Shivalkar B**, Van Loon J, Wieland W, Tjandra-Maga TB, Borgers M, Plets C, Flameng W. Variable effects of explosive or gradual increase of intracranial pressure on myocardial structure and function. *Circulation* 1993; **87**: 230-239 [PMID: 8419012 DOI: 10.1161/01.cir.87.1.230]

24 **Novitzky D**, Wicomb WN, Cooper DK, Rose AG, Reichart B. Prevention of myocardial injury during brain death by total cardiac sympathectomy in the Chacma baboon. *Ann Thorac Surg* 1986; **41**: 520-524 [PMID: 3707246 DOI: 10.1016/s0003-4975(10)63032-9]

25 **Guglin M**. How to increase the utilization of donor hearts? *Heart Fail Rev* 2015; **20**: 95-105 [PMID: 24858482 DOI: 10.1007/s10741-014-9434-y]

26 **Madias JE**. Donor hearts, hearts of resuscitated cardiac arrest victims, hearts of patients with neurogenic stress cardiomyopathy, and hearts of patients with Takotsubo syndrome: any commonalities? *Int J Cardiol* 2015; **199**: 33 [PMID: 26173172 DOI: 10.1016/j.ijcard.2015.06.184]

27 **Wheeldon DR**, Potter CD, Oduro A, Wallwork J, Large SR. Transforming the "unacceptable" donor: outcomes from the adoption of a standardized donor management technique. *J Heart Lung Transplant* 1995; **14**: 734-742 [PMID: 7578183]

28 **Zaroff JG**, Rordorf GA, Ogilvy CS, Picard MH. Regional patterns of left ventricular systolic dysfunction after subarachnoid hemorrhage: evidence for neurally mediated cardiac injury. *J Am Soc Echocardiogr* 2000; **13**: 774-779 [PMID: 10936822 DOI: 10.1067/mje.2000.105763]

29 **Madan S**, Saeed O, Vlismas P, Katsa I, Patel SR, Shin JJ, Jakobleff WA, Goldstein DJ, Sims DB, Jorde UP. Outcomes After Transplantation of Donor Hearts With Improving Left Ventricular Systolic Dysfunction. *J Am Coll Cardiol* 2017; **70**: 1248-1258 [PMID: 28859788 DOI: 10.1016/j.jacc.2017.07.728]

30 **Oras J**, Doueh R, Norberg E, Redfors B, Omerovic E, Dellgren G. Left ventricular dysfunction in potential heart donors and its influence on recipient outcomes. *J Thorac Cardiovasc Surg* 2020; **159**: 1333-1341.e6 [PMID: 31427100 DOI: 10.1016/j.jtcvs.2019.06.070]

31 **Schnuelle P**, Lorenz D, Mueller A, Trede M, Van Der Woude FJ. Donor catecholamine use reduces acute allograft rejection and improves graft survival after cadaveric renal transplantation. *Kidney Int* 1999; **56**: 738-746 [PMID: 10432416 DOI: 10.1046/j.1523-1755.1999.00567.x]

32 **Schnuelle P**, Berger S, de Boer J, Persijn G, van der Woude FJ. Effects of catecholamine application to brain-dead donors on graft survival in solid organ transplantation. *Transplantation* 2001; **72**: 455-463 [PMID: 11502976 DOI: 10.1097/00007890-200108150-00017]

33 **Schnuelle P**, Yard BA, Braun C, Dominguez-Fernandez E, Schaub M, Birck R, Sturm J, Post S, van der Woude FJ. Impact of donor dopamine on immediate graft function after kidney transplantation. *Am J Transplant* 2004; **4**: 419-426 [PMID: 14961996 DOI: 10.1111/j.1600-6143.2004.00331.x]

34 **Shapey IM**, Muiesan P. Regional perfusion by extracorporeal membrane oxygenation of abdominal organs from donors after circulatory death: a systematic review. *Liver Transpl* 2013; **19**: 1292-1303 [PMID: 24136827 DOI: 10.1002/lt.23771]

35 **Schnuelle P**, Benck U, Yard BA. Dopamine in transplantation: Written off or comeback with novel indication? *Clin Transplant* 2018; **32**: e13292 [PMID: 29790212 DOI: 10.1111/ctr.13292]

36 **Schnuelle P**, Gottmann U, Hoeger S, Boesebeck D, Lauchart W, Weiss C, Fischereder M, Jauch KW, Heemann U, Zeier M, Hugo C, Pisarski P, Krämer BK, Lopau K, Rahmel A, Benck U, Birck R, Yard BA. Effects of donor pretreatment with dopamine on graft function after kidney transplantation: a randomized controlled trial. *JAMA* 2009; **302**: 1067-1075 [PMID: 19738091 DOI: 10.1001/jama.2009.1310]

37 **Benck U**, Hoeger S, Brinkkoetter PT, Gottmann U, Doenmez D, Boesebeck D, Lauchart W, Gummert J, Karck M, Lehmkuhl HB, Bittner HB, Zuckermann A, Wagner F, Schulz U, Koch A, Bigdeli AK, Bara C, Hirt S, Berchtold-Herz M, Brose S, Herold U, Boehm J, Welp H, Strecker T, Doesch A, Birck R, Krämer BK, Yard BA, Schnuelle P. Effects of donor pre-treatment with dopamine on survival after heart transplantation: a cohort study of heart transplant recipients nested in a randomized controlled multicenter trial. *J Am Coll Cardiol* 2011; **58**: 1768-1777 [PMID: 21996389 DOI: 10.1016/j.jacc.2011.05.060]

38 **von Ziegler F**, Helbig S, Kreissl N, Meiser B, Becker A, Kaczmarek I. Norepinephrine versus dopamine pretreatment of potential heart donors - impact on long-term outcome. *Ann Transplant* 2013; **18**: 320-326 [PMID: 23792536 DOI: 10.12659/AOT.883960]

39 **Smits JM**, De Pauw M, de Vries E, Rahmel A, Meiser B, Laufer G, Zuckermann A. Donor scoring system for heart transplantation and the impact on patient survival. *J Heart Lung Transplant* 2012; **31**: 387-397 [PMID: 22177692 DOI: 10.1016/j.healun.2011.11.005]

40 **Holmes CL**, Walley KR. Bad medicine: low-dose dopamine in the ICU. *Chest* 2003; **123**: 1266-1275 [PMID: 12684320 DOI: 10.1378/chest.123.4.1266]

41 **Galley HF**. Renal-dose dopamine: will the message now get through? *Lancet* 2000; **356**: 2112-2113 [PMID: 11191531 DOI: 10.1016/S0140-6736(00)03484-X]

42 **Opdam HI**. Hormonal Therapy in Organ Donors. *Crit Care Clin* 2019; **35**: 389-405 [PMID: 30784617 DOI: 10.1016/j.ccc.2018.11.013]

43 **Plurad DS**, Bricker S, Neville A, Bongard F, Putnam B. Arginine vasopressin significantly increases the rate of successful organ procurement in potential donors. *Am J Surg* 2012; **204**: 856-860; discussion 860-861 [PMID: 23116641 DOI: 10.1016/j.amjsurg.2012.05.011]

44 **Birtan D**, Arslantas MK, Altun GT, Dincer PC, Gecegormez S, Demirel A, Ayanoglu HO. Effect of Vasoactive Therapy Used for Brain-Dead Donors on Graft Survival After Kidney Transplantation. *Transplant Proc* 2018; **50**: 1289-1291 [PMID: 29735214 DOI: 10.1016/j.transproceed.2018.02.058]

45 **Segovia J**, Cosío MD, Barceló JM, Bueno MG, Pavía PG, Burgos R, Serrano-Fiz S, García-Montero C, Castedo E, Ugarte J, Alonso-Pulpón L. RADIAL: a novel primary graft failure risk score in heart transplantation. *J Heart Lung Transplant* 2011; **30**: 644-651 [PMID: 21470878 DOI: 10.1016/j.healun.2011.01.721]

46 **Angleitner P**, Kaider A, Gökler J, Moayedifar R, Osorio-Jaramillo E, Zuckermann A, Laufer G, Aliabadi-Zuckermann A. High-dose catecholamine donor support and outcomes after heart transplantation. *J Heart Lung Transplant* 2018; **37**: 596-603 [PMID: 29370971 DOI: 10.1016/j.healun.2017.12.015]

47 **Kobashigawa J**, Khush K, Colvin M, Acker M, Van Bakel A, Eisen H, Naka Y, Patel J, Baran DA, Daun T, Luu M, Olymbios M, Rogers J, Jeevanandam V, Esmailian F, Pagani FD, Lima B, Stehlik J. Report From the American Society of Transplantation Conference on Donor Heart Selection in Adult Cardiac Transplantation in the United States. *Am J Transplant* 2017; **17**: 2559-2566 [PMID: 28510318 DOI: 10.1111/ajt.14354]

48 **Fiorelli AI**, Branco JN, Dinkhuysen JJ, Oliveira Junior JL, Pereira TV, Dinardi LF, Santos MM, Dias RR, Pereira LA, Stolf NA. Risk factor analysis of late survival after heart transplantation according to donor profile: a multi-institutional retrospective study of 512 transplants. *Transplant Proc* 2012; **44**: 2469-2472 [PMID: 23026622 DOI: 10.1016/j.transproceed.2012.07.025]

49 **Kutschmann M**, Fischer-Fröhlich CL, Schmidtmann I, Bungard S, Zeissig SR, Polster F, Kirste G, Frühauf NR. The joint impact of donor and recipient parameters on the outcome of heart transplantation in Germany after graft allocation. *Transpl Int* 2014; **27**: 152-161 [PMID: 24286113 DOI: 10.1111/tri.12221]

50 **Gramm HJ**, Meinhold H, Bickel U, Zimmermann J, von Hammerstein B, Keller F, Dennhardt R, Voigt K. Acute endocrine failure after brain death? *Transplantation* 1992; **54**: 851-857 [PMID: 1332223 DOI: 10.1097/00007890-199211000-00016]

51 **Powner DJ**, Hendrich A, Lagler RG, Ng RH, Madden RL. Hormonal changes in brain dead patients. *Crit Care Med* 1990; **18**: 702-708 [PMID: 2194745 DOI: 10.1097/00003246-199007000-00004]

52 **Masson F**, Thicoïpe M, Latapie MJ, Maurette P. Thyroid function in brain-dead donors. *Transpl Int* 1990; **3**: 226-233 [PMID: 2076172 DOI: 10.1007/BF00366971]

53 **Venkateswaran RV**, Steeds RP, Quinn DW, Nightingale P, Wilson IC, Mascaro JG, Thompson RD, Townend JN, Bonser RS. The haemodynamic effects of adjunctive hormone therapy in potential heart donors: a prospective randomized double-blind factorially designed controlled trial. *Eur Heart J* 2009; **30**: 1771-1780 [PMID: 19324916 DOI: 10.1093/eurheartj/ehp086]

54 **Kutsogiannis DJ**, Pagliarello G, Doig C, Ross H, Shemie SD. Medical management to optimize donor organ potential: review of the literature. *Can J Anaesth* 2006; **53**: 820-830 [PMID: 16873350 DOI: 10.1007/BF03022800]

55 **Novitzky D**, Cooper DK. Results of hormonal therapy in human brain-dead potential organ donors. *Transplant Proc* 1988; **20**: 59-62 [PMID: 3055561]

56 **Rosendale JD**, Kauffman HM, McBride MA, Chabalewski FL, Zaroff JG, Garrity ER, Delmonico FL, Rosengard BR. Hormonal resuscitation yields more transplanted hearts, with improved early function. *Transplantation* 2003; **75**: 1336-1341 [PMID: 12717226 DOI: 10.1097/01.TP.0000062839.58826.6D]

57 **Plurad DS**, Bricker S, Falor A, Neville A, Bongard F, Putnam B. Donor hormone and vasopressor therapy: closing the gap in a transplant organ shortage. *J Trauma Acute Care Surg* 2012; **73**: 689-694 [PMID: 22710780 DOI: 10.1097/TA.0b013e318250b122]

58 **Mangus RS**, Fridell JA, Vianna RM, Milgrom ML, Chestovich P, Vandenboom C, Tector AJ. Severe hypernatremia in deceased liver donors does not impact early transplant outcome. *Transplantation* 2010; **90**: 438-443 [PMID: 20679966 DOI: 10.1097/TP.0b013e3181e764c0]

59 **Totsuka E**, Dodson F, Urakami A, Moras N, Ishii T, Lee MC, Gutierrez J, Gerardo M, Molmenti E, Fung JJ. Influence of high donor serum sodium levels on early postoperative graft function in human liver transplantation: effect of correction of donor hypernatremia. *Liver Transpl Surg* 1999; **5**: 421-428 [PMID: 10477844 DOI: 10.1002/Lt.500050510]

60 **Cooper DK**, Novitzky D, Wicomb WN, Basker M, Rosendale JD, Myron Kauffman H. A review of studies relating to thyroid hormone therapy in brain-dead organ donors. *Front Biosci (Landmark Ed)* 2009; **14**: 3750-3770 [PMID: 19273308 DOI: 10.2741/3486]

61 **Zaroff JG**, Rosengard BR, Armstrong WF, Babcock WD, D'Alessandro A, Dec GW, Edwards NM, Higgins RS, Jeevanandum V, Kauffman M, Kirklin JK, Large SR, Marelli D, Peterson TS, Ring WS, Robbins RC, Russell SD, Taylor DO, Van Bakel A, Wallwork J, Young JB. Consensus conference report: maximizing use of organs recovered from the cadaver donor: cardiac recommendations, March 28-29, 2001, Crystal City, Va. *Circulation* 2002; **106**: 836-841 [PMID: 12176957 DOI: 10.1161/01.cir.0000025587.40373.75]

62 **Rosendale JD**, Kauffman HM, McBride MA, Chabalewski FL, Zaroff JG, Garrity ER, Delmonico FL, Rosengard BR. Aggressive pharmacologic donor management results in more transplanted organs. *Transplantation* 2003; **75**: 482-487 [PMID: 12605114 DOI: 10.1097/01.TP.0000045683.85282.93]

63 **Powner DJ**, Hernandez M. A review of thyroid hormone administration during adult donor care. *Prog Transplant* 2005; **15**: 202-207 [PMID: 16252625 DOI: 10.1177/152692480501500302]

64 **Novitzky D**, Mi Z, Videla LA, Collins JF, Cooper DK. Thyroid hormone therapy and procurement of livers from brain-dead donors. *Endocr Res* 2016; **41**: 270-273 [PMID: 26853445 DOI: 10.3109/07435800.2015.1111902]

65 **Novitzky D**, Mi Z, Sun Q, Collins JF, Cooper DK. Thyroid hormone therapy in the management of 63,593 brain-dead organ donors: a retrospective analysis. *Transplantation* 2014; **98**: 1119-1127 [PMID: 25405914 DOI: 10.1097/TP.0000000000000187]

66 **Halaris AE**, Belendiuk KT, Freedman DX. Antidepressant drugs affect dopamine uptake. *Biochem Pharmacol* 1975; **24**: 1896-1897 [PMID: 19 DOI: 10.1016/0006-2952(75)90412-8]

67 **Biondi B**, Palmieri EA, Lombardi G, Fazio S. Effects of thyroid hormone on cardiac function: the relative importance of heart rate, loading conditions, and myocardial contractility in the regulation of cardiac performance in human hyperthyroidism. *J Clin Endocrinol Metab* 2002; **87**: 968-974 [PMID: 11889145 DOI: 10.1210/jcem.87.3.8302]

68 **Macdonald PS**, Aneman A, Bhonagiri D, Jones D, O'Callaghan G, Silvester W, Watson A, Dobb G. A systematic review and meta-analysis of clinical trials of thyroid hormone administration to brain dead potential organ donors. *Crit Care Med* 2012; **40**: 1635-1644 [PMID: 22511141 DOI: 10.1097/CCM.0b013e3182416ee7]

69 **Novitzky D**, Mi Z, Collins JF, Cooper DK. Increased Procurement of Thoracic Donor Organs After Thyroid Hormone Therapy. *Semin Thorac Cardiovasc Surg* 2015; **27**: 123-132 [PMID: 26686437 DOI: 10.1053/j.semtcvs.2015.06.012]

70 **Holndonner-Kirst E**, Nagy A, Czobor NR, Fazekas L, Dohan O, Kertai MD, Lex DJ, Sax B, Hartyanszky I, Merkely B, Gal J, Szekely A. The Impact of l-Thyroxine Treatment of Donors and Recipients on Postoperative Outcomes After Heart Transplantation. *J Cardiothorac Vasc Anesth* 2019; **33**: 1629-1635 [PMID: 30467031 DOI: 10.1053/j.jvca.2018.10.024]

71 **Pinsard M**, Ragot S, Mertes PM, Bleichner JP, Zitouni S, Cook F, Pierrot M, Dube L, Menguy E, Lefèvre LM, Escaravage L, Dequin PF, Vignon P, Pichon N. Interest of low-dose hydrocortisone therapy during brain-dead organ donor resuscitation: the CORTICOME study. *Crit Care* 2014; **18**: R158 [PMID: 25056510 DOI: 10.1186/cc13997]

72 **Kotsch K**, Ulrich F, Reutzel-Selke A, Pascher A, Faber W, Warnick P, Hoffman S, Francuski M, Kunert C, Kuecuek O, Schumacher G, Wesslau C, Lun A, Kohler S, Weiss S, Tullius SG, Neuhaus P, Pratschke J. Methylprednisolone therapy in deceased donors reduces inflammation in the donor liver and improves outcome after liver transplantation: a prospective randomized controlled trial. *Ann Surg* 2008; **248**: 1042-1050 [PMID: 19092349 DOI: 10.1097/SLA.0b013e318190e70c]

73 **Venkateswaran RV**, Patchell VB, Wilson IC, Mascaro JG, Thompson RD, Quinn DW, Stockley RA, Coote JH, Bonser RS. Early donor management increases the retrieval rate of lungs for transplantation. *Ann Thorac Surg* 2008; **85**: 278-286; discussion 286 [PMID: 18154823 DOI: 10.1016/j.athoracsur.2007.07.092]

74 **Venkateswaran RV**, Dronavalli V, Lambert PA, Steeds RP, Wilson IC, Thompson RD, Mascaro JG, Bonser RS. The proinflammatory environment in potential heart and lung donors: prevalence and impact of donor management and hormonal therapy. *Transplantation* 2009; **88**: 582-588 [PMID: 19696643 DOI: 10.1097/TP.0b013e3181b11e5d]

75 **Dhar R**, Cotton C, Coleman J, Brockmeier D, Kappel D, Marklin G, Wright R. Comparison of high- and low-dose corticosteroid regimens for organ donor management. *J Crit Care* 2013; **28**: 111.e1-111.e7 [PMID: 22762934 DOI: 10.1016/j.jcrc.2012.04.015]

76 **Meyfroidt G**, Gunst J, Martin-Loeches I, Smith M, Robba C, Taccone FS, Citerio G. Management of the brain-dead donor in the ICU: general and specific therapy to improve transplantable organ quality. *Intensive Care Med* 2019; **45**: 343-353 [PMID: 30741327 DOI: 10.1007/s00134-019-05551-y]

77 **Kramer AH**, Baht R, Doig CJ. Time trends in organ donation after neurologic determination of death: a cohort study. *CMAJ Open* 2017; **5**: E19-E27 [PMID: 28401114 DOI: 10.9778/cmajo.20160093]

78 **Singh JN**, Nguyen T, Kerndt CC, Dhamoon AS. Physiology, Blood Pressure Age Related Changes. 2021 Jul 12. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan- [PMID: 30725982]

World Journal of Transplantation

Submit a Manuscript: https://www.f6publishing.com

World J Transplant 2021 October 18; 11(10): 421-431

DOI: 10.5500/wjt.v11.i10.421

ISSN 2220-3230 (online)

ORIGINAL ARTICLE

Retrospective Study

Factors predicting futility of liver transplant in elderly recipients: A single-center experience

Cerise Kleb, Muhammad Salman Faisal, Cristiano Quintini, Charles M Miller, K V Narayanan Menon, Jamak Modaresi Esfeh

ORCID number: Cerise Kleb 0000-0002-1489-8566; Muhammad Salmam Faisal 0000-0002-3275-0098; Cristiano Quintini 0000-0002-6802-1436; Charles M Miller 0000-0001-6413-7389; K V Narayanan Menon 0000-0003-4154-2220; Jamak Modaresi Esfeh 0000-0002-9429-5465.

Author contributions: Kleb C designed, performed the research and wrote the paper; Faisal MS contributed to the design of the study and performed analysis of the data; Quintini C, Miller CM and Menon KN helped with critical revisions of the study; Modaresi Esfeh J supervised, helped design the study, made critical revisions to the manuscript and gave final approval.

Institutional review board statement: This study was reviewed and approved by the Cleveland Clinic Foundation Institutional Review Board.

Informed consent statement: This study qualified by a Waiver of Informed Consent as determined by our hospital's IRB as it was a retrospective study that involved no more than minimal risk to the subjects, could not be reasonably carried out without the waiver, and was not a threat to the rights

Cerise Kleb, Muhammad Salman Faisal, Department of Internal Medicine, Cleveland Clinic Foundation, Cleveland, OH 44195, United States

Cristiano Quintini, Charles M Miller, Department of General Surgery, Cleveland Clinic Foundation, Cleveland, OH 44195, United States

K V Narayanan Menon, Jamak Modaresi Esfeh, Department of Gastroenterology & Hepatology, Cleveland Clinic Foundation, Cleveland, OH 44195, United States

Corresponding author: Jamak Modaresi Esfeh, MD, Assistant Professor, Department of Gastroenterology & Hepatology, Cleveland Clinic Foundation, 9500 Euclid Ave, Cleveland, OH 44195, United States. modarej@ccf.org

Abstract

BACKGROUND

As the population of the United States ages, there has been an increasing number of elderly patients with cirrhosis listed for transplant. Previous studies have shown variable results in terms of the relative survival benefit for elderly liver transplant (LT) recipients. There may be factors that are associated with a poor post-transplant outcome which may help determine which elderly patients should and should not be listed for LT.

AIM

To identify factors associated with futility of transplant in elderly patients.

METHODS

This was a retrospective study of all patients above the age of 45 who underwent liver transplantation at our tertiary care center between January 2010 and March 2020 (n = 1019). "Elderly" was defined as all patients aged 65 years and older. Futile outcome was defined as death within 90 d of transplant. Logistic regression analysis was performed to determine what variables, if any were associated with futile outcome in elderly patients. Secondary outcomes such as one year mortality and discharge to facility (such as skilled nursing facility or long-term acute care hospital) were analyzed in the entire sample, compared across three age groups (45-54, 55-64, and 65 + years).

RESULTS

or welfare of the subjects.

Conflict-of-interest statement: We have no financial relationships to disclose.

Data sharing statement: No additional data are available.

Manuscript source: Invited manuscript

Specialty type: Transplantation

Country/Territory of origin: United States

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): 0
Grade D (Fair): D
Grade E (Poor): 0

Received: February 23, 2021
Peer-review started: February 23, 2021
First decision: May 3, 2021
Revised: May 19, 2021
Accepted: September 19, 2021
Article in press: September 19, 2021
Published online: October 18, 2021

P-Reviewer: Wang K
S-Editor: Wang JJ
L-Editor: A
P-Editor: Yuan YY

There was a total of 260 elderly patients who received LT in the designated time period. A total of 20 patients met the definition of "futile" outcome. The mean Model of End-Stage Liver Disease scores in the futile and non-futile group were not significantly different (21.78 in the futile group *vs* 19.66 in the "non-futile" group). Of the variables tested, only congestive heart failure was found to have a statistically significant association with futile outcome in LT recipients over the age of 65 (P = 0.001). Of these patients, all had diastolic heart failure with normal ejection fraction and at least grade I diastolic dysfunction as measured on echocardiogram. Patients aged 65 years and older were more likely to have the outcomes of death within 1 year of LT [hazard ratio: 1.937, confidence interval (CI): 1.24-3.02, P = 0.003] and discharge to facility (odds ratio: 1.94, CI: 1.4-2.8, P < 0.001) compared to patients in younger age groups.

CONCLUSION

Diastolic heart failure in the elderly may be a predictor of futility post liver transplant in elderly patients. Elderly LT recipients may have worse outcomes as compared to younger patients.

Key Words: Liver transplantation; Liver cirrhosis; Heart failure; Diastolic; Medical futility; Liver diseases; Organ transplantation

Core Tip: This was a retrospective study to identify factors associated with futility of liver transplant (LT) in elderly recipients, as well as investigate the risk of certain outcomes such as discharge to facility in elderly LT recipients. Diastolic congestive heart failure (CHF) was found to be a predictor of futility of LT in elderly recipients (P = 0.001). Elderly patients also had nearly twice the risk of being discharged to a facility and had decreased survival at one year. Diastolic CHF may be an important comorbidity for liver transplant committees to consider when deciding whether or not to list elderly patients.

Citation: Kleb C, Faisal MS, Quintini C, Miller CM, Menon KVN, Modaresi Esfeh J. Factors predicting futility of liver transplant in elderly recipients: A single-center experience. *World J Transplant* 2021; 11(10): 421-431
URL: https://www.wjgnet.com/2220-3230/full/v11/i10/421.htm
DOI: https://dx.doi.org/10.5500/wjt.v11.i10.421

INTRODUCTION

As the population of the United States ages, the average age of patients awaiting liver transplantation has increased as well[1]. In 2018, adults aged 65 or older made up 24.1% of the United States liver transplant waiting list. This is twice the proportion of patients in this age group on the waiting list 10 years prior[2]. Along with the aging of the entire United States population, the increase in older patients awaiting transplant can also in part be attributed to the aging of those born between 1945 and 1965, a cohort that has high rates of hepatitis C virus infection[1,3]. The current American Association for the Study of Liver Disease (AASLD) guidelines state that age by itself is not a contraindication to liver transplant (LT), and when deciding whether or not to list a patient aged 70 years or older, functional status and comorbidities must be considered[4].

Transplant committees are faced with a difficult decision when deciding whether to list elderly recipients for LT. Despite efforts to expand the donor organ pool through practices such as living donor, split organ, and expanding eligible organs to include donation after cardiac death organs, there remains a critical shortage of donor organs in the United States[5]. Considering the scarcity of organs, transplant committees may be more motivated to allocate this precious resource to patients who would benefit the most from organ transplantation in terms of survival. For these reasons, avoiding futility in LT plays a major role in decision making.

In the literature, futility in LT has been defined in several different ways. Various definitions include situations in which the patient's post-transplant mortality is greater than the waiting list mortality, death within one year of transplant, death within 90 d, or more qualitative definitions such as poor quality of life and inability to survive outside of an intensive care unit (ICU) setting post-transplant[6].

Despite the extensive amount of research that exists on this topic, there is no conclusive guideline for how to select which elderly patients are suitable for LT. Nevertheless, it is important to avoid futility in transplant, especially when the donor pool is scarce. The purpose of this study is to identify LT recipient factors in the elderly associated with futility of LT. We also aimed to investigate whether certain secondary outcomes such as mortality at one year, discharge to facility [such as skilled nursing facility (SNF) or long-term acute care hospital] and hospital length of stay (LOS) are more common in elderly LT recipients.

MATERIALS AND METHODS

Futility analysis

This was a study of patients who underwent LT at our center. Inclusion criteria included having received LT between January 2010 and March of 2020, and age of 45 years and above. Exclusion criteria included patients who had multi-organ transplants or repeat transplants. This study was approved by our center's Institutional Review Board. All statistical work was done using SPSS v.26.0.

From these patients, we sought to identify factors associated with futility of LT. We defined a "futile" outcome as death within 90 d after transplant. We defined "elderly" as a patient aged 65 years or older. Student *t*-test or Mann-Whitney-*U* test were used to compare continuous variables. Kruskal Wallis test was used to compare continuous variables across three categories. Categorical variables were compared using chi-square tests or Fisher exact test.

From these results, multifactorial binary logistic regression analysis was carried out to analyze futile transplant data for ages greater than 65 years. Variables that were thought to have higher effect size and high clinical significance were chosen for the model [Model of End-Stage Liver Disease (MELD)-Sodium, Child-Pugh Score (CPS), age at transplant].

Additional post-LT outcomes and survival analysis

In addition to the futility analysis, we also investigated several other outcomes (one year mortality, ICU LOS, hospital LOS, and discharge to facility) in three age groups (45-54 years, 55-64 years, and 65 years and older). For comparison of ICU LOS and total hospital LOS, patients with death during the hospitalization were excluded to eliminate bias in the results, as they would have a falsely decreased LOS. Multivariable Cox proportional survival analysis was done to calculate hazard ratio (HR) for 1-year mortality and a Kaplan-Meier curve was constructed for comparison of the three groups. Time to event started from the date of transplant. Individuals who were lost to follow up are included until that time in the analysis.

RESULTS

Sample demographics

From our original sample of all patients who received LT at our center between January 2010 and March of 2020 aged 45 years and older (n = 1147), 128 patients who had multi-organ transplants or repeat transplants were excluded, resulting in a total sample size of 1019 patients. 266 patients were between the ages of 45 and 54 (26.1%), and 493 patients were between the ages of 55 and 64 (48.4%). 260 patients (25.5%) were 65 years of age or above. The average ages in the 45-54, 55-64, and 65 years and older groups were 50.7, 59.5 and 67.8, respectively. 67.3% of patients in the study population were male and 32.7% were female. All three age groups were majority male as well (63.2%, 71.0% and 64.3% in the 45-54, 55-64 and 65 years and older age groups, respectively). The most common underlying causes of liver disease were alcohol related cirrhosis (33.1%) in patients aged 45-54, viral hepatitis in the 55-64 years age group (33.7%) and non-alcoholic steatohepatitis in the 65 years and older age group (33.1%). The mean MELD-Na scores in the 45-54, 55-64, and 65 years and older groups were 21.4, 20.4 and 19.8, respectively (P = 0.236).

Futility analysis

Of the 260 patients above the age of 65, twenty of these met the definition of futile outcome (death within 90 d after transplant). The mean MELD-Na in the futile group was 21.8, compared with 19.7 in the non-futile group (P = 0.236). The mean age in the futile group was 67.3 years and 67.8 years in the non-futile group (P = 0.821).

Of the factors we investigated, including various comorbidities, Karnofsky performance index (KPI), and indicators of severity of liver disease (MELD-Na and CPS), only congestive heart failure (CHF) was more common in the patient group with futile outcome (30% in the futile group as compared to 5% in the non-futile group, P = 0.001) (Table 1). Chart review indicated that all these patients in both the futile and non-futile group had heart failure with preserved ejection fraction, and all had diastolic dysfunction seen on echocardiogram prior to LT. Four of these patients (20%) had grade I diastolic dysfunction, and 16 (80%) had grade II diastolic dysfunction.

We performed binary logistic regression analysis to determine if CHF was an independent predictor of the outcome of death within 90 d of transplant after adjusting for possible confounders such as MELD-Sodium, age at transplant, and CPS. We found that even after adjusting for these factors, a diagnosis of diastolic CHF was still associated with mortality within 90 d of transplant with an adjusted odds ratio (OR) of 9.44 [confidence interval (CI): 2.89-30.81, P < 0.0001]. MELD-Sodium, age, and CPS were not predictors of 90 d mortality (Table 2).

Additional post-LT outcomes analysis

In addition to investigating factors associated with futility of LT, we also investigated several additional outcomes in patients split into three age groups, to see if these outcomes were more likely to occur in the older cohort. Table 3 shows the results of our analysis of secondary outcomes between the three age groups. Our analysis found that patients aged 65 and older were more likely to have the outcome of death within one year of LT, and had longer total hospital lengths of stay (16.8 +/- standard deviation of 23.9 d, compared to 13.22 +/- 15.4 and 14.14 +/- 24 d in the 45-54 years and 55-64 years age groups, respectively). Patients aged 65 years and older were also less likely to be discharged to home or home with home health care, compared to discharge to facilities such as rehabilitation or nursing facilities. Patients 65 or older were almost twice as likely to be discharged to a facility: Long term acute care hospital/SNF/acute rehab facility, OR: 1.94 (CI: 1.4-2.8, P < 0.001) compared to patients younger than 65. Patients who died during hospitalization following LT were excluded from this analysis.

Survival analysis

In addition, we also performed Cox Regression Survival Analysis to determine if patients 65 years and older had increased mortality after one year after adjusting for severity of liver disease and comorbidities (Table 4, Figure 1). This showed that even after adjusting for severity of liver disease with MELD-Sodium and multiple co-morbidities, patients aged 65 years and older had higher one year mortality as compared to patients younger than 65 (HR: 1.937, CI: 1.244-3.017). This difference was not seen when comparing the 45-54 years age group to the 55-64 years age group.

DISCUSSION

The purpose of this study was to identify factors that are associated with futility of LT in elderly recipients, in order to help with difficult decisions LT selection committees face when choosing whether to list elderly patients. Regardless of their age, LT candidates must go through rigorous screening processes before being listed for LT [4]. This is to ensure that the donor organ, which is a scarce resource in our country[5] is going to candidates that will benefit the most from it. This decision is made even more complex when the candidate in question is elderly, and by virtue of age already has a shorter life expectancy than younger candidates.

Previous research has produced conflicting results about survival in elderly LT recipients as compared to younger patients. A 2007 single-center study of survival outcomes in orthotopic liver transplantation recipients aged 70 years and older as compared to those aged 50 to 59 years found that the unadjusted patient survival at 1, 3, 5 and 10 years was not significantly different between these two groups. This study also found that on multivariate analysis in this population, age ≥ 70 was not an independent predictor of increased mortality in this population[7]. However, a 2018 Korean study found that patients aged 70 years or older had a fourfold higher risk of

Table 1 Comparison of patients over the age of 65 who underwent transplant and died within 90 d from transplant compared to those who survived beyond 90 d

Characteristic	Death within 90 d, *N* = 20	Survival beyond 90 d, *N* = 240	*P* value
Age, mean ± SD	67.30 ± 1.78	67.81 ± 2.71	0.821
Year of transplant, median (percentiles)	2014 (2012-2016)	2015 (2013-2018)	0.183
Comorbid conditions, *n* (%)			
Obesity	6 (30.0)	57 (23.8)	0.590
CHF	6 (30.0)	12 (5.0)	0.001[a]
CKD	1 (5.0)	23 (9.6)	0.705
HTN	14 (70.0)	152 (63.3)	0.550
DM	9 (45.0)	109 (45.4)	0.971
CAD	8 (40.0)	73 (30.4)	0.374
PH	2 (10.0)	9 (3.8)	0.203
Arrhythmias	3 (15.0)	32 (13.3)	0.739
Pre-transplant severity of disease			
Ascites			
None	2 (10.0)	34 (14.2)	0.269
Mild	7 (35.0)	111 (46.3)	
Moderate	3 (15.0)	45 (18.8)	
Severe	8 (40.0)	50 (20.8)	
Encephalopathy			
None	3 (15.0)	61 (25.4)	0.397
Grade 1-2	17 (85.0)	172 (71.7)	
Grade 3-4	0 (0)	7 (2.9)	
Child-Pugh Score	9.8 +/- 1.7	9.08 +/- 2.0	0.127
A	0 (0)	26 (10.5)	0.257
B	8 (40)	116 (48.3)	
C	12 (60.0)	98 (40.8)	
Karnofsky performance index	53.50 ± 20.1	55.69 ± 21.6	0.555
Indication for transplant, *n* (%)			
Cirrhosis	16 (80.0)	147 (56.5)	0.143
NASH	6 (30.0)	54 (22.5)	0.419
Autoimmune	2 (10.0)	3 (1.3)	0.049
Alcohol	2 (10.0)	32 (13.3)	0.999
Hepatitis C	2 (10.0)	18 (7.5)	0.658
Cryptogenic	1 (5.0)	14 (5.8)	0.999
PSC	0 (0)	11 (4.6)	0.999
PBC	2 (10.0)	11 (4.6)	0.263
Hemochromatosis	0 (0)	4 (1.7)	0.999
HCC and cirrhosis	4 (20.0)	87 (36.3)	0.143
Acute liver failure	0 (0)	6 (2.5)	0.999
Primary etiology of liver disease, *n* (%)			
Alcohol related cirrhosis	2 (10)	46 (19.2)	0.55

NASH cirrhosis	8 (40)	78 (32.5)	0.49
Cirrhosis due to viral hepatitis	2 (10)	48 (20)	0.38
Other	8 (40)	68 (28.3)	0.27
Lab values, mean ± SD			
Sodium	135.70 ± 4.3	136.12 ± 4.3	0.678
INR	1.51 ± 0.4	1.49 ± 0.5	0.241
Creatinine	1.68 ± 1.0	1.45 ± 1.0	0.133
Total Bili	6.34 ± 6.8	5.46 ± 7.8	0.271
MELD-Sodium	21.78 ± 8.6	19.66 ± 9.0	0.236
Albumin	3.16 ± 0.6	3.18 ± 0.6	0.889

[a]$P < 0.05$. CHF: Congestive heart failure; CKD: Chronic kidney disease; HTN: Hypertension; DM: Diabetes mellitus; CAD: Coronary artery disease; PH: Pulmonary hypertension; NASH: Non-alcoholic steatohepatitis; PSC: Primary sclerosing cholangitis; PBC: Primary biliary cholangitis; HCC: Hepatocellular carcinoma; INR: International normalized ratio; MELD: Model of End-Stage Liver Disease.

Table 2 Binary Logistic Regression analysis to calculate adjusted odds ratio for death within 90 d of transplant

Variable	Adjusted OR	Confidence interval	*P* value
MELD-Na	1.02	0.95-1.09	0.615
Age at transplant	1.09	0.89-1.32	0.421
CPS-C *vs* CPS A and B	3.25	0.86-12.25	0.081
CHF	9.44	2.89-30.81	< 0.0001

OR: Odds ratio; MELD: Model of End-Stage Liver Disease; CPS: Child-Pugh Score; CHF: Congestive heart failure.

in-hospital mortality when adjusting for baseline cause of liver disease, and a threefold higher risk of in-hospital mortality when controlling for cause of liver disease and perioperative complications such as need for vasopressor support, ventilator support and extracorporeal membrane oxygenation[8]. A large-scale study utilizing data from the United Network for Organ Sharing (UNOS) transplant database found that post-transplant survival decreased with increased age. However, when stratifying patients with the same MELD score into different age groups, there was no statistically significant difference in survival benefit at five years between these groups. However, this study noted that the reason that the survival benefit was preserved in older age groups was likely because pre-transplantation survival (*i.e.*, waitlist mortality) and post-transplantation survival were equally reduced in older patients. Therefore, the net difference in waitlist and post-transplantation life expectancy was the same between elderly patients and younger cohorts[1].

There have been a few studies investigating what factors are associated with futility of LT. One study found that in patients who received LT while requiring ICU level care, factors associated with the primary outcome of 90-d mortality included high pre-transplant lactate level and the presence of acute respiratory distress syndrome[9]. A second study identifying factors associated with futility of LT in patients with MELD score ≥ 40 (defined as death within 90 d of transplant) found that pretransplant septic shock, cardiac risk, and comorbidities were independent predictors of this outcome [10]. There have also been some studies investigating which recipient factors are associated with a poor outcome in elderly patients. A study of LT patients above the age of 60 who received LT between 2004 and 2010 at our own center showed that hepatic encephalopathy, significant thrombocytopenia (platelet count less than 45000), total serum bilirubin > 3.5 mg/dL, and hypoalbuminemia (< 2.65 mg/dL) were independent predictors of one year mortality[11]. A second study using data from the UNOS database found that on multivariate analysis, factors such as low albumin, recipient diabetes mellitus, elevated creatinine, and recipient hepatitis C positivity were associated with increased mortality in LT recipients above the age of 60 years[12].

Table 3 Outcomes analysis for different age groups

Age category	45-54 years	55-64 years	≥ 65 years	*P* value
30-d mortality (*n*, %)	8 (3.0)	12 (2.4)	10 (3.8)	0.55
1-yr mortality (*n*, %)	32 (12.0)	75 (15.2)	59 (22.7)	0.03
ICU LOS				
mean ± SD	3.80 ± 6.8	3.99 ± 6.8	4.17 ± 6.6	0.320
Median (IQR)	2.0 (1.0-3.0)	2.0 (1.0-4.0)	2.0 (1.0-4.0)	
Total hospitalization				
mean ± SD	13.22 ± 15.4	14.14 ± 24.0	16.8 ± 23.9	0.034
Median (IQR)	10.0 (7.0-14.0)	10.0 (7.0-15.0)	11.0 (8.0-17.0)	
Discharge disposition (*n* = 890) (*n*, %)				
Home	182 (76.2)	314 (73.4)	133 (59.6)	0.000
Home or HHC	190 (79.5)	329 (76.9)	142 (63.7)	0.000
Any facility other than home [excluding patients who died during hospitalization, *n* = 854)]	42 (18.1)	84 (20.3)	67 (32.1)	0.001
Acute Rehab	13 (5.4)	7 (4.0)	9 (4.0)	
LTAC	9 (3.8)	21 (4.9)	13 (5.8)	
SNF	20 (8.4)	45 (10.5)	45 (20.2)	
Deceased	7 (2.9)	15 (3.5)	14 (6.3)	
Hospice	0	1 (0.2)	0	

ICU: Intensive care unit; LOS: Length of stay; IQR: Interquartile range; HHC: Hand hygiene compliance; LTAC: Long-term acute care hospital; SNF: Skilled nursing facility.

Table 4 Cox Regression Survival Analysis for comparison between different age groups for 1-year mortality

Factor	Hazard ratio	*P* value	95%CI	
			Lower	Upper
MELD-Na	1.011	0.174	0.995	1.028
CHF	1.425	0.210	0.819	2.480
Obesity	0.907	0.618	0.617	1.333
Hypertension	0.967	0.839	0.697	1.341
Type 2 diabetes	1.210	0.252	0.873	1.678
Coronary artery disease	1.054	0.781	0.726	1.532
Age 55-64 *vs* Age < 55	1.252	0.293	0.824	1.902
Pulmonary hypertension	1.209	0.539	0.660	2.217
Age > 65 *vs* Age <65	1.937	.003	1.244	3.017

MELD: Model of End-Stage Liver Disease; CHF: Congestive heart failure.

For the purpose of this study, we defined "futile" as death within 90 d of transplant. This definition was derived from previous studies that have defined futility in this way[9,10]. Our study found that patients who had a futile outcome after LT were significantly more likely to have a diagnosis of heart failure with preserved ejection fraction, with diastolic dysfunction seen on echocardiogram (30% *vs* 5%, $P = 0.001$). This association persisted with logistic regression modeling adjusting for MELD, age at transplant and CPS. Other factors such as KPI, MELD, CPS or other comorbidities did not show any significant difference in scale or incidence between the futile and

Figure 1 Kaplan-Meier survival curve for different age groups. We generated a Kaplan-Meier survival curve to compare the one-year mortality of the three age groups (45-54 years, 55-64 years, ≥ 65 years). One year survival was significantly lower in the group of patients aged 65 years and older.

non-futile groups.

Though to our knowledge ours is the first study to demonstrate the strong linkage between futility of LT in elderly patients and diastolic heart failure, there has been some research in the past on diastolic dysfunction's role in patients with cirrhosis. One study found that diastolic dysfunction seen on echocardiogram was associated with decreased survival, was a predictor of hepatorenal syndrome, and that survival decreased with increased severity of diastolic dysfunction (*i.e.*, grade I *vs* grade II)[13]. This is thought to be due to the phenomenon of "cirrhotic cardiomyopathy", characterized by a blunted cardiovascular response to stress and impaired relaxation of the ventricles. Cirrhotic cardiomyopathy has been attributed to various physiologic and chemical changes in cirrhotic patients, and is essentially heart failure due to impaired diastolic function that occurs in the absence of primary heart disease. It is thought that in patients with cirrhotic cardiomyopathy, after an event such as liver transplantation there is a dramatic increase in preload to a heart that has profound diastolic dysfunction, which may result in worsened heart failure and pulmonary edema[14]. This physiologic change may account for the increased probability of futile outcome in our sample of elderly patients with diastolic CHF.

Since we have found that diastolic CHF was an independent predictor of futile outcome in elderly patients, it may be useful to screen elderly patients more carefully for diastolic dysfunction, and use this as a tool when deciding whether to list elderly patients for LT. However, heart failure with preserved ejection fraction is difficult to diagnose based on echocardiogram as there are many different echocardiographic features that can be associated with diastolic heart failure, but few that are diagnostic [15]. The clinical diagnosis of heart failure with preserved ejection fraction includes the presence of exertional dyspnea and peripheral edema; however, these are symptoms that can be seen as a result of liver disease as well, so it may be difficult to make the diagnosis of diastolic heart failure in these patients[14].

The presence of coronary artery disease (CAD) was not significantly different between the futile and non-futile group, nor between patients who died within one year of transplant and patients who survived beyond one year. Interestingly, this is in contrast to a 2014 study done at our institution of patients aged 60 years or older who received LT between the years of 2004-2010, which found that CAD was an independent predictor of both short-term mortality (defined as within 30 d of LT) and the composite outcome of mortality and/or graft failure at one year[11]. One possible explanation for this difference could be improved screening methods for coronary disease in LT recipients over the past 10 years. In addition, while the aforementioned study included heart failure in their data analysis by way of left ventricular ejection fraction, this would exclude patients with diastolic heart failure (otherwise known as heart failure with preserved ejection fraction) from their analysis[11].

A clear limitation to our futility analysis is the small number of people who met our definition of "futile outcome", or death within 90 d of LT. In our sample, only 20 patients aged 65 and older died within 90 d of LT, out of 260 total patients in this age group that received LT at our center. This small number reduced our study's power.

Therefore, it may be that some of the factors we investigated (MELD, CPS, KPI and various comorbidities) are linked to futility and our small sample size prevents us from seeing these associations. An interesting future direction would be to expand this analysis to include multiple centers to see if any of the other factors we investigated would be significantly associated with futility if the study were adequately powered. The small sample size also prohibited us from adjusting for more than a few covariates in our logistic regression analysis. We chose to adjust for MELD, CPS, and age at transplant since we thought these might be the biggest confounders, but there are other factors such as concurrent comorbidities that may have confounded our data.

The fact that elderly LT recipients have longer hospital LOS and are more likely to be discharged to facility is an important finding because both longer LOS and facility care are costly to our healthcare system[16]. This is also important because improvement in functional status is likely important to patients pursuing LT, and if they are less likely to return home due to need for an extended period of recovery or a higher level of care, this should be considered. It is important to note that our study did not account for the patients' previous living situation (home, nursing facility, *etc*.) and did not investigate how long these patients needed to stay in facilities after discharge from the hospital. This would be an interesting future direction.

Survival analysis showed that patients aged 65 years or older had decreased one-year survival even when adjusting for severity of liver disease and comorbidities. This adds to the body of literature that has produced somewhat conflicting results about whether age has a significant impact on post-LT survival. However, it should be noted that though we found that one year mortality after LT was higher in elderly patients, it may be that these results are confounded by the fact that elderly patients have decreased survival overall. One previous study accounted for this in their survival analysis and found that though survival after LT is reduced in elderly patients, the survival benefit is preserved[1]. It may be that this is also the case in our patient population, but calculation of survival benefit is complex and beyond the scope of this paper.

CONCLUSION

In conclusion, heart failure with preserved ejection fraction and diastolic dysfunction should be used as an important tool when prognosticating elderly LT candidates. Diastolic dysfunction may be an indicator of cirrhotic cardiomyopathy, which is associated with very severe liver disease[14] and may be an indicator of poor outcome after LT as well. It may be useful to consider screening for diastolic heart failure more aggressively in elderly patients. When considering elderly patients for LT, patients and transplant committees should be aware that elderly LT recipients may be more likely to need post-acute placement in a facility and have a longer hospital course, which have important financial implications. It is important to consider the impact of transplanting elderly individuals may have on healthcare expenditures, and make these patients aware of the possible need for an extended recovery. We hope that this study will contribute to the body of evidence on this topic to aid LT selection committees in the allocation of a precious resource.

ARTICLE HIGHLIGHTS

Research background

The average age of patients awaiting liver transplant (LT) in the United States is increasing. Previous research on the effect of age on post-LT outcomes has produced conflicting results.

Research motivation

The donor pool for LT remains limited and donor organs is a precious resource. Thus, avoiding futility of transplant is important.

Research objectives

The objective of this study was to identify factors associated with futility of LT in elderly patients, to help inform the decision whether or not to list elderly patients with liver disease for transplant. We also aimed to investigate relevant post-transplant outcomes in elderly patients.

Research methods

This study included all patients above the age of 45 who underwent LT at our center over a ten-year period (2010-2020). Of these patients, 260 were 65 years of age or older. In the elderly cohort, several patient factors were analyzed to determine if they were associated with a "futile" outcome defined as death within 90 d after transplant. We also analyzed three different age groups for secondary outcomes such as hospital length of stay (LOS), intensive care unit LOS and discharge to facility.

Research results

Diastolic congestive heart failure (CHF) was independently associated with futility of LT after adjusting for potential confounders. Elderly LT recipients had higher one year mortality, longer hospital LOS and were more likely to be discharged to a facility.

Research conclusions

Diastolic CHF may be a prognostic indicator for futility of LT in elderly patients. This comorbidity should be considered as part of the pre-LT evaluation.

Research perspectives

Further research is needed with a larger sample size, perhaps including multiple centers to determine if there are any other patient comorbidities (or other factors such as functional status and primary cause of liver disease) are associated with futility of LT in elderly patients.

REFERENCES

1 **Su F**, Yu L, Berry K, Liou IW, Landis CS, Rayhill SC, Reyes JD, Ioannou GN. Aging of Liver Transplant Registrants and Recipients: Trends and Impact on Waitlist Outcomes, Post-Transplantation Outcomes, and Transplant-Related Survival Benefit. *Gastroenterology* 2016; **150**: 441-53.e6; quiz e16 [PMID: 26522262 DOI: 10.1053/j.gastro.2015.10.043]

2 **Kwong A**, Kim WR, Lake JR, Smith JM, Schladt DP, Skeans MA, Noreen SM, Foutz J, Miller E, Snyder JJ, Israni AK, Kasiske BL. OPTN/SRTR 2018 Annual Data Report: Liver. *Am J Transplant* 2020; **20** Suppl s1: 193-299 [PMID: 31898413 DOI: 10.1111/ajt.15674]

3 **Edlin BR**, Eckhardt BJ, Shu MA, Holmberg SD, Swan T. Toward a more accurate estimate of the prevalence of hepatitis C in the United States. *Hepatology* 2015; **62**: 1353-1363 [PMID: 26171595 DOI: 10.1002/hep.27978]

4 **Martin P**, DiMartini A, Feng S, Brown R Jr, Fallon M. Evaluation for liver transplantation in adults: 2013 practice guideline by the American Association for the Study of Liver Diseases and the American Society of Transplantation. *Hepatology* 2014; **59**: 1144-1165 [PMID: 24716201 DOI: 10.1002/hep.26972]

5 **Saidi RF**, Hejazii Kenari SK. Challenges of organ shortage for transplantation: solutions and opportunities. *Int J Organ Transplant Med* 2014; **5**: 87-96 [PMID: 25184029]

6 **Linecker M**, Krones T, Berg T, Niemann CU, Steadman RH, Dutkowski P, Clavien PA, Busuttil RW, Truog RD, Petrowsky H. Potentially inappropriate liver transplantation in the era of the "sickest first" policy - A search for the upper limits. *J Hepatol* 2018; **68**: 798-813 [PMID: 29133246 DOI: 10.1016/j.jhep.2017.11.008]

7 **Lipshutz GS**, Hiatt J, Ghobrial RM, Farmer DG, Martinez MM, Yersiz H, Gornbein J, Busuttil RW. Outcome of liver transplantation in septuagenarians: a single-center experience. *Arch Surg* 2007; **142**: 775-781; discussion 781-784 [PMID: 17709732 DOI: 10.1001/archsurg.142.8.775]

8 **Chen HP**, Tsai YF, Lin JR, Liu FC, Yu HP. Recipient Age and Mortality Risk after Liver Transplantation: A Population-Based Cohort Study. *PLoS One* 2016; **11**: e0152324 [PMID: 27019189 DOI: 10.1371/journal.pone.0152324]

9 **Michard B**, Artzner T, Lebas B, Besch C, Guillot M, Faitot F, Lefebvre F, Bachellier P, Castelain V, Maestraggi Q, Schneider F. Liver transplantation in critically ill patients: Preoperative predictive factors of post-transplant mortality to avoid futility. *Clin Transplant* 2017; **31** [PMID: 28895204 DOI: 10.1111/ctr.13115]

10 **Petrowsky H**, Rana A, Kaldas FM, Sharma A, Hong JC, Agopian VG, Durazo F, Honda H, Gornbein J, Wu V, Farmer DG, Hiatt JR, Busuttil RW. Liver transplantation in highest acuity recipients: identifying factors to avoid futility. *Ann Surg* 2014; **259**: 1186-1194 [PMID: 24263317 DOI: 10.1097/SLA.0000000000000265]

11 **Sonny A**, Kelly D, Hammel JP, Albeldawi M, Zein N, Cywinski JB. Predictors of poor outcome among older liver transplant recipients. *Clin Transplant* 2015; **29**: 197-203 [PMID: 25528882 DOI: 10.1111/ctr.12500]

12 **Aloia TA**, Knight R, Gaber AO, Ghobrial RM, Goss JA. Analysis of liver transplant outcomes for United Network for Organ Sharing recipients 60 years old or older identifies multiple model for end-stage liver disease-independent prognostic factors. *Liver Transpl* 2010; **16**: 950-959 [PMID:

20589647 DOI: 10.1002/lt.22098]
13 **Ruíz-del-Árbol L**, Achécar L, Serradilla R, Rodríguez-Gandía MÁ, Rivero M, Garrido E, Natcher JJ. Diastolic dysfunction is a predictor of poor outcomes in patients with cirrhosis, portal hypertension, and a normal creatinine. *Hepatology* 2013; **58**: 1732-1741 [PMID: 23703953 DOI: 10.1002/hep.26509]
14 **Zardi EM**, Zardi DM, Chin D, Sonnino C, Dobrina A, Abbate A. Cirrhotic cardiomyopathy in the pre- and post-liver transplantation phase. *J Cardiol* 2016; **67**: 125-130 [PMID: 26074443 DOI: 10.1016/j.jjcc.2015.04.016]
15 **Obokata M**, Reddy YNV, Borlaug BA. Diastolic Dysfunction and Heart Failure With Preserved Ejection Fraction: Understanding Mechanisms by Using Noninvasive Methods. *JACC Cardiovasc Imaging* 2020; **13**: 245-257 [PMID: 31202759 DOI: 10.1016/j.jcmg.2018.12.034]
16 **De Nardi M**, French E, Jones JB, McCauley J. Medical Spending of the US Elderly. *Fisc Stud* 2016; **37**: 717-747 [PMID: 31404348 DOI: 10.1111/j.1475-5890.2016.12106]

World Journal of Transplantation

Submit a Manuscript: https://www.f6publishing.com

World J Transplant 2021 October 18; 11(10): 432-442

DOI: 10.5500/wjt.v11.i10.432

ISSN 2220-3230 (online)

META-ANALYSIS

Impact of immunosuppression on incidence of post-transplant diabetes mellitus in solid organ transplant recipients: Systematic review and meta-analysis

Sreelakshmi Kotha, Bishoy Lawendy, Saira Asim, Charlene Gomes, Jeffrey Yu, Ani Orchanian-Cheff, George Tomlinson, Mamatha Bhat

ORCID number: Sreelakshmi Kotha 0000-0003-3144-503X; Bishoy Lawendy 0000-0002-0447-3871; Saira Asim 0000-0002-7398-1554; Charlene Gomes 0000-0001-8897-3904; Jeffrey Yu 0000-0003-1699-7039; Ani Orchanian-Cheff 0000-0002-9943-2692; George Tomlinson 0000-0002-9328-6399; Mamatha Bhat 0000-0003-1960-8449.

Author contributions: Kotha S and Bhat M designed the study; Kotha S, Lawendy B, Asim S, Gomes C, Yu J and Bhat M collected the data; Kotha S, Lawendy B, Tomlinson G and Bhat M wrote the paper; Orchanian-Cheff A did the literature search; Tomlinson G made the data analysis; and All authors finally approved this manuscript.

Conflict-of-interest statement: There is no conflict of interest for any of the authors

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

Open-Access: This article is an open-access article that was selected by an in-house editor and

Sreelakshmi Kotha, Department of Gastroenterology, Guy's and St Thomas' Hospital, London SE1 7JD, United Kingdom

Bishoy Lawendy, Charlene Gomes, Jeffrey Yu, Ani Orchanian-Cheff, Department of Multi-Organ Transplantation, Toronto General Hospital, Toronto M5G 2C4, Canada

Saira Asim, Multi Organ Transplant Program, Toronto General Hospital, Toronto M5G 2C4, Canada

George Tomlinson, Dalla Lana School of Public Health, Department of Medicine, University Health Network - Toronto General Hospital, University of Toronto, Toronto M5G 2C4, Canada

Mamatha Bhat, Multi-organ Transplant, Toronto General Hospital, Toronto M5G 2C4, Canada

Corresponding author: Sreelakshmi Kotha, MBBS, MRCP, Staff Physician, Department of Gastroenterology, Guy's and St Thomas' Hospital, Westminster B ridge Road, London SE1 7JD, United Kingdom. sreelakshmi.kotha@gstt.nhs.uk

Abstract

BACKGROUND

Solid organ transplantation is a life-saving intervention for end-stage organ disease. Post-transplant diabetes mellitus (PTDM) is a common complication in solid organ transplant recipients, and significantly compromises long-term survival beyond a year.

AIM

To perform a systematic review and meta-analysis to estimate incidence of PTDM and compare the effects of the 3 major immunosuppressants on incidence of PTDM.

METHODS

Two hundred and six eligible studies identified 75595 patients on Tacrolimus, 51242 on Cyclosporine and 3020 on Sirolimus. Random effects meta-analyses was used to calculate incidence.

RESULTS

Manuscript source: Unsolicited manuscript

Specialty type: Transplantation

Country/Territory of origin: Canada

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

Received: June 20, 2021
Peer-review started: June 20, 2021
First decision: July 28, 2021
Revised: August 27, 2021
Accepted: September 19, 2021
Article in press: September 19, 2021
Published online: October 18, 2021

P-Reviewer: Gonzalez FM
S-Editor: Ma YJ
L-Editor: A
P-Editor: Yuan YY

Network meta-analysis estimated the overall risk of developing PTDM was higher with tacrolimus (OR = 1.4 95%CI: 1.0–2.0) and sirolimus (OR = 1.8; 95%CI: 1.5–2.2) than with Cyclosporine. The overall incidence of PTDM at years 2-3 was 17% for kidney, 19% for liver and 22% for heart. The risk factors for PTDM most frequently identified in the primary studies were age, body mass index, hepatitis C, and African American descent.

CONCLUSION

Tacrolimus tends to exhibit higher diabetogenicity in the short-term (2-3 years post-transplant), whereas sirolimus exhibits higher diabetogenicity in the long-term (5-10 years post-transplant). This study will aid clinicians in recognition of risk factors for PTDM and encourage careful evaluation of the risk/benefit of different immunosuppressant regimens in transplant recipients.

Key Words: Post-transplant diabetes mellitus; solid organ transplantation; Tacrolimus; Cyclosporin; Sirolimus

Core Tip: The aim of this study is to perform a systematic review and meta-analysis to estimate incidence of post-transplant diabetes mellitus (PTDM) and the relative effects of the 3 major immunosuppressants on incidence of PTDM. This study will aid clinicians in recognizing the risk factors for PTDM and careful evaluation of the risk/benefit of different immunosuppressant regimens in transplant recipients.

Citation: Kotha S, Lawendy B, Asim S, Gomes C, Yu J, Orchanian-Cheff A, Tomlinson G, Bhat M. Impact of immunosuppression on incidence of post-transplant diabetes mellitus in solid organ transplant recipients: Systematic review and meta-analysis. *World J Transplant* 2021; 11(10): 432-442
URL: https://www.wjgnet.com/2220-3230/full/v11/i10/432.htm
DOI: https://dx.doi.org/10.5500/wjt.v11.i10.432

INTRODUCTION

Solid organ transplantation (SOT) has achieved an excellent long-term survival in various end-stage organ diseases. However, it is still associated with several complications including post-transplant diabetes mellitus (PTDM) in the transplant recipients. PTDM may result from both transplant-related factors like immunosuppression as well as traditional risk factors like obesity, ethnicity, lifestyle and genetics. It is associated with significant morbidity and mortality, with increased cardiovascular risk, infection and graft failure [1,2]. The reported incidence of PTDM has been variable due to varying definitions over time, diverse transplant patient populations and variation in immunosuppression regimens. The reported incidence ranges from 4%-25% in renal transplant recipients, 2.5%-25% in liver transplant recipients, 4%-40% in heart transplant recipients, and 30%-35% in lung transplant recipients[3,4]. In some instances, hyperglycemia develops in response to steroid doses and pulsed steroids required during episodes of acute rejection rather than baseline immunosuppression and care must be taken in making the diagnosis.

Based on the 2013 International Consensus meeting[3], the older term new onset diabetes after transplant has been replaced by PTDM, which is defined as newly diagnosed diabetes post-transplant irrespective of timing or whether it was present but undetected prior to transplant. The criteria for diagnosis of PTDM are symptoms of diabetes plus random plasma glucose (PG) concentrations ≥ 200 mg/dL (11.1 mmol/L) or fasting blood glucose ≥ 126 mg/dL (7.0 mmol/L) (on two occasions) or 2-hour PG ≥ 200 mg/dL (11.1 mmol/L) during an oral glucose tolerance test or HbA1C ≥ 6.5%[3]. However, these guidelines mainly focus on kidney transplant patients as most studies were conducted in this cohort.

Historically, PTDM has been attributed to insulin resistance like type 2 diabetes mellitus (DM2). The pathophysiology is incompletely understood, both insulin resistance and impaired insulin secretion due to destruction of pancreatic B-cells have been implicated[5,6]. PTDM is associated with traditional DM2 risk factors such as older age, ethnicity, obesity, family history of DM2 and unique post-transplant risk factors such as immunosuppressant use, CMV positivity, hepatitis C and weight gain [7,8].

PTDM has a significant impact on post-transplant outcomes. Various studies have reported decreased graft survival and an increase in cardiovascular, renal and infection complications[1,2]. Identification of risk factors is helpful in guiding the implementation of measures to prevent PTDM and its associated morbidity and mortality in solid organ transplant recipients. A network meta-analysis (NMA) allows for the comparison of multiple treatments in a single analytical model, allowing direct and indirect comparisons between several treatments.

The objective of this NMA is to determine the relative impact of the 3 main immunosuppressants ie tacrolimus, sirolimus and cyclosporine used in transplant medicine on the incidence of PTDM, thus providing information on clinical risk stratification and prompting physicians to carefully evaluate risk-benefit ratios in transplant recipients.

MATERIALS AND METHODS

Study design

We performed a systematic review and meta-analysis as per the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement standards. An experienced librarian at the University of Toronto performed the literature search on February 16, 2017.

A systematic literature search was performed in peer reviewed databases of Medline, Medline epub/in-process, EMBASE, CDSR and CCRCCT (search last conducted on February 16, 2017 including studies from 1995 onwards). The search strategy was developed using a combination of database-specific subject headings and text words. Additional key words were mined from sample articles and generated through input from subject specialists on the team. The search strategy was then customized for each database. Appendix 1 outlines the detailed search strategy.

Selection criteria and data extraction

Two independent reviewers screened the titles and abstracts using the inclusion criteria**.** Disagreement was resolved after discussion.

The inclusion criteria were: (1) English-language studies; (2) Studies with an adult (> 18 years old) human patient population; (3) Studies published between 1995 and the date of the search; (4) Studies using an intervention of maintenance immunosuppression with standard-dose tacrolimus, cyclosporine or sirolimus; (5) Studies about solid-organ transplant recipients (*i.e.*, not hand, pancreatic islet, stem cell transplant); and (6) Studies with a follow-up period of 1 year or longer.

Statistical analysis

Estimation of incidence: Random effects meta-analyses of the treatment-specific incidence of PTDM overall (using the earliest reported time in each study) as well as at various time points post-transplant (1 year, 2-3 years, and 5 or more years) were conducted using generalized linear mixed models; the input data were the number of patients with follow-up and the number with PTDM at the time point. In this analysis, we only pooled data from cohort and randomized studies where patients with pre-existing DM were excluded. Heterogeneity was assessed using Cochran's Q, and I^2. Meta-regression was used to quantify the variation in incidence attributable to the following study characteristics: mean patient age, mean body mass index (BMI), percentage male, concomitant use of steroids and study design.

Comparisons of relative incidence: To compare incidence between the three immunosuppressants, NMA was used. This allows comparison of multiple treatments in a single analytical model, allowing for direct and indirect comparisons between numerous treatments, so all studies could be included simultaneously. The direct and indirect estimates were compared using the node-splitting procedure. For example, the directly estimated odds ratio from studies comparing sirolimus and tacrolimus can be compared to the indirect estimate that would be expected based on the comparisons of

each of them to cyclosporine. When these direct and indirect estimates are consistent, the pooled network estimate can be more precise than the direct estimate. Odds ratios (OR) between pairs of treatments were calculated as well as the 95% credible intervals. All analyses were done in R 4.02 using the Meta package for meta-analysis of incidence and the gemtc packages for NMA[9-11].

Quality grading of studies: The quality of each study in the analysis was assessed based on Newcastle-Ottawa scale (NOS). The scale includes three categories, using scores of 1-9 for assessment. The total score is 9, comprising of 4 for selection, 2 for comparability, and 3 for outcome. Total score ≥ 7 represents a high-quality study.

RESULTS

The literature search yielded 7638 records. Following elimination of 1768 duplicates, 5870 articles were identified for screening, of which 5144 records were excluded by title and abstract, leaving 726 eligible for full-text assessment. Case reports/series, conference proceedings, and editorials, reviews, articles in which PTDM was not the primary or secondary outcome of interest, or there was unclear duration of follow-up, or the intervention was not an immunosuppressant regimen of interest and articles with inadequate information were excluded after a full text review. Ultimately, 206 studies were included in our study as shown in the PRISMA diagram (Figure 1). Most of the studies had a NOS score of 7, with a mean of 7.2 indicating that the overall study quality was high. The median year of publication was 2009, and most of the papers were published between 2006 and 2013. The breakdown of the studies by design was as follows: 151 studies were cohort studies, 6 were case-control studies, 10 were cross-sectional studies and 39 studies were randomized controlled trials. The studies included various solid organ transplant patients, with the majority being kidney transplant (163 studies) and liver transplant (26 studies).

Population characteristics

A total of 206 eligible studies identified 75595 patients on Tacrolimus, 51242 on Cyclosporine and 3020 on Sirolimus. All patients underwent SOT and received immunosuppression. The mean age of the patients was 45 years old, 62.4% were male and the mean BMI was 24.7.

Outcome measures

Incidence of PTDM: Figure 2 illustrates the first reported time point per study for incidence of PTDM presented by immunosuppressant and stratified by studies reporting the number of patients with pre-transplant diabetes. It is important to note the wide heterogeneity of incidence rates within every time point. Most studies reported the first time point, with PTDM incidence within the first-year post-transplant.

One hundred and twenty-one studies were used in the meta-analysis of the incidence of PTDM at one-year post-transplant. Forty-five, 65, and 11 studies were used in the analysis of the one-year incidence in studies, which used cyclosporine, tacrolimus, and sirolimus respectively as the main immunosuppressant. The overall proportion of patients developing PTDM at 1 year was 12.3% (95%CI: 10.6%-14.3%, I^2 = 95.4 %). Among patients on cyclosporine as the main immunosuppressant, the proportion of patients developing PTDM was 9.9% (95%CI: 7.6%-12.7%, I^2 = 96.1%). Whereas the proportions of patients developing PTDM at one year were 14.9% (95%CI: 12.4%-17.8%, I^2 = 94.3 %) with tacrolimus and 9.5% (95%CI: 6.1%–14.5%, I^2 = 77.0%) with sirolimus.

The analysis of incidence of PTDM at 2-3 years post-transplant included 103 study arms. Forty-one, 46 and 16 studies used cyclosporine, tacrolimus and sirolimus respectively. The overall proportion of patients developing PTDM at 2-3 years was 18.1% (95%CI: 16.2%-20.3%, I^2 = 98.2%). The percentages of patients who developed PTDM with each immunosuppression therapy were 15.3% for cyclosporine (95%CI 12.9%-18.1%, I^2 = 94.2 %), 20.7% for tacrolimus (95%CI: 17.4%-24.4%, I^2 = 99.1%), and 20.8% for sirolimus (95%CI: 17.3%-24.9%, I^2 = 58.6%).

The analysis of incidence of PTDM at 5-10 years post-transplant included 78 study arms, 8 with cyclosporine, 31 with tacrolimus, and 9 with sirolimus as the main immunosuppressant. The overall proportion of patients developing PTDM at 5-10 years was (95%CI: 0.1362-0.1840, I^2 = 93.2%). The percentages of patients who de-

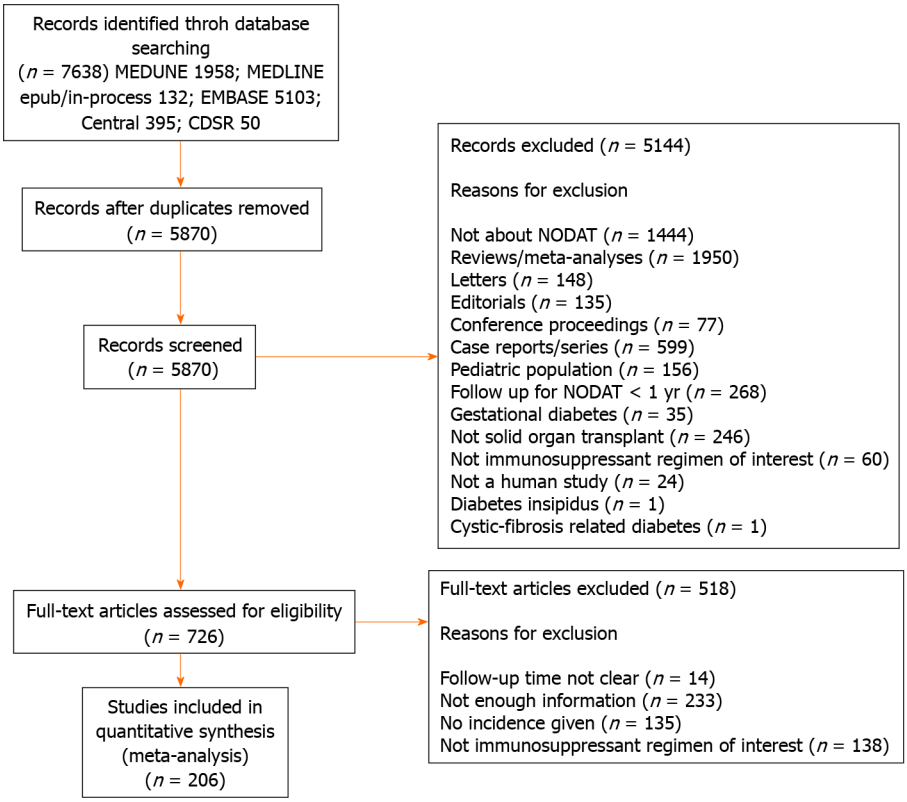


Figure 1 PRISMA flow diagram illustrating the results of search strategy and study selection. NODAT: New onset diabetes after transplantation.

veloped PTDM with each immunosuppression therapy were 12.6% for cyclosporine (95%CI: 10.51-14.99, I^2 = 91.7%), 19.9% for tacrolimus (95%CI: 15.89%-24.81%, I^2 = 90.8%), and 19.2% for sirolimus (95CI: 10.03–33.69%, I^2 = 91.4%).

NMA comparing tacrolimus, sirolimus and cyclosporine: The results of the NMA are presented in Figure 3. The direct and indirect estimates were inconsistent, with the exception of one comparison at 5 year that involved a study with zero events in one arm. The overall odds of developing PTDM were higher when tacrolimus or sirolimus were used as main immunosuppressant than with cyclosporine. Across all time points, compared to cyclosporine, the odds of developing PTDM were 1.4 times higher (95%CI: 1.1–1.9) with sirolimus and 1.7 times higher (95%CI: 1.5–2.1) with tacrolimus. The odds ratio between tacrolimus and sirolimus was 1.2 (95%CI: 0.9–1.6). The increased risk with tacrolimus compared to cyclosporine was seen at all time points post-transplant (1-year: 1.6, 95%CI: 1.2–2.3; 2-3 years: 1.7; 95%CI: 1.4-2.1; 5 or more years: 1.7; 95%CI: 1.1-2.6). The increased risk with tacrolimus compared to cyclosporine appeared mainly in the studies reporting 5+ years of follow-up data (OR 2.3; 95%CI: 1.2-4.5).

Subgroup analysis by type of solid organ transplanted: Table 1 shows the incidence of PTDM, number of studies in the analysis, incidence, 95%CI and I^2 by organ transplanted (liver, kidney, heart and lung) at various time points. This analysis excluded studies where pre-existing DM was unknown. At 2-3 years post-transplant, incidence of PTDM was 18.9% (95%CI: 14.2–24.7) in liver transplant patients, 17.2% (95%CI: 14.9-19.8) in kidney transplant patients, 22.4% (95%CI: 17.1-28.8) in heart transplant patients and 18.8% (95%CI: 8.6-36.3) in lung transplant patients. Heterogeneity in the incidence of PTDM was related to X, Y and Z in meta-regression, but the I^2 for each organ-time combination remained high even after accounting for differences between studies in these characteristics.

Risk factors for developing PTDM: We did not conduct a meta-analysis of predictors of developing PTDM. However, for each variable assessed as a predictor any paper in the review, we present the number of studies assessing it, and the number of studies that found it to be statistically significant in multivariable analyses (Table 2). Some of the noteworthy variables and the proportions, where they were significant include age (44/50), BMI (36/39), HCV (14/18), and African American ethnicity (22/52).

Table 1 Incidence of post-transplant diabetes mellitus stratified by organ transplanted at various time points

Organ	Year	Number of studies	Incidence (%)	95%CI	I^2 (%)
Liver	Year 1	7	12.3	5.6-24.8	89.3
Liver	Years 2-3	16	18.9	14.2-24.7	94.4
Liver	Years 5+	5	9.0	2.9-24.5	95.0
Kidney	Year 1	108	12.2	10.5-14.1	95.3
Kidney	Years 2-3	73	17.3	15.1-19.7	98.2
Kidney	Years 5+	71	16.3	13.9-19	93.2
Heart	Year 1	3	29.3	9.5-62	84.9
Heart	Years 2-3	10	22.4	17.1-28.8	93.6
Heart	Years 5+	2	17.7	14.1-22	0.0
Lung	Year 1	3	6.4	0.9-34	92.8
Lung	Years 2-3	5	18.8	8.6-36.3	96.8
Lung	Years 5+	0	N/A		N/A

Incidence of post-transplant diabetes mellitus by organ transplanted and year. Number of studies, incidence, 95%CI and I^2 by organ and year.

DISCUSSION

PTDM is a recognized complication of SOT, with reported incidence varying widely between 10 and 40%, depending on the transplanted organ[3,4]. This variability is mainly due to lack of definitive diagnostic criteria. PTDM is associated with substantially increased risk of cardiovascular disease, graft failure and premature death across all organ transplant groups[1,2]. Various factors have been noted to influence the development of PTDM.

In this systematic review and meta-analysis, we estimated incidence of PTDM for each of the 3 major immunosuppressants used in SOT (tacrolimus, sirolimus and cyclosporine), both overall and at key time points post-transplant, and used NMA to compare incidence between agents. A total of 206 eligible studies involving 129857 post-transplant patients fulfilling the inclusion criteria were included in one or more parts of the meta-analysis. Renal transplant recipients constituted the largest number of participants.

The overall pooled incidence of PTDM was higher in arms using tacrolimus and sirolimus than in those using cyclosporine across all SOT. The pattern across agents was similar at one, two and 5-10 years following SOT. In NMA combining studies that examined two or more immunosuppressants, tacrolimus had a consistently higher odds of PTDM at each time point than cyclosporine, with increased risk from sirolimus compared to cyclosporine being mainly restricted to the period 5-10 years post-transplant.

There is biological plausibility to sirolimus inducing insulin resistance in the longer term, with *in vivo* evidence that chronic usage of Sirolimus leads to insulin resistance and diabetes. It has been demonstrated that Sirolimus induces gluconeogenesis in liver and well as downregulation of GLUT-4 Leading to the development of severe glucose intolerance[12,13]. These effects are mediated through the blockade of the mTOR/S6K1 pathway. Moreover, there is evidence of increased β-cell toxicity induced by the chronic mTOR inhibitor treatment also possibly leading to insulin resistance and diabetes[14]. Conversely, tacrolimus affects the pancreatic B-cells, thereby decreasing insulin secretion resulting in hyperglycemia.

This review found that the variables most frequently associated with PTDM were age, BMI, tacrolimus use and hepatitis C virus. In the literature, numerous risk factors such as age, race, ethnicity, family history, hepatitis C infection, BMI, acute rejection and immunosuppressive agents have been implicated in the development of PTDM (15-19). Increased age as a risk factor for PTDM has been investigated in numerous studies within the transplant population. Khalili *et al*[20] reported increased age as a predictor of PTDM in 555 Liver transplant recipients whereas Mirabella *et al*[21] reported an increased age at transplant (> 45 years) as a risk factor in a cohort of 899 recipients. In contrast, studies by Saliba *et al*[22] and Driscoll *et al*[23] reported no

Table 2 Most commonly reported predictors for developing post-transplant diabetes mellitus

Predictor	*n*	Fraction
African-American	59	27/59
Age	56	51/56
BMI	43	39/43
Tac use	31	24/31
HCV	20	15/20
BPAR	13	10/13
Male	11	4/11
Family history of diabetes	7	6/7
Pre transplant triglycerides	7	7/7
Pre transplant impaired fasting glucose	6	6/6
CMV infection	5	2/5
Proteinuria at post-operative day 5	3	3/3
Number of rejections	3	2/3
Triglyceride lipid increase	2	2/2
HLA mismatch	2	0/2
HBV	1	1/1
Non-Caucasian	1	1/1
Cystic fibrosis	1	1/1
Cadaveric donor	1	1/1

BMI: Body mass index; HCV: Hepatitis C virus; BPAR: Biopsy proven acute rejection; CMV: Cytomegalovirus; HLA: Human leukocyte antigen; HBV: Hepatitis B virus.

association with age. Biopsy proven acute rejection is a risk factor for PTDM as bolus doses of steroids along with increase in maintenance immunosuppression with tacrolimus, cyclosporine or sirolimus is used as standard of treatment which lead to increased risk of PTDM.

Evaluating the incidence and predictors of PTDM is important, aspatient survival is significantly compromised by renal disease, cardiovascular disease and infection[24]. However, there is variable evidence regarding the relationship of PTDM with mortality in the post-transplant cohort. In a study by Kasiske *et al*[7], PTDM was associated with mortality ($P < 0.0001$), graft failure ($P < 0.0001$), and death-censored graft failure ($P < 0.0001$). In contrast, a retrospective analysis of the UNOS/OPTN database ($n > 37000$) by Kuo *et al*[25] did not demonstrate the negative impact of PTDM on transplant survival or cardiovascular mortality. Similarly, a retrospective analysis of the UNOS/OPTN database by Kuo *et al*[26] consisting of over 13000 Liver transplant recipients demonstrated that the presence of both PTDM and acute rejection at 1-year post-transplant but not PTDM alone was associated with higher overall graft failure and mortality risk. This suggests that more robust studies are required to investigate this association further.

Strengths of this study include: (1) Use of a comprehensive and exhaustive search strategy, in order to identify all potentially relevant studies; (2) Evaluation of eligible studies and data extraction by two investigators independently, with discrepancies resolved by consensus; (3) The large total number of studies and participants; (4) Use of rigorous analytic methods to summarize and compare estimates and investigate heterogeneity; (5) Tabulation of all identified risk factors for PTDM across solid organ transplant groups; and (6) Adherence to the PRISMA guidelines and use of standardized tools for quality assessment of cohort studies.

Limitations

An important limitation to the interpretation of results is the significant clinical heterogeneity across studies in immunosuppression protocols, patient populations, and

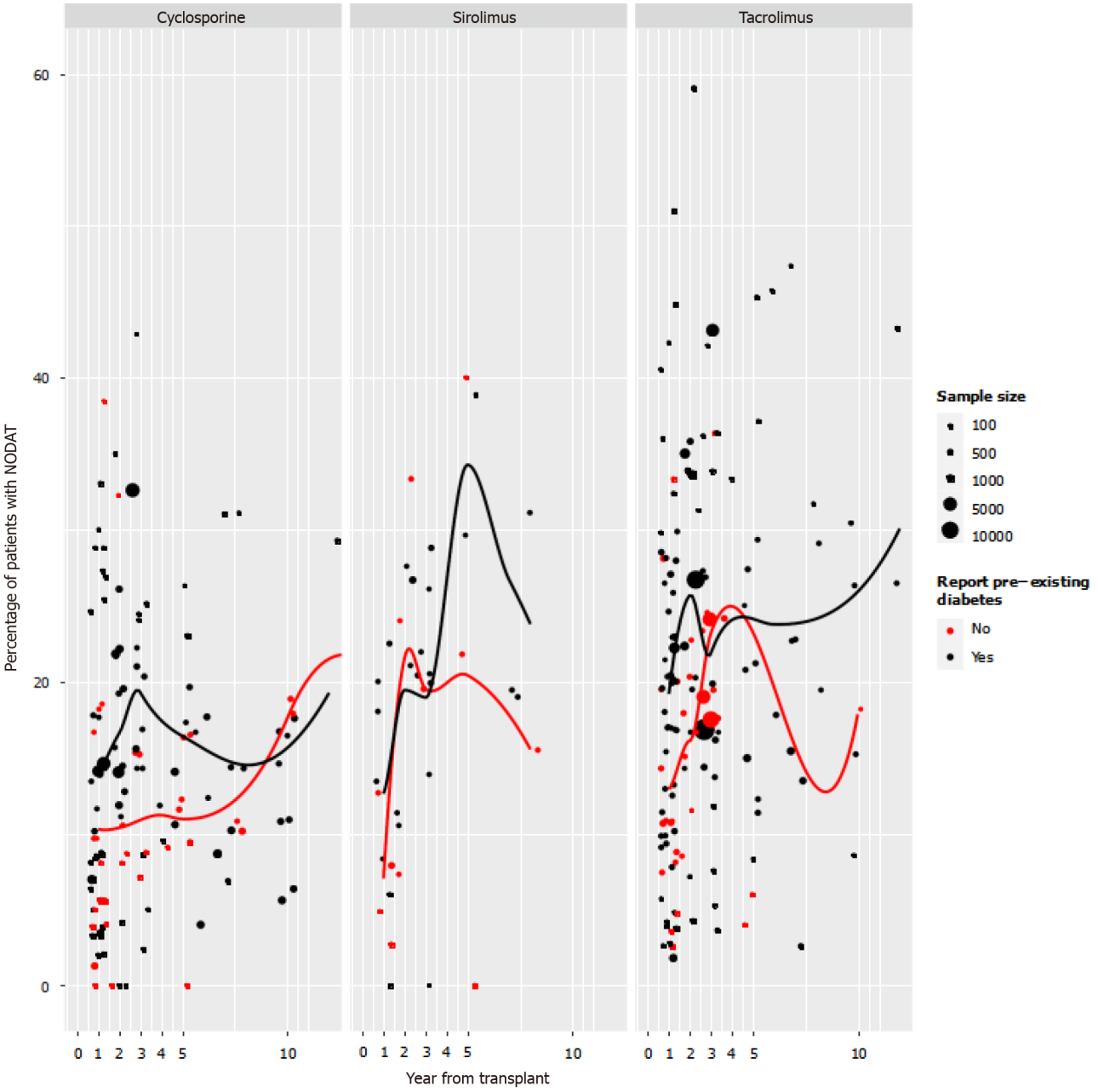


Figure 2 First-reported Incidence of post-transplant diabetes mellitus in each study plotted against the timing of the assessment, grouped according to mainstay of immunosuppression, with separate estimates of average incidence for studies excluding and not-excluding patients with pre-existing diabetes mellitus. Plotting symbols indicate the number of patients contributing to the estimate. The red data points denotes the studies which did not report the percentage of diabetes pre-existing before transplant. The black data points denote the studies, which report the percentage of pre-transplant diabetes in the patients. NODAT: New onset diabetes after transplantation.

criteria used to define PTDM. In meta-regression, such study-level variables explained only a small amount of heterogeneity in incidence estimates. I^2, with or without meta-regression, mainly fell in the range of 'substantial heterogeneity, meaning that most variability in incidence remains unexplained. Where a study reported incidence at multiple times, we used the earliest time to minimize issues related to loss-to-follow-up in the individual study. This has consequences for the comparisons of incidence of PTDM at different time points; these comparisons should be made with the proviso that the estimates may be based on somewhat different types of patients, as a result of differential drop-out and death. In the NMA, where we compare risk of PTDM between immunosuppressant regimens, RCTs and observational studies were combined. This would not be recommended practice when the outcome in the meta-analysis is the outcome in the original studies, as there could be confounding in the observational studies. However, the choice of immunosuppressant at the time of transplant is largely made without regard to long-term risk of PTDM, so confounding

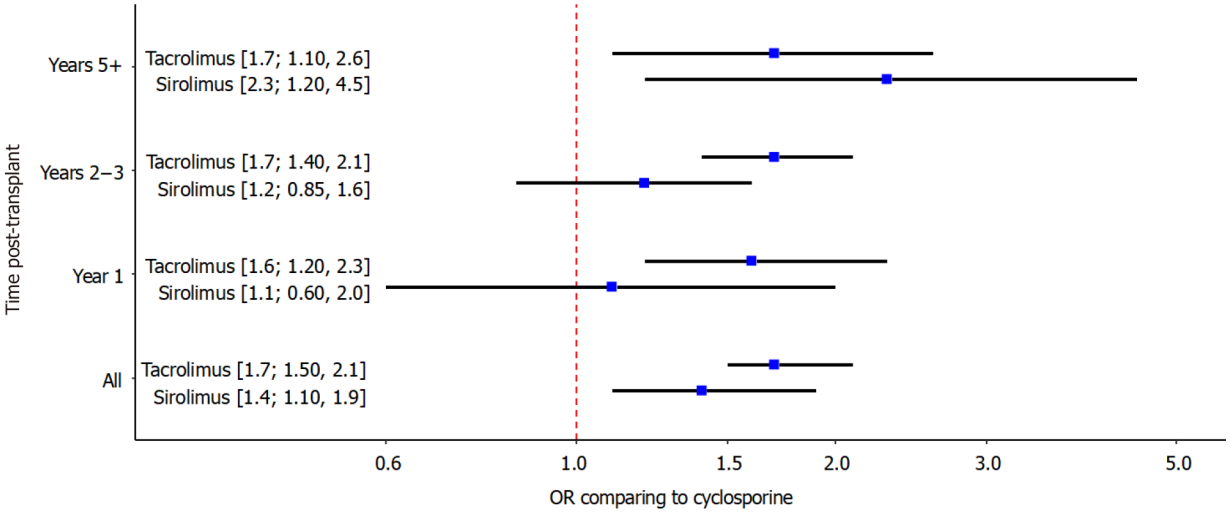


Figure 3 Estimates and 95% confidence intervals from the network meta-analysis comparing the odds of developing post-transplant diabetes mellitus in patients receiving tacrolimus or sirolimus compared to the odds with cyclosporine as the mainstay of treatment. The "All" estimate uses the first time-point from each study. The other estimates are presented according to the timing of that post-transplant diabetes mellitus assessment.

should be minimal. Another important limitation is that PTDM could be related to pulses of steroids required for treatment of rejection and increasing doses of immunosuppressant, however the studies did not report this consistently and thus this factor was not included in our meta-analysis. Finally, the summary of the predictors of PTDM may be subject to publication bias, as it would be common for individual studies not to report variables that were investigated but found to be non-statistically significant.

Nonetheless, our study represents the most comprehensive study review and meta-analysis to date on the relative impact of the principal maintenance immunosuppressants.

CONCLUSION

This NMA compares the relative impact of the 3 major immunosuppressants on the development of PTDM, revealing sirolimus and tacrolimus to be significantly more diabetogenic than cyclosporine. Tacrolimus has higher diabetogenicity in the short-term (2-3 years post-transplant), whereas sirolimus tends to exhibit higher diabetogenicity in the long-term (5-10 years post-transplant). This research will aid clinicians in understanding the important risk factors for PTDM, and encourages careful evaluation of the risk-benefit ratio of different immunosuppressant regimens in the transplant recipients.

ARTICLE HIGHLIGHTS

Research background

Post-transplant diabetes mellitus (PTDM) is associated with significant morbidity and mortality, with increased cardiovascular risk, infection and graft failure. The reported incidence of PTDM ranges from 4%-25% in renal transplant recipients, 2.5%-25% in liver transplant recipients, 4%-40% in heart transplant recipients, and 30%-35% in lung transplant recipients.

Research motivation

This research will help clinicians recognise the risk-benefit of various immunosuppressants for PTDM.

Research objectives

The aim of this study is to perform a systematic review and meta-analysis to estimate

incidence of PTDM and compare the effects of the 3 major immunosuppressants on incidence of PTDM

Research methods

The authors performed a systematic review and meta-analysis as per the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement standards.

Research results

This network meta-analysis (NMA) reveals sirolimus and tacrolimus to be significantly more diabetogenic than cyclosporine. Tacrolimus is more diabetogenic in the short-term (2-3 years post-transplant), whereas sirolimus tends to exhibit higher diabetogenicity in the long-term (5-10 years post-transplant).

Research conclusions

This NMA reveals sirolimus and tacrolimus to be significantly more diabetogenic than cyclosporine. Tacrolimus is more diabetogenic in the short-term (2-3 years post-transplant), whereas sirolimus tends to exhibit higher diabetogenicity in the long-term (5-10 years post-transplant). This research will aid clinicians in understanding the important risk factors for PTDM, and encourages careful evaluation of the benefit–risk ratio of different immunosuppressant regimens in the transplant patients.

Research perspectives

Focused studies on patients on sirolimus to get more information on pathophysiology of PTDM development required.

REFERENCES

1 **Matas AJ**, Gillingham KJ, Humar A, Ibrahim HN, Payne WD, Gruessner RW, Dunn TB, Sutherland DE, Najarian JS, Kandaswamy R. Posttransplant diabetes mellitus and acute rejection: impact on kidney transplant outcome. *Transplantation* 2008; **85**: 338-343 [PMID: 18301329 DOI: 10.1097/TP.0b013e318160ee42]

2 **Siraj ES**, Abacan C, Chinnappa P, Wojtowicz J, Braun W. Risk factors and outcomes associated with posttransplant diabetes mellitus in kidney transplant recipients. *Transplant Proc* 2010; **42**: 1685-1689 [PMID: 20620501 DOI: 10.1016/j.transproceed.2009.12.062]

3 **Sharif A**, Hecking M, de Vries AP, Porrini E, Hornum M, Rasoul-Rockenschaub S, Berlakovich G, Krebs M, Kautzky-Willer A, Schernthaner G, Marchetti P, Pacini G, Ojo A, Takahara S, Larsen JL, Budde K, Eller K, Pascual J, Jardine A, Bakker SJ, Valderhaug TG, Jenssen TG, Cohney S, Säemann MD. Proceedings from an international consensus meeting on posttransplantation diabetes mellitus: recommendations and future directions. *Am J Transplant* 2014; **14**: 1992-2000 [PMID: 25307034 DOI: 10.1111/ajt.12850]

4 **Ye X**, Kuo HT, Sampaio MS, Jiang Y, Bunnapradist S. Risk factors for development of new-onset diabetes mellitus after transplant in adult lung transplant recipients. *Clin Transplant* 2011; **25**: 885-891 [PMID: 21175848 DOI: 10.1111/j.1399-0012.2010.01383.x]

5 **Chakkera HA**, Mandarino LJ. Calcineurin inhibition and new-onset diabetes mellitus after transplantation. *Transplantation* 2013; **95**: 647-652 [PMID: 23076551 DOI: 10.1097/TP.0b013e31826e592e]

6 **Soleimanpour SA**, Crutchlow MF, Ferrari AM, Raum JC, Groff DN, Rankin MM, Liu C, De León DD, Naji A, Kushner JA, Stoffers DA. Calcineurin signaling regulates human islet {beta}-cell survival. *J Biol Chem* 2010; **285**: 40050-40059 [PMID: 20943662 DOI: 10.1074/jbc.M110.154955]

7 **Kasiske BL**, Snyder JJ, Gilbertson D, Matas AJ. Diabetes mellitus after kidney transplantation in the United States. *Am J Transplant* 2003; **3**: 178-185 [PMID: 12603213 DOI: 10.1034/j.1600-6143.2003.00010.x]

8 **Cruzado JM**, Bestard O, Grinyó JM. Impact of extrahepatic complications (diabetes and glomerulonephritis) associated with hepatitis C virus infection after renal transplantation. *Contrib Nephrol* 2012; **176**: 108-116 [PMID: 22310786 DOI: 10.1159/000332389]

9 R: A language and environment for statistical computing. 2013. Available from: http://www.R-project.org/

10 **Balduzzi S**, Rücker G, Schwarzer G. How to perform a meta-analysis with R: a practical tutorial. *Evid Based Ment Health* 2019; **22**: 153-160 [PMID: 31563865 DOI: 10.1136/ebmental-2019-300117]

11 **van Valkenhoef G**, Kuiper J, van Valkenhoef MG. Package 'gemtc'. 2016. Available from: https://github.com/gertvv/gemtc

12 **Houde VP**, Brûlé S, Festuccia WT, Blanchard PG, Bellmann K, Deshaies Y, Marette A. Chronic rapamycin treatment causes glucose intolerance and hyperlipidemia by upregulating hepatic gluconeogenesis and impairing lipid deposition in adipose tissue. *Diabetes* 2010; **59**: 1338-1348

[PMID: 20299475 DOI: 10.2337/db09-1324]
13 **Veilleux A**, Houde VP, Bellmann K, Marette A. Chronic inhibition of the mTORC1/S6K1 pathway increases insulin-induced PI3K activity but inhibits Akt2 and glucose transport stimulation in 3T3-L1 adipocytes. *Mol Endocrinol* 2010; **24**: 766-778 [PMID: 20203102 DOI: 10.1210/me.2009-0328]
14 **Kezic A**, Popovic L, Lalic K. mTOR Inhibitor Therapy and Metabolic Consequences: Where Do We Stand? *Oxid Med Cell Longev* 2018; **2018**: 2640342 [PMID: 30034573 DOI: 10.1155/2018/2640342]
15 **Bergrem HA**, Valderhaug TG, Hartmann A, Hjelmesaeth J, Leivestad T, Bergrem H, Jenssen T. Undiagnosed diabetes in kidney transplant candidates: a case-finding strategy. *Clin J Am Soc Nephrol* 2010; **5**: 616-622 [PMID: 20133490 DOI: 10.2215/CJN.07501009]
16 **Bhat V**, Tazari M, Watt KD, Bhat M. New-Onset Diabetes and Preexisting Diabetes Are Associated With Comparable Reduction in Long-Term Survival After Liver Transplant: A Machine Learning Approach. *Mayo Clin Proc* 2018; **93**: 1794-1802 [PMID: 30522594 DOI: 10.1016/j.mayocp.2018.06.020]
17 **Aravinthan AD**, Fateen W, Doyle AC, Venkatachalapathy SV, Issachar A, Galvin Z, Sapisochin G, Cattral MS, Ghanekar A, McGilvray ID, Selzner M, Grant DR, Selzner N, Lilly LB, Renner EL, Bhat M. The Impact of Preexisting and Post-transplant Diabetes Mellitus on Outcomes Following Liver Transplantation. *Transplantation* 2019; **103**: 2523-2530 [PMID: 30985734 DOI: 10.1097/TP.0000000000002757]
18 **Kuo HT**, Sampaio MS, Ye X, Reddy P, Martin P, Bunnapradist S. Risk factors for new-onset diabetes mellitus in adult liver transplant recipients, an analysis of the Organ Procurement and Transplant Network/United Network for Organ Sharing database. *Transplantation* 2010; **89**: 1134-1140 [PMID: 20386364 DOI: 10.1097/TP.0b013e3181d2fec1]
19 **Oufroukhi L**, Kamar N, Muscari F, Lavayssière L, Guitard J, Ribes D, Esposito L, Alric L, Hanaire H, Rostaing L. Predictive factors for posttransplant diabetes mellitus within one-year of liver transplantation. *Transplantation* 2008; **85**: 1436-1442 [PMID: 18497684 DOI: 10.1097/TP.0b013e31816f1b7c]
20 **Khalili M**, Lim JW, Bass N, Ascher NL, Roberts JP, Terrault NA. New onset diabetes mellitus after liver transplantation: the critical role of hepatitis C infection. *Liver Transpl* 2004; **10**: 349-355 [PMID: 15004760 DOI: 10.1002/Lt.20092]
21 **Mirabella S**, Brunati A, Ricchiuti A, Pierini A, Franchello A, Salizzoni M. New-onset diabetes after liver transplantation. *Transplant Proc* 2005; **37**: 2636-2637 [PMID: 16182771 DOI: 10.1016/j.transproceed.2005.06.084]
22 **Saliba F**, Lakehal M, Pageaux GP, Roche B, Vanlemmens C, Duvoux C, Dumortier J, Salamé E, Calmus Y, Maugendre D; Diapason Study Group. Risk factors for new-onset diabetes mellitus following liver transplantation and impact of hepatitis C infection : an observational multicenter study. *Liver Transpl* 2007; **13**: 136-144 [PMID: 17192854 DOI: 10.1002/Lt.21010]
23 **Driscoll CJ**, Cashion AK, Hathaway DK, Thompson C, Conley Y, Gaber O, Vera S, Shokouh-Amiri H. Posttransplant diabetes mellitus in liver transplant recipients. *Prog Transplant* 2006; **16**: 110-116 [PMID: 16789699 DOI: 10.7182/prtr.16.2.h26210543651l13p]
24 **Boudreaux JP**, McHugh L, Canafax DM, Ascher N, Sutherland DE, Payne W, Simmons RL, Najarian JS, Fryd DS. The impact of cyclosporine and combination immunosuppression on the incidence of posttransplant diabetes in renal allograft recipients. *Transplantation* 1987; **44**: 376-381 [PMID: 3307061 DOI: 10.1097/00007890-198709000-00010]
25 **Kuo HT**, Sampaio MS, Vincenti F, Bunnapradist S. Associations of pretransplant diabetes mellitus, new-onset diabetes after transplant, and acute rejection with transplant outcomes: an analysis of the Organ Procurement and Transplant Network/United Network for Organ Sharing (OPTN/UNOS) database. *Am J Kidney Dis* 2010; **56**: 1127-1139 [PMID: 20934793 DOI: 10.1053/j.ajkd.2010.06.027]
26 **Kuo HT**, Lum E, Martin P, Bunnapradist S. Effect of diabetes and acute rejection on liver transplant outcomes: An analysis of the organ procurement and transplantation network/united network for organ sharing database. *Liver Transpl* 2016; **22**: 796-804 [PMID: 26850091 DOI: 10.1002/lt.24414]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com