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OPINION REVIEW

Tolerance protocol of living kidney transplant for developing countries through basic strategy of lymphocyte depletion

Sufi M Suhail

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Abstract

End-stage kidney failure (ESKD) is a global issue where kidney replacement therapy imposes enormous economic burden to people of developing countries, in addition to the severe limitations to the availability of hemodialysis and peritoneal dialysis technique. The best option of kidney transplantation also requires lifelong combination immunosuppressive medicines, the cost of which is equally comparable to lifelong dialysis. A strategy of achieving transplant tolerance that requires minimum immunosuppressive medicines, although in experimental stage, also requires state-of-art technology with costly medicines and interventions. This is evidently beyond the reach of ESKD patients of developing countries. Hence, globally in developing countries, a need for an innovative but cost-effective tolerance protocol is a burning need for a successful transplant program. In brief, transplant tolerance is defined as a state of donor-specific unresponsiveness to the allograft antigens without the need for ongoing pharmacologic immunosuppression or with a minimal need. Current state-of-art techniques involves: (1) A state of hematological chimera, for complete tolerance; (2) Prope or partial tolerance where immune-reactive T-lymphocytes are inhibited using monoclonal antibodies; and (3) Chimeric antigen receptor for T-regulatory (T-reg) cell therapy using genetically engineered T-reg cells targeting specific T-lymphocyte receptors for inducing anergy. From our real-world experience in transplant management in post-transplant lympho-proliferative disorders (PTLD), we noticed frequently a drastic reduction in the need of immunosuppressive medicines following lympho-ablative therapy for PTLD. We recently published a case study on a real-world experience transplant case where we explained a partial or prope tolerance that developed after lymphocyte ablation therapy, following which the allograft was maintained with low dose dual standard immunosuppressive medicines. Based on this publication, we propose here an innovative tolerance protocol for living related low risk kidney transplantation for

developing countries, in this opinion review.

Key Words: Renal allograft; B and T lymphocytes depletion; Tolerance protocol; Immunosuppressive medicines; Living renal transplant

Core Tip: In this opinion review that is based on our recent publication, the core tip concentrates on achieving a partial or prope tolerance in renal allograft through sequential B and T lymphocyte depletion in an approved and in-practice strategy, for living related and low risk kidney transplantation. The allograft would require a half dose dual immunosuppressive therapy subsequently.

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INTRODUCTION

Renal allograft, unlike autograft or isograft, would invoke rejection process through cellular and humoral immune mechanism by the nonself-antigen mediated alloimmune response. This results in rejection of the grafted organ unless immunosuppressive medicines targeting the donor/recipient T and B lymphocytes are in place. As opposed to the rejection process, tolerance is a state of unresponsiveness to the allograft, where the graft can be maintained without or with minimal immunosuppression. This is achieved by the use of effective innovative and aggressive immunosuppressive protocols[1].

Even though, safe and reliable strategies of achieving transplant tolerance are not in place, anecdotal reports and experimental animal studies targeting T and B lymphocyte ablation, offer hope[2]. However, these need cost and state-of-art infrastructures which are beyond the reach of end-stage renal failure patients in developing countries. Finding an innovative but cost-effective tolerance protocol remains an allusive goal for a successful transplant program for low economic zones.

In real-world experience (RWE) of transplant management when transplanted patients develop post-transplant lympho-proliferative disorders (PTLD), we noticed frequently a drastic reduction in the need of immunosuppressive medicines following lympho-ablative therapy for PTLD. Recently we published a case study of a living kidney transplant who achieved immunologic tolerance requiring low dose calcineurin inhibitor (CNI) with minimal prednisolone after the patient was treated by lympho-ablative therapy for Lymphoma that developed during the post-transplant period[3]. Based on this publication and our RWE with PTLD cases management[3], we would propose in this opinion review a partial or prope tolerance protocol that can be achieved through depletion of lymphocytes pre-emptively in low risk kidney transplant recipients. The added advantages being considered are the reduced requirements of stat-of-the-art technologies and reduced cost that are needed for achieving current desensitization and immunosuppressive protocols required for tolerance.

WHAT ARE THE CURRENT EVIDENCES OF TOLERANCE IN ALLOGRAFT?

In anecdotal case reports, complete tolerance was achieved in subsequent renal allograft where bone marrow transplant was done in case of Multiple Myeloma (MM) patients with lymphocyte ablation done by radiation and chemotherapy prior to kidney transplantation from the marrow donor. The grafted kidney did not require immunosuppressive medicines afterward[4]. This is a kind of tolerance obtained because of a form of hematologic chimera thus developed during treatment of MM through allogeneic bone marrow transplant where host immune system was replaced by donor marrow.

WHAT ARE THE MECHANISMS OF TOLERANCE AND REJECTION?

A brief outline of gross immunology physiology in fetal life and life after birth is presented in Figure 1A. Immune reactive cells undergo apoptosis on exposure of fetal self-antigens, thus leaving behind the cells which are naïve to any other foreign antigens. In life after birth, immune response shifts to proliferation and activation state in contrast to fetal state of apoptosis[5].

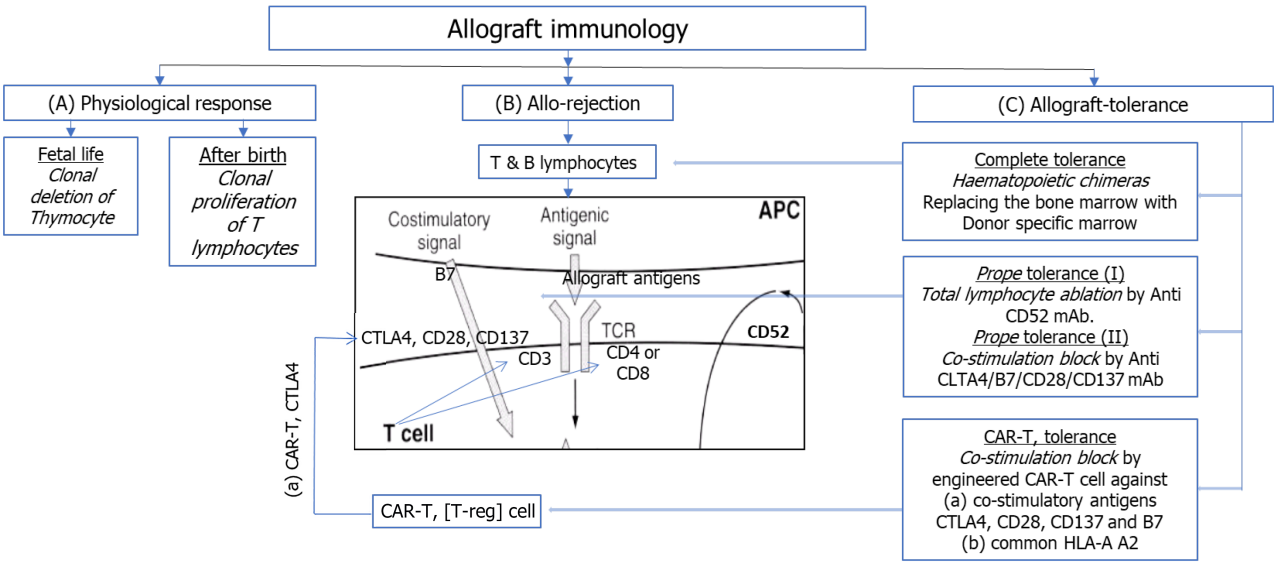

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Figure 1 The mechanisms of tolerance and rejection. A: In fetal life, T-lymphocyte response as the clonal deletion of auto reactive T-lymphocytes in the thymus to the fetal antigens so that the organism is rendered self-tolerant to self-antigens, whereas after birth these changes to the state of clonal proliferation on exposure to exogenous antigens; B: In presence of allograft the immune reactive T-lymphocytes and subsequently B-lymphocytes, carry out the process of immune response and rejection as carried out by hematologic immune cells. Suppression of this mechanism leads to graft maintenance; C: Possible tolerance inducing strategies. APC: Antigen presenting cell; CD: Cluster differentiation; T-eff: T-effector; T-reg: T-regulator lymphocyte; CTLA4: Cytotoxic T-lymphocyte associated antigen 4; mAb: Monoclonal antibody; CAR-T: Chimeric antigen receptor encoded T-reg cell.

Thus immune cells show immune response by proliferating and reacting to foreign antigens and allograft, as shown in Figure 1B. This induces T-cell proliferation, and results in cell mediated cytotoxicity and inflammation that results in acute rejection unless immunosuppressive therapies are imposed[6].

Figure 1C summarizes the current research-based adoptable protocols for achieving anergy (tolerance). Firstly, achieving a state of hematologic chimera, in other ward, complete tolerance; Second, a state of partial or prope tolerance, where immunoreactive T-lymphocytes are depleted or suppressed; and third, the newer, CAR-T (Chimeric Antigen Receptor for T-reg therapy). T-reg cells are genetically manipulated to express co-stimulatory receptors on their surfaces, that results in blocking of co-stimulatory signal-2. This causes ablation of T-cell immunoreactivity resulting in anergy or tolerance.

WHAT ARE THE CURRENT PRACTICES OF TOLERANCE PROTOCOLS IN RENAL ALLOGREAFT?

Road to complete tolerance has not opened yet because of lack of available protocols.

Transplantation among monozygotic twins does not require immunosuppressive medications, hence is an example of complete tolerance[7].

Partial or prope tolerance is available using Campath-1H where allograft could be maintained with minimal immunosuppression with Low dose Cyclosporine-A (CSA) alone. CAMPATH-1H is monoclonal antibody (mAb) against CD52 antigen present on surface of all lymphocytes. Anti-CD52 mAb administration causes ablation of all lymphocytes that lasts for long period. The new lymphocytes that are subsequently produced from lymphoreticular tissues are naïve to the grafted kidney, inducing tolerance[8]. This was demonstrated in 3C, INTAC and other studies, showing promising evidences to tolerance[9]. This is costly and requires infrastructures where infections and patient safety protocols can be monitored. In many low economic zones, expected to be not feasible.

Current approach to tolerance is focused on inducing anergy to the reactive host or graft T-lymphocytes by blocking the co-stimulatory signal to CD-3 T-lymphocytes either by unique mAb against receptors for T-lymphocyte co-stimulation [CTLA-4 (cytotoxic T-lymphocyte associated antigen 4), CD28, B7, CD137]—the so called signal-2 co-stimulation, inducing T-lymphocyte anergy, or by CAR-T therapy targeting T-regulatory lymphocyte's CTLA-4 antigen, to block co-stimulation of CD3 T-lymphocytes, inducing tolerance (anergy) for all T-lymphocytes.

BENEFIT study used Belatacept, a selective co-stimulation blocking mAb against CTLA-4 mentioned above for inducing anergy, to show a partial tolerance[10]. But the results were not promising.

Most recently, research on CAR-T therapy targeting CTLA-4 co-stimulatory receptor on the CD-3 T-lymphocytes for induction of T-lymphocyte anergy, produced promising results in pancreatic islet cell graft, as well as cutaneous graft[11,12]. Furthermore, these therapies are exceedingly costly.

HOW RECIPIENT AND DONOR FACTORS AFFECT IMMUNOSUPPRESSION AND TOLERANCE?

Highly sensitized recipients and marginal donors would impact the outcome of immunosuppression and concepts of tolerance.

A higher immunosuppressive protocol for graft survival is required for recipients with preformed antibodies against donor antigens that includes pre-transplant desensitization[13]. ABO incompatible recipient and recipient with donor specific antibodies requires desensitization protocol. Recipients with multiple blood transfusion recipients, multigravida, cases of repeat transplant, are highly immunogenic showing frequent cross-match positive results for both B and T-lymphocytes[14]. Consequently, tolerance protocols may not be appropriate for these groups of highly immunogenic recipients.

Organ donors with high immunogenicity are ABO incompatible and HLA mismatch donors, deceased donors, and harvested kidney with long cold ischemia time. These require increased immunosuppression[15,16]. In addition, may require desensitization protocol with cascade plasmapheresis and immuno-adsorbtion techniques. This is combined with use of various anti-lymphocyte antibodies and combination of potent immunosuppressive medicines. These protocols are available to be practised in targeted high risk kidney transplantation. Obviously achieving a successful protocol of tolerance could be a matter of ingenuity here.

HOW SHOULD BE THE PARADIGM SHIFT TO TOLERANCE FROM CONVENTIONAL IMMUNOSUPPRESSION?

The objectives of tolerance protocol are: (1) Minimum acute rejections; (2) minimum use of immunosuppressive medicines; (3) normal graft function; and (4) reduced short term and long term complications.

Shift to tolerance from conventional immunosuppression should be planned for minimally and normally immunogenic kidney donors and recipients, as described above. ABO compatible, better HLA matching, closer family members and matching body parameters are important considerations. All other donor recipient relationships are not appropriate for any tolerance protocol.

Available protocols for partial tolerance involve depletion of lymphocytes at the initial period of transplant surgery. The examples are, 3C, INTAC studies, where lymphocyte depletion was achieved using CAMPATH-1H mAb[8,9]. Sadly, lack of generalization and limiting factors of higher incidences of sepsis and malignancy limit their application[10]. Use of CAR-T therapy against T-lymphocyte receptors is also in infancy for renal transplantation[11,12]. For low socio-economic zones, nonetheless, they are irrelevant.

WHAT COULD BE THE TOLERANCE PROTOCOL FOR DEVELOPING COUNTRIES WHERE BURDEN OF END-STAGE KIDNEY FAILURE ALSO EQUALLY HIGH?

In RWE cases of PTLD, the point to note is depletion of lymphocytes with use of R-CHOP cycles for PTLD as mentioned in earlier sections. Profound lymphocytopenia and neutropenia that resulted from these R-CHOP therapy, required withdrawal of some immunosuppression like Mycophenolate Mofetil (MMF). The grafted kidney was subsequently maintained with a small dose of prednisone and a low dose of CSA[3].

Thus we summarize the protocol in Figure 2 as follows: The protocol starts with selection of donor and recipient, as shown in Figure 2A—the donor would be living ABO compatible donor with maximum possible HLA match and negative for B and T-lymphocyte cross match. The recipient needs to be of low immunologic risk with Panel Reactive Antibody titer less than 26%.

The subsequent steps are shown in Figure 2B as follows: First step is elective bone marrow suppression with a few R-CHOP cycles as described, each cycle consisted of IV Rituximab, IV Cyclophosphamide, IV Doxorubicin and IV Vincristine. This is followed by oral Prednisolone 50 mg daily for 5 days. This cycle is repeated 3 to 6 times till the desired depletion of Lymphocytes is achieved as mentioned earlier[3].

Second step: For low risk renal transplant, induction with Anti-CD25 mAb along with MMF, CNI and IV Hydrocortisone (or Solumedrol) at standard doses till stable graft function is achieved. We used 2 doses of IV Basiliximab as anti-CD25 mAb 20 mg IV at interval of 4 d at induction. We used CSA as CNI with a target Peak level of 1000 to 1200 μg/L at the beginning with reduction to 600 to 800 μg/L at

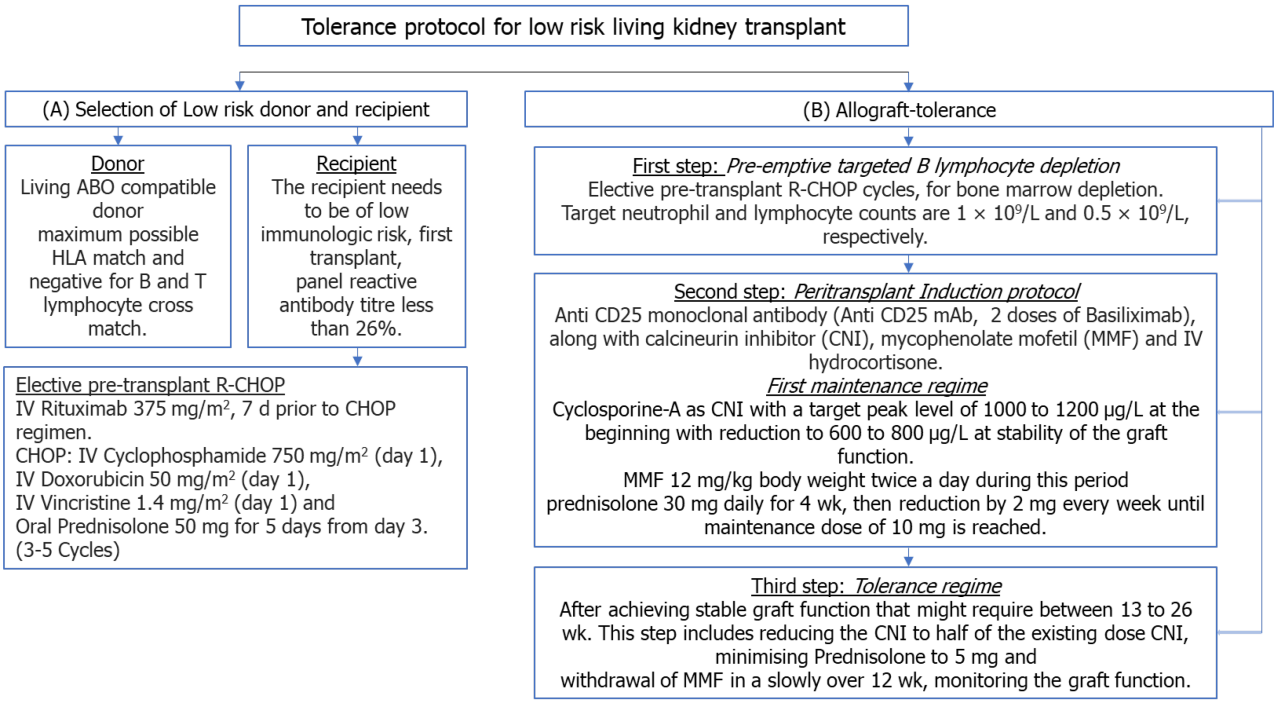

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Figure 2 The tolerance protocol methodology for low immunogenic living kidney transplantation. A: Selection of Living donor and low immunogenic recipient; B: Sequence of peri-transplant protocol for B lymphocyte depletion, followed by transplantation and induction of immunosuppression. Subsequently, migration to tolerance regime.

stability of the graft function. MMF was used at 12 mg/kg body weight twice a day during this period. We used Prednisolone 30 mg daily for 4 wk, then reduction by 2 mg every week until maintenance dose of 10 mg is reached.

Third step: After achieving stable graft function that might require between 13 to 26 wk, to reduce CNI to half of the existing dose (target peak level and trough levels, 300 and 50 µg/L respectively). Over time, Prednisolone to be reduced to 5 mg daily and MMF to be withdrawn slowly over 12 wk, monitoring the graft function[17].

HOW COULD THIS TOLERANCE PROTOCOL FOR LOW RISK LIVING TRANSPLANT BE VALIDATED?

Firstly, the use of R-CHOP therapy is validated as B-lymphocyte depleting treatment in Lympho-proliferative diseases as a standard therapy[3]. This was used in the RWE scenario for treating the PTLD that developed later. Subsequently, the allograft was maintained with low dose dual immunosuppression with stable graft function for long time. Following this practical experience, use of this B-lymphocyte depletion regime is aimed to achieve predominant B-lymphocyte depletion prior to transplant surgery. Subsequently following the transplant of the allograft, the recipient's marrow would produce B-lymphocytes (now new host B-lymphocytes) that are naïve to the renal allograft antigens (resident antigens). Consequently, as the new host B-lymphocytes are naïve to the grafted resident antigens, it would not display humoral immune response against the graft tissue.

Secondly, the validity for using MMF and CNI at the beginning is to avoid incidence of acute cellular rejection by depleting resident and host T-lymphocytes at the engraftment period post-transplant[18]. New batch of T-lymphocytes are produced by lymphoreticular system that are naïve to the renal graft. Thus, the newer lymphocytes (host T-lymphocytes), appear to take the allograft antigens (resident antigens) as self, thus do not cause cellular immune rejection.

Thirdly, B-lymphocyte depletion in a sequential manner as above before transplant surgery followed by immediate post-transplant T-lymphocyte depletion by anti CD25 mAb with CSA and MMF, enables the host acquire a state of prope tolerance to the renal allograft that was observed in the RWE scenario. The dual immunosuppressive medicines at lower dose maintain the graft and avoids long and short term complications of currently used medicines[19].

Lastly, risk of infection post-lymphocyte depletion, as described, would be similar to current existing strategies used in high risk renal transplant programs as well as same as lymphocyte ablative therapies used in Lymphoma. Paradoxically, the risk of infection would be rather reduced following the cycle of

lymphocyte depletion strategy as mentioned, because the strategy is time limited. This therapy would be followed by rather a reduced and dual immunosuppressive low CNI trough level therapy to maintain the renal graft. In practical situations of Lymphoma treatment, infection and recurrent malignancies are rather infrequent. In the RWE case and several other similar situations, recurrent malignancies and infections were not of frequent impediments.

HOW WILL THIS TOLERANCE PROTOCOL IMPACT CURRENT TRANSPLANT PROGRAM?

Current transplant protocols with newer monoclonal antibodies, desensitization procedures and newer drugs, may impact disastrously in many programs of transplantation[18]. Nevertheless, kidney transplant is considered best renal replacement therapy in End-stage kidney failure (ESKD).

For a sustainable transplant program guideline-based immunosuppressive regimens and opinion based protocols are required for highly immunogenic donor-recipient relationship. The parody lies in the disparity of the economics and infrastructures for provision, and extent of ESKD cases in developing regions. In such situation, an alternative approach may be considered.

This tolerance protocol could be suitable and applicable in RWE situations for low risk transplant scenario. In developing countries ethics committee may contribute to the feasibility of low risk living renal transplantation for maintaining a reasonable transplant program to reduce the burden of ESKD at lower cost and feasible infrastructures.

HOW THIS TOLERANCE PROTOCOL DIFFERS FROM EXISTING TOLERANCE PROTOCOLS?

We aimed at a sequential lymphocyte depletion therapy rather than an ablative therapy. The sequence starts with B lymphocyte depletion with cycles of R-CHOP therapy to achieve the target Neutrophil and lymphocyte levels, pre-transplant. Following living kidney donation (LKD) transplant with a low immunogenic donor-recipient risk-relation, standard triple immunosuppressive protocol with CNI, MMF and prednisolone will resume for achieving stable graft function. This will be followed by step wise and monitored reduction of immunosuppression to a half trough level CNI and minimum alternate day Prednisolone regimen. Thus, episodes of immediate acute rejections are minimized and a prope or partial tolerance with low dose dual immunosuppressive strategy is achieved.

The strategy of CNI half trough level as described, and alternate day low dose prednisolone is described as prope or partial tolerance. The monitoring of this tolerance would be the regular monitoring of graft function by serum creatinine levels and hematuria and proteinuria levels. In essence, it is the equivalent monitoring of a standard graft kidney.

This strategy to induce partial or prope tolerance, even though is meant for facilitating low risk LKD transplant in developing countries for reasons explained in the epilog, in fact, it will benefit the recipients world-wide. I would rather think that developed countries are better equipped with ancillary supportive infrastructure to consider this proposed protocol.

In the abstract, a detailed background introduction was mentioned in order to simplify the understanding of issues related to scope of transplant needs, especially in developing countries with marked limitations in infrastructure, finance, and scarcity of dialysis facilities for an increasing population of ESKD. To maintain a universal understanding of different stakeholders of chronic kidney disease, the article did a little elaboration before focusing on the strategy of partial tolerance.

CONCLUSION

In our recent publication[3], we discussed the real world experience scenario renal transplant case who achieved prope or partial tolerance requiring a low dose dual immunosuppression following B lymphocyte depletion therapy for PTLD. In this opinion review, we extrapolate that B lymphocyte depletion protocol to living kidney transplant of low immunogenic risk. Considering the impact of ESKD burden in developing nations, respective transplant societies with their corresponding ethics committee, would consider this proposed protocol for low risk living kidney transplant program.

ACKNOWLEDGEMENTS

We felt impulse for attracting relevant transplant organizations in particular, in the developing nations, where discrepancy in the availability of infrastructure for state-of-the-art technology for immunosup-

pressive protocols and the ESKD burden, makes a successful transplant program, difficult. With that view in mind we progressed to this opinion review based on our recent publication on this subject[3]. The opinion and conclusion of this opinion review are those of the author only.

FOOTNOTES

Author contributions: Suhail SM has contributed to the opinion and conclusion of this opinion review solely. He based this opinion review based on his recent publication with a view to confer generalizability of the protocol for the greater interest of ESKD patients of developing countries with an intention to attracting relevant transplant organizations there, where the ESKD burden is high and the availability kidney transplant program is low. The planning of contents of the review and the designs of the figures were done by the author based on the existing information in transplant medicine.

Conflict-of-interest statement: This opinion review is done based on our recent publication with a view to confer generalizability of the protocol for the greater interest of ESKD patients of developing countries.

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REFERENCES

1 **Vignali DA**, Collison LW, Workman CJ. How regulatory T cells work. *Nat Rev Immunol* 2008; **8**: 523-532 [PMID: 18566595 DOI: 10.1038/nri2343]
2 **Calne R**, Moffatt SD, Friend PJ, Jamieson NV, Bradley JA, Hale G, Firth J, Bradley J, Smith KG, Waldmann H. Campath IH allows low-dose cyclosporine monotherapy in 31 cadaveric renal allograft recipients. *Transplantation* 1999; **68**: 1613-1616 [PMID: 10589966 DOI: 10.1097/00007890-199911270-00032]
3 **Suhail SM**, Woo KT. Paradigm Shift to Tolerance from Conventional Immunosuppression in Renal Transplant: A Basic Strategy through Lymphocyte Depletion. *J Nephrol Ren Dis* 2020; **4**: 1 [DOI: 10.4172/2576-3962]
4 **Bühler LH**, Spitzer TR, Sykes M, Sachs DH, Delmonico FL, Tolkoff-Rubin N, Saidman SL, Sackstein R, McAfee S, Dey B, Colby C, Cosimi AB. Induction of kidney allograft tolerance after transient lymphohematopoietic chimerism in patients with multiple myeloma and end-stage renal disease. Transplantation 2002; 74: 1405-1409 [PMID: 12451240 DOI: 10.1097/00007890-200211270-00011]
5 **Ander SE**, Diamond MS, Coyne CB. Immune responses at the maternal-fetal interface. *Sci Immunol* 2019; **4** [PMID: 30635356 DOI: 10.1126/sciimmunol.aat6114]
6 **Ciancio G**, Burke GW, Gaynor JJ, Carreno MR, Cirocco RE, Mathew JM, Mattiazzi A, Cordovilla T, Roth D, Kupin W, Rosen A, Esquenazi V, Tzakis AG, Miller J. A randomized trial of three renal transplant induction antibodies: early comparison of tacrolimus, mycophenolate mofetil, and steroid dosing, and newer immune-monitoring. *Transplantation* 2005; **80**: 457-465 [PMID: 16123718 DOI: 10.1097/01.tp.0000165847.05787.08]
7 **Niederhuber J**, Feller I. Permanent skin homografting in identical twins. *Arch Surg* 1970; **100**: 126-128 [PMID: 4903965 DOI: 10.1001/archsurg.1970.01340200014002]
8 **Wang H**, Dong J, Zuo L, Liu J, Zhu W, Li Y, Gu L, Zhao J, Zhang L, Gong J, Zhang W, Li N, Li J. Anti-mouse CD52 monoclonal antibody ameliorates iron-deficient anaemia in IL-10 knockout mice. *Br J Nutr* 2014; **111**: 987-995 [PMID: 24160470 DOI: 10.1017/S0007114513003413]
9 **Hanaway MJ**, Woodle ES, Mulgaonkar S, Peddi VR, Kaufman DB, First MR, Croy R, Holman J; INTAC Study Group. Alemtuzumab induction in renal transplantation. *N Engl J Med* 2011; **364**: 1909-1919 [PMID: 21591943 DOI: 10.1056/NEJMoa1009546]
10 **Vincenti F**, Charpentier B, Vanrenterghem Y, Rostaing L, Bresnahan B, Darji P, Massari P, Mondragon-Ramirez GA, Agarwal M, Di Russo G, Lin CS, Garg P, Larsen CP. A phase III study of belatacept-based immunosuppression regimens versus cyclosporine in renal transplant recipients (BENEFIT study). *Am J Transplant* 2010; **10**: 535-546 [PMID: 20415897 DOI: 10.1111/j.1600-6143.2009.03005.x]
11 **Boardman DA**, Philippeos C, Fruhwirth GO, Ibrahim MA, Hannen RF, Cooper D, Marelli-Berg FM, Watt FM, Lechler RI, Maher J, Smyth LA, Lombardi G. Expression of a Chimeric Antigen Receptor Specific for Donor HLA Class I Enhances the Potency of Human Regulatory T Cells in Preventing Human Skin Transplant Rejection. *Am J Transplant* 2017; **17**: 931-943 [PMID: 28027623 DOI: 10.1111/ajt.14185]

12 **Salomon B**, Bluestone JA. Complexities of CD28/B7: CTLA-4 costimulatory pathways in autoimmunity and transplantation. *Annu Rev Immunol* 2001; **19**: 225-252 [PMID: 11244036 DOI: 10.1146/annurev.immunol.19.1.225]

13 **Amico P**, Hönger G, Mayr M, Steiger J, Hopfer H, Schaub S. Clinical relevance of pretransplant donor-specific HLA antibodies detected by single-antigen flow-beads. *Transplantation* 2009; **87**: 1681-1688 [PMID: 19502960 DOI: 10.1097/TP.0b013e3181a5e034]

14 **Couzi L**, Araujo C, Guidicelli G, Bachelet T, Moreau K, Morel D, Robert G, Wallerand H, Moreau JF, Taupin JL, Merville P. Interpretation of positive flow cytometric crossmatch in the era of the single-antigen bead assay. *Transplantation* 2011; **91**: 527-535 [PMID: 21192319 DOI: 10.1097/TP.0b013e31820794bb]

15 **Stuart F**. Overview of living and deceased organ donors, immunosuppression, and outcomes. In: Stuart F, Abecassis M, Kaufman D. Organ transplantation. Georgetown: Landes Bioscience, 2000: 52-53 [DOI: 10.1201/9781498713788-8]

16 **Al Meshari K**, Pall A, Chaballout A, El Gamal H, Al Mana H, Humaidan H, Alzayer F, Al Talhi M. Outcome of desensitization in human leukocyte antigen- and ABO-incompatible living donor kidney transplantation: a single-center experience in more than 100 patients. *Transplant Proc* 2013; **45**: 1423-1426 [PMID: 23726587 DOI: 10.1016/j.transproceed.2013.01.081]

17 **Marfo K**, Lu A, Ling M, Akalin E. Desensitization protocols and their outcome. *Clin J Am Soc Nephrol* 2011; **6**: 922-936 [PMID: 21441131 DOI: 10.2215/CJN.08140910]

18 **Halloran P**, Mathew T, Tomlanovich S, Groth C, Hooftman L, Barker C. Mycophenolate mofetil in renal allograft recipients: a pooled efficacy analysis of three randomized, double-blind, clinical studies in prevention of rejection. The International Mycophenolate Mofetil Renal Transplant Study Groups. *Transplantation* 1997; **63**: 39-47 [PMID: 9000658 DOI: 10.1097/00007890-199701150-00008]

19 **Vincenti F**, Ramos E, Brattstrom C, Cho S, Ekberg H, Grinyo J, Johnson R, Kuypers D, Stuart F, Khanna A, Navarro M, Nashan B. Multicenter trial exploring calcineurin inhibitors avoidance in renal transplantation. *Transplantation* 2001; **71**: 1282-1287 [PMID: 11397963 DOI: 10.1097/00007890-200105150-00017]

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Retrospective Study

Reduced upper limb lean mass on dual energy X-ray absorptiometry predicts adverse outcomes in male liver transplant recipients

Penelope Hey, Rudolf Hoermann, Paul Gow, Timothy P Hanrahan, Adam G Testro, Ross Apostolov, Marie Sinclair

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Peer-review report's scientific quality classification

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Abstract

BACKGROUND

Pre-transplant muscle wasting measured by computed tomography has been associated with adverse clinical outcomes after liver transplantation including increased rates of sepsis and hospitalisation days. Upper limb lean mass (LM) measured by dual-energy X-ray absorptiometry (DEXA) was recently identified as a novel predictor of sarcopenia-associated mortality in men waitlisted for transplantation.

AIM

To investigate the use of DEXA LM in predicting gender-stratified early post-transplant outcomes.

METHODS

Liver transplant recipients who underwent pre-transplant DEXA body composition imaging between 2002 and 2017 were included. Endpoints included post-transplant mortality and graft failure, bacterial infections, acute cellular rejection (ACR) and intensive care and total hospital length of stay.

RESULTS

Four hundred and sixty-nine patients met inclusion criteria of which 338 were male (72%). Median age was 55.0 years (interquartile range 47.4, 59.7) and model for end-stage liver disease (MELD) score 16. Median time from assessment to transplantation was 7 mo (3.5, 12). Upper limb LM was inversely associated with bacterial infections at 180 d post-transplant (hazard ratio = 0.42; 95% confidence interval: 0.20-0.89; P = 0.024) in males only. There was a negative correlation between upper limb LM and intensive care (τ_b = -0.090, P = 0.015) and total

hospital length of stay (τ_b = -0.10, P = 0.0078) in men. In women, neither MELD nor body composition parameters were associated with post-transplant adverse outcomes or increased length of stay. Body composition parameters, MELD and age were not associated with 90-d mortality or graft failure in either gender. There were no significant predictors of early ACR.

CONCLUSION
Sarcopenia is an independent and potentially modifiable predictor of increased post-transplant bacterial infections and hospital length of stay in men with cirrhosis. DEXA upper limb LM provides a novel measure of muscle wasting that has prognostic value in this cohort. The lack of association in women requires further investigation.

Key Words: Dual-energy X-ray absorptiometry; Sarcopenia; Body composition; Liver transplantation; Survival

Core Tip: Pre-transplant sarcopenia as measured by single-slice computed tomography has prognostic value in predicting outcomes in liver transplant recipients. In this retrospective study, we explore the association of pre-transplant dual-energy X-ray absorptiometry (DEXA) body composition analysis with early post-transplant outcomes. Low upper limb lean mass (LM) was a predictor of 180-d post-transplant bacterial infections and longer hospital and intensive care length of stay in men but not women. Upper limb LM was superior to other measures of LM including appendicular LM in predicting adverse outcomes. There was no association between pre-transplant body composition and post-transplant mortality, graft failure or early acute cellular rejection. In conclusion, pre-transplant sarcopenia is associated with adverse outcomes in men after liver transplantation. Upper limb LM provides a novel measure of muscle mass that is superior to other measures of LM on DEXA in predicting early post-transplant outcomes.

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INTRODUCTION

Sarcopenia is a syndrome defined by decreased muscle mass and reduced strength or function[1]. It is estimated to affect between 40% and 70% of patients waitlisted for liver transplantation depending on the modality used to measure muscle mass[2]. Sarcopenia is a predictor of waitlist mortality, independent of model for end-stage liver disease (MELD) score[3]. Muscle wasting measured using the cross-sectional muscle area at the third lumbar vertebrae on computed tomography (CT) is associated with longer hospital length of stay and increased risk of post-operative complications following liver transplantation[4,5].

There is emerging evidence for the role of dual-energy X-ray absorptiometry (DEXA) body composition to quantify muscle mass in cirrhosis. DEXA provides whole body compartmentalised measurements of bone mineral content, fat mass and lean tissue. It has the advantage of being a simple, reproducible, low-cost technique that can be performed easily on outpatients being worked up for transplantation. Results are readily available without the need for further analysis or dedicated software. The major limitation for the use of DEXA in cirrhosis is that it can be influenced by hydration status including the presence of ascites and oedema. To reduce the impact of ascites, appendicular lean mass (APLM), the sum of LM in arms and legs corrected for height is the preferred measure for sarcopenia in cirrhosis.

We recently identified that upper limb LM was a novel, independent predictor of sarcopenia-associated mortality in men waitlisted for transplantation[6]. Upper limb LM rather than total APLM has the advantage of being unaffected by peripheral oedema. This study aims to describe the associations between pre-transplant gender-specific body composition measurements and early post-transplant outcomes.

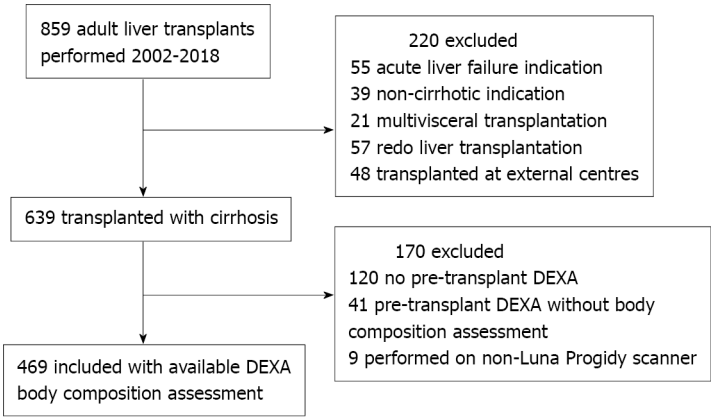

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Figure 1 Flowchart of inclusion and exclusion of patients undergoing liver transplantation. DEXA: Dual-energy X-ray absorptiometry.

MATERIALS AND METHODS

Study design

This study retrospectively analysed data of all adult patients (> 18 years) who underwent liver transplantation at a tertiary centre in Melbourne, Australia, between January 2002 and July 2018. Exclusion criteria included transplantation for non-cirrhotic indications, redo liver transplantation, multi-visceral transplants and those missing DEXA body composition data at transplant assessment. Approval was obtained by the Austin Health Human Ethics Research Committee.

Clinical and laboratory assessments

Baseline demographics including age and aetiology of liver disease were recorded at transplant assessment. Clinical examination findings including presence of hepatic encephalopathy and ascites were recorded by a transplant hepatologist. Ascites was graded as requiring no treatment, diuretic therapy alone or paracentesis. Body mass index was calculated at the time of the DEXA. Biochemistry and haematology were measured at transplant assessment, all within 6 wk of the DEXA scan. Laboratory assessments included bilirubin, serum creatinine, international normalized ratio and serum albumin to enable calculation of MELD and Child Pugh Scores. Operative data at the time of liver transplantation was collected including cold and warm ischaemic time (minutes), operative time (minutes), and blood transfusion requirement (units).

Body composition assessment

DEXA body composition analysis was performed at the time of transplant assessment using a Lunar Prodigy DEXA scanner (GE Healthcare, Madison, WI. United States). This quantified compartmentalised total body composition including LM, fat mass and bone mass. Variables analysed included appendicular, upper limb, lower limb and total LM and fat mass. All measurements were corrected for height^2. Sarcopenia was defined by previously reported cut-off values for APLM from the European Working Group on Sarcopenia in older people (males < 7.26 kg/m^2, females < 5.5 kg/m^2)[7,8].

Clinical endpoints

Clinical endpoints were examined at 90 d, 180 d and 12 mo post transplantation and included mortality, graft failure, bacterial infections, and acute cellular rejection (ACR). Graft failure was defined as graft loss requiring re-transplantation or due to patient death. Bacterial infections required the identification of a causative pathogen treated with systemic antimicrobial therapy. ACR was biopsy proven, defined as a rejection activity index ≥ 4 based on Banff criteria. Other outcomes included post-transplant intensive care stay (hours), hospital length of stay (days) and discharge destination (discharge to home or subacute care). Length of stay data excluded patients who died within the early post-operative period, within 48 h of transplantation.

Peri-operative and early post-operative management

Orthotopic liver transplantation was performed according to unit protocol and included both donation after brain death and donation after cardiac death. Organ allocation was based on the MELD scoring system. Protocolised immunosuppression comprised intravenous corticosteroids administered from day 0 to day 5 post-transplantation followed by a weaning course of oral corticosteroids. A combination of oral calcineurin inhibitors (cyclosporin or tacrolimus) and either mycophenolate mofetil or azathioprine were initiated early post-transplantation. A gradual switch from azathioprine to mycophenolate mofetil

was made following Therapeutic Goods Administration approval of the latter medication in Australia in 2012. Intravenous basiliximab was administered at day 0 and 5 in patients with impaired renal function to allow delayed commencement of calcineurin inhibitors.

Statistical analysis

Continuous variables were expressed as a median and interquartile range (25th and 75th percentile). Chi squared and fisher's exact tests were used for categorical variables. Continuous variables were compared using students *t* test (normal distribution) or Mann-Whitney *U* test (without normal distribution). Kendall Rank correlations were used to assess correlations between pre-transplant variables and post-transplant intensive care and hospital length of stay.

Survival analysis was used to follow patients after liver transplantation until they had died, experienced a complication such as bacterial infection or graft failure, or their status had last been audited. Univariate Cox proportional hazard regression analysis was used to identify predictors of 90-d and 12-mo post-transplant mortality and graft failure. Univariate and multivariate Cox regression analyses were used to identify predictors of 90 and 180-d post-transplant bacterial infections and 90-d ACR. Two-sided $P < 0.05$ conferred significance for all tests. The statistical software package R 4.1.2 for Mac with the survival package 3.2-13 was used for the analyses[9,10].

RESULTS

Baseline patient characteristics

Between January 2002 and December 2018, 859 adults underwent liver transplantation (Figure 1). Four-hundred and sixty-nine patients had available pre-transplant DEXA body composition data and met the inclusion criteria. Three-hundred and thirty-eight (72%) were male. The median age was 55.0 years (interquartile range 47.4, 59.7) and MELD score 16 (Table 1). The most common indications for liver transplantation were decompensated cirrhosis caused by viral hepatitis (n = 138, 29%) and alcohol (n = 51, 11%). Hepatocellular carcinoma in the context of cirrhosis was the primary indication for transplantation in 122 patients (26%). At transplant assessment, 259 (55%) patients had ascites, of which 137 (29%) had required recent paracentesis. A history of hepatic encephalopathy was reported in 220 patients (47%). The median time from assessment to transplantation was 7 mo (3.5, 12).

Body composition assessment

Using DEXA body composition assessment, the median APLM was 7.91 kg/m^2 (7.15, 8.71) for males and 6.50 kg/m^2 (5.87, 7.36) for females. Based on previously reported cut-off values[7], 95 men (28%) and 19 women (15%) were sarcopenic (Table 1). Women had higher fat mass, 7.56 kg/m^2 (5.48, 9.95) compared to men, 6.41 kg/m^2 (4.70, 9.31), P = 0.018.

Mortality and graft failure

At 90 d and 12 mo post transplantation, 15 (3.2%) and 33 (7.0%) of patients respectively had died. 12-mo post-transplant survival increased in the latter half of the period examined from 90% in 2002-2009 to 96% in 2010-2018. Pre-transplant body composition parameters, MELD and age were not associated with 90-d or 12-mo post-transplant mortality in men. Higher total LM but no other LM parameters was associated with 12-mo mortality in women [hazard ratio (HR) = 1.22; 95% confidence interval (CI): 1.04-1.44; P = 0.017]. Peri-operative blood transfusion requirements was associated with 90-d and 12-mo mortality in both men (HR = 1.21; 95%CI: 1.06-1.39; P = 0.006) and women (HR = 1.24; 95%CI: 1.10-1.40, P = 0.006). Of the 15 patients who died within 90 d of transplantation, only 3 met previously reported DEXA-based gender-specific diagnostic criteria for sarcopenia using APLM[7].

At 90 d and 12 mo post transplantation, 22 (4.6%) and 43 (9.2%) of patients respectively had graft failure. Body composition parameters, MELD and presence of ascites at workup were not associated with 90-d or 12-mo graft failure in men. Higher intra-operative blood transfusion requirement was associated with 90-d graft failure in both genders. Longer operative time was also associated with 90-d graft failure in men only (HR = 1.004; 95%CI: 0.001-1.008; P = 0.017).

Post-transplant bacterial infection

At 90 d and 180 d post-transplant, 59 (17.5%) and 73 (21.6%) men respectively had suffered a bacterial infection. Reduced upper limb LM was associated with bacterial infections in men at 180 d only, HR = 0.42; 95%CI: 0.20-0.89 (Table 2). The presence of ascites at transplant assessment was associated with 90-d and 180-d post-transplant bacterial infection in men only. Body composition parameters, MELD score, ascites and operative variables did not show an association with 90-d or 180-d bacterial infections in women.

ACR

At 90 d post transplantation, 105 patients (22.4%) had an episode of moderate to severe ACR. In men,

Table 1 Baseline patient characteristics based on gender and presence of sarcopenia defined by low appendicular lean mass[8]

	Non-sarcopenic (*n* = 355, 75.7%)	Sarcopenic (*n* = 114, 24.3%)	*P* value
Age, indication for transplantation	55 (48, 60)	54 (46, 58)	0.253
Viral hepatitis	106 (30%)	32 (28%)	0.715
Alcohol	30 (8%)	21 (18%)	0.003[a]
Hepatoma	96 (27%)	26 (23%)	0.370
PBC/PSC/AIH	66 (19%)	18 (16%)	0.497
Bilirubin (μmol/L)	57 (28, 114)	47.5 (25, 91.5)	0.324
Albumin (g/L)	29 (24, 33)	30 (25, 25)	0.172
INR	1.4 (1.2, 1.7)	1.4 (1.2, 1.6)	0.786
Ascites	188 (53%)	71 (62%)	0.082
Encephalopathy	163 (46%)	57 (50%)	0.401
MELD score	16 (12, 20)	16 (12, 19)	0.934
Operative data			
Total operative time (min)	465 (397, 534)	445 (291, 510)	0.162
Peak ALT	884 (509, 1525)	933 (496, 1494)	0.991
Cold ischaemic time (min)	381 (318, 479)	384 (303, 473)	0.530
Warm ischaemic time (min)	45 (39, 52)	44 (38, 50)	0.212
RBC transfusions (units)	2 (0, 4)	2 (0, 5)	0.008[a]

[a]*P* value < 0.05.

PBC: Primary biliary cholangitis; PSC: Primary sclerosing cholangitis; AIH: Autoimmune hepatitis; INR: International normalized ratio; MELD: Model for end stage liver disease; ALT: Alanine transaminase; RBC: Red blood cell.

Table 2 The association of pre-transplant variables and 180-d post-transplant sepsis

	Males (*n* = 338)		Females (*n* = 131)	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value
MELD	1.04 (1.00, 1.08)	0.051	1.06 (0.99, 1.12)	0.074
APLM	1.03 (0.87, 1.21)	0.76	0.93 (0.70, 1.24)	0.63
Upper limb LM	0.42 (0.20, 0.89)	0.024[a]	0.74 (0.19, 2.95)	0.67
Lower limb LM	1.09 (0.92, 1.30)	0.33	0.93 (0.67, 1.28)	0.66
Total LM	1.07 (0.99, 1.15)	0.08	0.89 (0.76, 1.03)	0.12
Total fat mass	0.98 (0.91, 1.05)	0.50	0.99 (0.90, 1.08)	0.76
Ascites	2.18 (1.32, 3.59)	0.002[a]	2.14 (0.95, 4.82)	0.06

[a]*P* value < 0.05.

MELD: Model for end stage liver disease; APLM: Appendicular lean mass; LM: Lean mass; HR: Hazard ratio; CI: Confidence interval.

90-d ACR was negatively associated the presence of ascites (HR = 0.93; 95%CI: 0.89-0.97, *P* = 0.0021) and MELD sore (Table 3). Similarly, lower total lean mass (TLM) was associated with higher 90-d ACR (HR = 0.83; 95%CI: 0.75-0.92; *P* < 0.001) whereas APLM and upper limb mass were not. 90-d ACR was not associated with body composition parameters, MELD or the presence of ascites in women. Peri-operative blood transfusion requirement was negatively associated with 90-d ACR in men but not women (HR = 0.89; 95%CI: 0.81-0.99; *P* = 0.026). Other operative data was not associated with ACR in either gender.

Length of stay

The median intensive care stay following liver transplantation was 66 and hospital length of stay was 15

Table 3 The association of pre-transplant variables and acute cellular rejection within ninety days of liver transplantation

	Males (*n* = 338)		Females (*n* = 131)	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value
MELD	0.93 (0.89, 0.97)	0.002	1.04 (0.99, 1.09)	0.14
APLM	0.87 (0.72, 1.05)	0.16	1.10 (0.87. 1.4)	0.43
Upper limb LM	1.34 (0.67, 2.68)	0.41	0.43 (0.12, 1.51)	0.19
Lower limb LM	0.80 (0.63, 1.01)	0.063	1.17 (0.90, 1.52)	0.23
Total LM	0.83 (0.74, 0.92)	< 0.001[a]	1.05 (0.95, 1.17)	0.32
Total fat mass	0.93 (0.87, 1.00)	0.062	1.03 (0.95, 1.12)	0.50
BMI	0.91 (0.86, 0.96)	< 0.001[a]	1.02 (0.97, 1.08)	0.45
Ascites	0.43 (0.26, 0.70)	< 0.001[a]	1.51 (0.76, 3.00)	0.24

[a]*P* value < 0.05.

MELD: Model for end stage liver disease; APLM: Appendicular lean mass; LM: Lean mass; BMI: Body mass index; HR: Hazard ratio; CI: Confidence interval.

d in men but not women, upper limb LM was inversely associated with longer intensive care stay (τ_b = -0.090, *P* = 0.015) and hospital length of stay (τ_b = -0.10, *P* = 0.0078) (Figure 2 and Table 4). The presence of ascites at transplant assessment was associated with longer intensive care and hospital stay in men (median 15 d *vs* 4 d, *P* = 0.024) but not women (Figure 3). In men only, a higher peak alanine transaminase also correlated with longer intensive care stay (τ_b = 0.13, *P* < 0.001), but not total hospital length of stay. There was no significant difference in intensive care or hospital length of stay in patients who were classified as sarcopenic based on gender-specific cut offs for APLM.

Interaction between MELD, ascites and DEXA body composition parameters

Pre-transplant MELD and the presence of ascites at work up showed differing relationships with DEXA body composition parameters.

MELD and body composition: Upper limb LM negatively correlated with increasing MELD score in men but not women (men: τ_b = -0.14, *P* < 0.001, women; τ_b = -0.077, *P* = 0.20). Increasing TLM and lower limb LM correlated with higher MELD score in both genders (Table 5).

Ascites and body composition: Compared to those without, ascites was associated with lower upper limb LM in men [median 1.83 kg/m^2 (1.63, 2.03) *vs* 2.02 kg/m^2 (1.86, 2.20), *P* < 0.001). Conversely, TLM was higher in those with ascites [median 20.0 kg/m^2 (18.4, 22.1) *vs* 18.7 kg/m^2 (17.2, 20.2), *P* < 0.001]. In women, the presence of ascites was associated with TLM only [median 16.9 kg/m^2 (15.7, 19) *vs* 16.2 kg/m^2 (14.4, 17.3), *P* = 0.004].

Ascites and MELD: With rising MELD, the prevalence of ascites increased (risk ratio for ascites 4.79 ± 0.58, *P* < 0.001).

DISCUSSION

This study investigates the impact of pre-transplant DEXA body composition on outcomes after liver transplantation. We identified reduced upper limb LM as a novel predictor of adverse outcomes including bacterial infections and longer hospital stay in men only. We did not find any significant association between body composition and post-transplant graft-failure or mortality, which suggests that prioritizing patients with sarcopenia for transplantation may be an appropriate strategy to minimize waitlist mortality without a negative impact on post-transplant survival[6].

Previous studies investigating the impact of pre-transplant sarcopenia on post-transplant survival have shown conflicting outcomes[5,11,12]. This disparity may relate to differing definitions of sarcopenia, modalities used for muscle mass assessment, severity of liver disease and inadequate power of some studies to adequately assess mortality. In this study, we describe excellent patient and graft survival of 93% and 91% respectively at 12 mo post-transplant. Era of transplantation may also be a factor as advancements in peri-operative care and immunosuppressive agents have improved post-transplant survival in the modern era. The higher 12-mo post-transplant survival observed in the latter half of the period likely reflects improvements in medical care, despite the increasing medical complexity and older age of transplant recipients. Further large-scale multi-centre studies using

Table 4 Correlation of variables at transplant assessment with post-transplant total hospital and intensive care length of stay

	Males (*n* = 338)				Females (*n* = 131)			
	Correlation[1] (τ_b)	*P* value[1]	Correlation[2] (τ_b)	*P* value[2]	Correlation[1] (τ_b)	*P* value[1]	Correlation[2] (τ_b)	*P* value[2]
Age	< -0.001	0.98	0.055	0.14	0.084	-0.18	0.047	0.44
Total APLM	-0.027	0.48	-0.004	0.91	-0.029	0.65	-0.012	0.84
Upper limb LM	-0.10	0.0078[a]	-0.090	0.015[a]	-0.079	0.21	0.019	0.75
Lower limb LM	< 0.001	0.99	0.017	0.64	-0.018	0.76	-0.018	0.76
Total LM	0.32	0.037[a]	0.055	0.13	-0.012	0.84	-0.012	0.84
Total fat mass	0.036	0.33	0.048	0.20	0.039	0.53	0.039	0.53
MELD	0.078	0.045[a]	0.0087	0.058	-0.037	0.56	0.087	0.17

[a]*P* value < 0.05.
[1]Correlation of variables at transplant assessment with post-transplant total hospital length of stay.
[2]Correlation of variables at transplant assessment with post-transplant intensive care length of stay.
APLM: Appendicular lean mass; LM: Lean mass; MELD: Model for end stage liver disease.

Table 5 Correlation of model for end stage liver disease score and body composition parameters

	Males (τ_b)	*P* value	Females (τ_b)	*P* value
APLM	0.071	0.056	0.15	0.01[a]
Upper limb LM	-0.14	< 0.001[a]	-0.077	0.20
Lower limb LM	0.12	< 0.001[a]	0.18	0.0024[a]
Total LM	0.22	< 0.001[a]	0.18	0.0036[a]
Fat mass	-0.04	0.27	-0.097	0.11

[a]*P* value < 0.05.
APLM: Appendicular lean mass; LM: Lean mass.

reproducible measures of sarcopenia that incorporate muscle function and potential deterioration on the waitlist are required to better elucidate the impact of pre-transplant sarcopenia on post-transplant survival. This will help to determine whether prioritising sarcopenic patients is appropriate and whether a threshold exists below which these patients are indeed too sick for transplantation.

Pre-transplant sarcopenia, as defined by CT imaging, has been consistently reported to be associated with increased post-transplant sepsis. In keeping with this, our study found that upper limb LM was associated with bacterial infections in men at 180-d post-transplant. No significant association was found at 90-d post-transplant, likely reflecting our relatively low infection rate of 21% at this time point as compared to other studies[13]. Our definition of bacterial infections, requiring the identification of a causative pathogen, may result in a lower incidence of early post-transplant bacterial infection leading to inadequate power to detect an association with pre-transplant muscle parameters. The influence of pre-transplant sarcopenia and frailty on early post-transplant ACR is also uncertain with conflicting reports in the literature[14,15]. This study found no association between pre-transplant sarcopenia and early ACR. This provides reassurance that optimising sarcopenia pre-transplant does not appear to result in higher rates of ACR.

While muscle area measured on transverse abdominal CT is often considered gold standard for quantifying muscle mass in cirrhosis, practice guidelines recommend against the use of CT for the sole purposes of sarcopenia assessment due to high radiation doses[16]. In addition to CT, DEXA and bioelectrical impedance are recommended by the European Working Group for Sarcopenia in Older People for assessment of muscle mass[1]. DEXA has advantages over CT due to its reproducibility, low cost and radiation and no requirement for further analysis. However, the inability of DEXA to differentiate fluid and lean tissue is particularly problematic in decompensated cirrhosis where the occurrence of ascites and peripheral oedema are high.

Current guidelines recommend the use of APLM for defining sarcopenia using DEXA with cut-off values extrapolated from non-cirrhotic cohorts for both men and women[1,7]. In a small prospective series of men with cirrhosis, APLM did not change following large volume paracentesis suggesting this is not confounded by ascites[17]. However, the influence of peripheral oedema in this population has

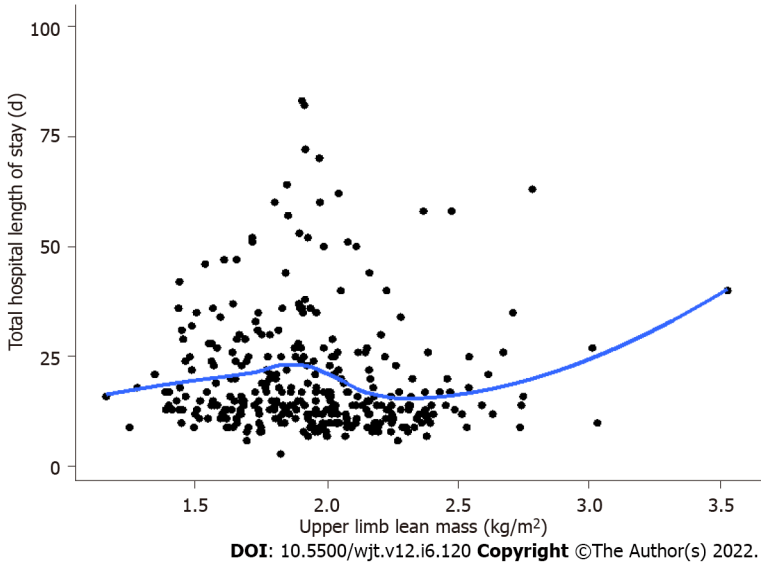

Figure 2 Correlation of upper limb lean mass and hospital length of stay in men. Correlations are given in the text.

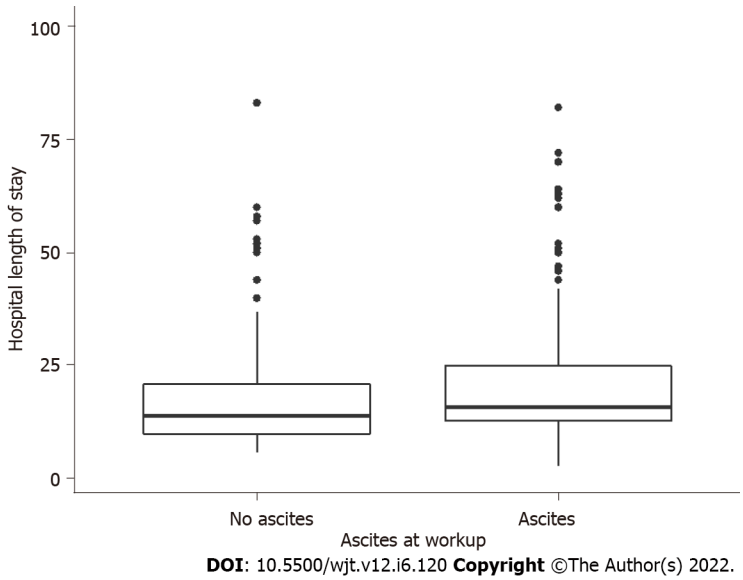

Figure 3 The presence of ascites at transplant assessment and the impact on hospital length of stay in men. *P* values are given in the text.

not been well described. Similar to our prior work[6], this study demonstrates the superiority of upper limb LM in predicting post-transplant outcomes in patients with cirrhosis when compared to APLM, lower limb LM and TLM. As MELD rose, upper limb LM decreased whereas lower limb LM and TLM increased. This suggests that in decompensated cirrhosis, upper limb LM more accurately reflects true muscle mass as it is not confounded by peripheral oedema or ascites. A cut-off of upper limb LM of < 1.6 kg/m^2 was the best predictor of waitlist mortality in a single-centre cohort of men with cirrhosis[6]. This cut-off requires validation in multicentre cohorts and as yet no definitions for sarcopenia using upper limb LM have been proposed for women.

A major finding in this study is the lack of association of pre-transplant muscle parameters with post-transplant outcomes in women. This remains an unanswered question in the literature. While a sex-stratified approach to diagnose sarcopenia is required, most studies fail to report on gender-specific mortality analyses. Like most studies in the field of cirrhosis, women accounted for less than a third of patients transplanted for cirrhosis in this cohort. This may lead to inadequate power to detect significant associations between sarcopenia and outcomes.

It is possible that muscle mass has greater prognostic significance in men than women. The pathogenesis of sarcopenia in cirrhosis is a complex interplay between multiple factors. Testosterone, a potent promoter of muscle growth, plays a particularly important role in the development of sarcopenia in men. Testosterone levels fall with progression of liver disease and correlate with muscle mass in men

with cirrhosis[18,19]. Furthermore, there is a clear association between testosterone levels in cirrhotic men and the adverse outcomes of hepatic decompensation, need for liver transplantation and death [20]. This may explain the higher prevalence of low muscle mass in men waitlisted for transplantation compared to women[21].

Functional measures of muscle such as handgrip strength and the liver frailty index may carry better prognostic utility in women. A multi-centre study of patients waitlisted for liver transplantation in the United States found that women had higher frailty scores than men and that increased frailty was associated with higher waitlist mortality[22]. A major limitation of this study is that muscle strength was not included due to the lack of available data over the timeframe described. Larger studies describing sarcopenia-related outcomes in cirrhotic and liver transplant cohorts need to include functional measures of sarcopenia and provide gender-stratified analyses so we can better understand the role of muscle in predicting outcomes in each gender.

CONCLUSION

In conclusion, this study is the first to comprehensively describe the association of reduced muscle mass as measured by DEXA on post-liver transplant outcomes providing gender-stratified analyses. We identify upper limb LM as a novel measure of sarcopenia that is associated with adverse outcomes post-liver transplant in men, without a corresponding increase in mortality. Larger multi-centre studies that provide gender-stratified monitoring of muscle mass and function serially on the waitlist are required to assess the full impact of sarcopenia on post-transplant outcomes. This will help determine whether prioritizing patients with sarcopenia for transplantation may be an appropriate strategy to minimize waitlist mortality without compromising post-transplant survival.

ARTICLE HIGHLIGHTS

Research background

Pre-transplant sarcopenia defined by reduced skeletal muscle index measured by transverse abdominal computed tomography (CT) is associated with adverse outcomes after liver transplantation. These include increased rates of sepsis, longer hospital length of stay and a possible increase in post-transplant mortality.

Research motivation

CT is not recommended for use solely for the purpose of diagnosing sarcopenia given the high radiation doses. Dual-energy X-ray absorptiometry (DEXA) body composition assessment provides a low radiation and reproducible alternative for measuring muscle mass with prognostic utility in the pre-transplant setting. Upper limb lean mass (LM) has recently been identified as a novel assessment of sarcopenia using DEXA.

Research objectives

This study investigates the use of DEXA body composition assessment in predicting gender-stratified early post-transplant outcomes.

Research methods

This study retrospectively analysed liver transplant recipients who underwent pre-transplant DEXA body composition imaging between 2002 and 2017 at a single-centre. DEXA variables analysed included appendicular LM (APLM), total, upper and lower limb LM and fat mass corrected for height^2. Endpoints included post-transplant mortality and graft failure, bacterial infections, acute cellular rejection and intensive care and total hospital length of stay (days).

Research results

Four hundred and sixty-nine patients met inclusion criteria of which 338 were male (72%). Upper limb LM was inversely associated with bacterial infections at 180 d post-transplant in males only. There was a negative correlation between upper limb LM and intensive care and total hospital length of stay in men. In women, neither model for end-stage liver disease (MELD) nor body composition parameters were associated with post-transplant adverse outcomes or increased length of stay. Body composition parameters, MELD and age were not associated with 90-d mortality or graft failure in either gender.

Research conclusions

Upper limb LM measured on DEXA is a novel measure of sarcopenia with better prognostic value compared to APLM in predicting adverse outcomes after liver transplantation. Reduced upper limb LM

was a predictor of post-transplant bacterial infection and longer length of stay in men only, but was not associated with increased mortality or graft failure. The lack of association in women requires further investigation.

Research perspectives

Larger multi-centre studies that provide gender-stratified analysis of muscle mass and function serially on the waitlist are required to assess the full impact of pre-transplant sarcopenia on post-transplant outcomes. This will help determine whether prioritizing patients with sarcopenia for transplantation may be an appropriate strategy to minimize waitlist mortality without compromising post-transplant survival.

FOOTNOTES

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REFERENCES

1 **Cruz-Jentoft AJ**, Bahat G, Bauer J, Boirie Y, Bruyère O, Cederholm T, Cooper C, Landi F, Rolland Y, Sayer AA, Schneider SM, Sieber CC, Topinkova E, Vandewoude M, Visser M, Zamboni M; Writing Group for the European Working Group on Sarcopenia in Older People 2 (EWGSOP2), and the Extended Group for EWGSOP2. Sarcopenia: revised European consensus on definition and diagnosis. *Age Ageing* 2019; **48**: 16-31 [PMID: 30312372 DOI: 10.1093/ageing/afy169]

2 **Kim G**, Kang SH, Kim MY, Baik SK. Prognostic value of sarcopenia in patients with liver cirrhosis: A systematic review and meta-analysis. *PLoS One* 2017; **12**: e0186990 [PMID: 29065187 DOI: 10.1371/journal.pone.0186990]

3 **Lai JC**, Feng S, Terrault NA, Lizaola B, Hayssen H, Covinsky K. Frailty predicts waitlist mortality in liver transplant candidates. *Am J Transplant* 2014; **14**: 1870-1879 [PMID: 24935609 DOI: 10.1111/ajt.12762]

4 **Hamaguchi Y**, Kaido T, Okumura S, Kobayashi A, Shirai H, Yagi S, Kamo N, Okajima H, Uemoto S. Impact of Skeletal Muscle Mass Index, Intramuscular Adipose Tissue Content, and Visceral to Subcutaneous Adipose Tissue Area Ratio on Early Mortality of Living Donor Liver Transplantation. *Transplantation* 2017; **101**: 565-574 [PMID: 27926595 DOI: 10.1097/TP.0000000000001587]

5 **Montano-Loza AJ**, Meza-Junco J, Baracos VE, Prado CM, Ma M, Meeberg G, Beaumont C, Tandon P, Esfandiari N, Sawyer MB, Kneteman N. Severe muscle depletion predicts postoperative length of stay but is not associated with survival after liver transplantation. *Liver Transpl* 2014; **20**: 640-648 [PMID: 24678005 DOI: 10.1002/lt.23863]

6 **Sinclair M**, Hoermann R, Peterson A, Testro A, Angus PW, Hey P, Chapman B, Gow PJ. Use of Dual X-ray Absorptiometry in men with advanced cirrhosis to predict sarcopenia-associated mortality risk. *Liver Int* 2019; **39**: 1089-1097 [PMID: 30746903 DOI: 10.1111/liv.14071]

7 **Baumgartner RN**, Koehler KM, Gallagher D, Romero L, Heymsfield SB, Ross RR, Garry PJ, Lindeman RD. Epidemiology of sarcopenia among the elderly in New Mexico. *Am J Epidemiol* 1998; **147**: 755-763 [PMID: 9554417 DOI: 10.1093/oxfordjournals.aje.a009520]

8 **Cruz-Jentoft AJ**, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, Martin FC, Michel JP, Rolland Y, Schneider SM, Topinková E, Vandewoude M, Zamboni M; European Working Group on Sarcopenia in Older People. Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. *Age Ageing* 2010; **39**: 412-423 [PMID: 20392703 DOI: 10.1093/ageing/afq034]

9 **R Core Team**. R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna. 2021. [cited 13 December 2021]. Available from: https://www.R-project.org/

10 **Therneau TM**, Grambsch PM. Modelling Survival Data: Extending the Cox Model. New York: Springer, 2000

11 **Hanai T**, Shiraki M, Nishimura K, Ohnishi S, Imai K, Suetsugu A, Takai K, Shimizu M, Moriwaki H. Sarcopenia impairs prognosis of patients with liver cirrhosis. *Nutrition* 2015; **31**: 193-199 [PMID: 25441595 DOI: 10.1016/j.nut.2014.07.005]

12 **van Vugt JL**, Levolger S, de Bruin RW, van Rosmalen J, Metselaar HJ, IJzermans JN. Systematic Review and Meta-Analysis of the Impact of Computed Tomography-Assessed Skeletal Muscle Mass on Outcome in Patients Awaiting or Undergoing Liver Transplantation. *Am J Transplant* 2016; **16**: 2277-2292 [PMID: 26813115 DOI: 10.1111/ajt.13732]

13 **Kalafateli M**, Mantzoukis K, Choi Yau Y, Mohammad AO, Arora S, Rodrigues S, de Vos M, Papadimitriou K, Thorburn D, O'Beirne J, Patch D, Pinzani M, Morgan MY, Agarwal B, Yu D, Burroughs AK, Tsochatzis EA. Malnutrition and sarcopenia predict post-liver transplantation outcomes independently of the Model for End-stage Liver Disease score. *J Cachexia Sarcopenia Muscle* 2017; **8**: 113-121 [PMID: 27239424 DOI: 10.1002/jcsm.12095]

14 **Wakabayashi T**, Shinoda M, Obara H, Kitago M, Yagi H, Abe Y, Matsubara K, Yamada Y, Oshima G, Hirukawa K, Mizota T, Hibi T, Itano O, Hoshino K, Kuroda T, Kitagawa Y. Decreased Incidence of Acute Cellular Rejection in Low-Muscle-Mass Recipients After Living-donor Liver Transplantation. *Transplant Proc* 2018; **50**: 3626-3634 [PMID: 30577248 DOI: 10.1016/j.transproceed.2018.06.028]

15 **Fozouni L**, Mohamad Y, Lebsack A, Freise C, Stock P, Lai JC. Frailty Is Associated With Increased Rates of Acute Cellular Rejection Within 3 Months After Liver Transplantation. *Liver Transpl* 2020; **26**: 390-396 [PMID: 31655014 DOI: 10.1002/lt.25669]

16 **Lai JC**, Tandon P, Bernal W, Tapper EB, Ekong U, Dasarathy S, Carey EJ. Malnutrition, Frailty, and Sarcopenia in Patients With Cirrhosis: 2021 Practice Guidance by the American Association for the Study of Liver Diseases. *Hepatology* 2021; **74**: 1611-1644 [PMID: 34233031 DOI: 10.1002/hep.32049]

17 **Belarmino G**, Gonzalez MC, Sala P, Torrinhas RS, Andraus W, D'Albuquerque LAC, Pereira RMR, Caparbo VF, Ferrioli E, Pfrimer K, Damiani L, Heymsfield SB, Waitzberg DL. Diagnosing Sarcopenia in Male Patients With Cirrhosis by Dual-Energy X-Ray Absorptiometry Estimates of Appendicular Skeletal Muscle Mass. *JPEN J Parenter Enteral Nutr* 2018; **42**: 24-36 [PMID: 28402708 DOI: 10.1177/0148607117701400]

18 **Grossmann M**, Hoermann R, Gani L, Chan I, Cheung A, Gow PJ, Li A, Zajac JD, Angus P. Low testosterone levels as an independent predictor of mortality in men with chronic liver disease. *Clin Endocrinol (Oxf)* 2012; **77**: 323-328 [PMID: 22280063 DOI: 10.1111/j.1365-2265.2012.04347.x]

19 **Sinclair M**, Grossmann M, Angus PW, Hoermann R, Hey P, Scodellaro T, Gow PJ. Low testosterone as a better predictor of mortality than sarcopenia in men with advanced liver disease. *J Gastroenterol Hepatol* 2016; **31**: 661-667 [PMID: 26414812 DOI: 10.1111/jgh.13182]

20 **Deng N**, Mallepally N, Peng FB, Kanji A, Marcelli M, Hernaez R. Serum testosterone levels and testosterone supplementation in cirrhosis: A systematic review. *Liver Int* 2021; **41**: 2358-2370 [PMID: 33966337 DOI: 10.1111/liv.14938]

21 **Tandon P**, Ney M, Irwin I, Ma MM, Gramlich L, Bain VG, Esfandiari N, Baracos V, Montano-Loza AJ, Myers RP. Severe muscle depletion in patients on the liver transplant wait list: its prevalence and independent prognostic value. *Liver Transpl* 2012; **18**: 1209-1216 [PMID: 22740290 DOI: 10.1002/lt.23495]

22 **Lai JC**, Ganger DR, Volk ML, Dodge JL, Dunn MA, Duarte-Rojo A, Kappus MR, Rahimi RS, Ladner DP, Boyarsky B, McAdams-DeMarco M, Segev DL, McCulloch CE, Verna EC. Association of Frailty and Sex With Wait List Mortality in Liver Transplant Candidates in the Multicenter Functional Assessment in Liver Transplantation (FrAILT) Study. *JAMA Surg* 2021; **156**: 256-262 [PMID: 33377947 DOI: 10.1001/jamasurg.2020.5674]

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SYSTEMATIC REVIEWS

Risk factors of extraneural spreading in astrocytomas and oligodendrogliomas in donors with gliomas: A systematic review

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Abstract

BACKGROUND

Patients with a history of primary brain tumors can be eligible for organ donation under extended criteria. The risk assessment of tumor transmission *via* organ transplant in primary brain tumors is primarily based on the assessment of tumor histotype and grade. Previous surgeries, chemo-/radiotherapy, and ventriculo-peritoneal shunt placement can lead to a disruption of the blood-brain barrier, concurring to an increase in the transmission risk.

AIM

To investigate the role of tumor transmission risk factors in donors with oligodendrogliomas and astrocytomas.

METHODS

We searched PubMed and EMBASE databases for studies reporting extraneural spreading of oligoden-drogliomas and astrocytomas and extracted clinical-pathological data on the primary tumor histotype and grade, the elapsed time from the diagnosis to the onset of metastases, sites and number of metastases, prior surgeries, prior radiotherapy and/or chemotherapy, ventriculo-atrial or ventriculo-peritoneal shunt placement, and the presence of isocitrate dehydrogenase 1/2 mutation and 1p/19q codeletion. Statistical analysis was performed using R software. Statistical correlation between chemotherapy or radiotherapy and the presence of multiple extra-central nervous system metastases was analyzed using χ^2 and Fischer exact test. The Kaplan-Meier method was used to evaluate the presence of a correlation between the metastasis-free time and: (1) Localization of metastases; (2) The occurrence of intracranial recurrences; and (3) The occurrence of multiple metastases.

RESULTS

Data on a total of 157 patients were retrieved. The time from the initial diagnosis to metastatic spread ranged from 0 to 325 mo in patients with oligodendrogliomas and 0 to 267 mo in those with astrocytomas. Respectively, 19% and 39% of patients with oligodendroglioma and astrocytoma did not receive any adjuvant therapy. The most frequent metastatic sites were bone, bone marrow, and lymph nodes. The lungs and the liver were the most commonly involved visceral sites. There was no significant correlation between the occurrence of multiple metastases and the administration of adjuvant chemo-/radiotherapy. Patients who developed intracranial recurrences/metastases had a significantly longer extraneural metastasis-free time compared to those who developed extraneural metastases in the absence of any intra- central nervous system spread.

CONCLUSION

A long follow-up time does not exclude the presence of extraneural metastases. Therefore, targeted imaging of bones and cervical lymph nodes may improve safety in the management of these donors.

Key Words: Metastatic gliomas; Extra-central nervous system metastases; Tumor transmission; Expanded donor; Risk factors; Transplantation

Core Tip: Recognized risk factors of tumor transmission from donors with a history of primary brain tumors are previous surgery, chemotherapy,and radiotherapy. We performed a systematic review of the literature on oligodendroglioma and astrocytomas with extraneural metastases, aiming to clarify the role of tumor transmission risk factors. We searched PubMed and EMBASE databases for studies reporting extraneural spreading of these gliomas. Performed treatments do not seem to impact on the timing of metastatic spread, and a long follow-up time does not exclude extraneural spread. Targeted imaging of bones and cervical lymph nodes may improve safety in the management of these donors.

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INTRODUCTION

The transplant community has been struggling with the chronic shortage of donor's organs for transplantation. In order to increase the donor pool, criteria for donation have been expanded[1,2], accepting as donors individuals with a history of malignancies of low metastatic potential. However, transplantation from these donors carries a risk of cancer transmission that should be carefully assessed for each tumor type[1-4].

Organs from donors with a history of a primary brain tumor (PBT) may be considered eligible for transplantation under extended criteria since these tumors have a low propensity to metastasize outside the central nervous system (CNS). These patients represent a relevant subgroup of donors that can increase the number of transplants performed, reducing times on the waiting list[5]. According to the 7th

edition of the guidelines on quality and safety of organ transplantation, the risk of transmission for patients with a history of PBT is mainly influenced by the tumor histotype and grade[6]. The risk of tumor transmission in donors with a history of CNS tumors is graded as minimal, low to intermediate, and high or unacceptable; in detail, donors with World Health Organization (WHO) grade I and II PBTs are considered at minimal risk of tumor transmission, while grade III tumors are now considered at low to intermediate risk in the absence of any recognized risk factors, such as previous surgical resections, ventriculo-peritoneal (VP) or ventriculo-atrial shunt placement, and/or chemotherapy/radiotherapy that increase the risk from intermediate to high[6]. These procedures disrupt the blood-brain barrier, increasing the risk of hematogenous and lymphovascular spread of these tumors[7]. Extra-CNS metastases from PBTs do however occur, with a reported prevalence of up to 4.3%[7], and metastases mainly occur in patients with a history of high-grade gliomas and, in particular, of glioblastoma[8-10]. Ventriculo-atrial and VP shunts have also been reported as risk factors for tumor spread[11].

However, the studies on PBT transmission after solid organ transplantation often include limited data on the tumor histological features and the patients' clinical management[9-13]. In the United Network for Organ Sharing registry, among 642 patients who received organs from a donor with a PBT, three died due to the transmission of a glioblastoma[8,13]. However, no cases of transmission were reported among 96 recipients in the Australian and New Zealand Organ Donation Registry[14], 89 recipients from the Czech Republic registry[15], and 448 recipients from the United Kingdom registry[16]. More recently, Lee *et al*[17] reported that none of 87 transplant recipients had tumor transmission from 28 donors with PBTs.

To date, there are no reports of transmission of oligodendroglioma to organ transplant recipients, while donor-to-recipient transmission of grade III/IV astrocytic tumors have been previously reported [6]. Though the metastatic potential of these tumors in the context of transplantation needs to be clarified and kept up-to-date. Oligodendrogliomas are CNS diffuse gliomas mainly occurring in adulthood, with a peak incidence in the fourth and fifth decade and a slight male predominance (1.3:1), preferentially arising in the cerebral hemispheres and mostly in the frontal lobe[18]. According to the WHO, oligodendroglioma is defined by the co-occurrence of isocitrate dehydrogenase 1/2 (*IDH1/2*) mutation and chromosome 1p/19q whole arm codeletion and classified into grade II and grade III (anaplastic oligodendrogliomas) based on the presence of histologic features of anaplasia, such as microvascular proliferation and/or brisk mitotic activity[18].

Tumors of astrocytic lineage, contrary to oligodendrogliomas, have a four-tiered grading system that encompasses a wide spectrum of clinical entities, from grade I tumors characterized by a benign clinical course to grade IV tumors carrying a dismal prognosis[18]. About 5% of all PBTs with extra-CNS metastatic spread are reported to be oligodendrogliomas, while astrocytomas account for about 10% of extraneural metastatic PBTs[19]. However, data on extraneural metastatic spread mostly come from case reports or small case series, and there is no systematic appraisal of the risk factors or patterns of metastatic spread.

In this study, we performed a systematic review of the literature on oligodendrogliomas and astrocytomas with extra-CNS metastases with the aim of identifying clinical or pathological factors that can be helpful to predict the tumor transmission risk and guide decision making in organ transplantation from donors with these tumors.

MATERIALS AND METHODS

Search strategy

This literature review was performed in accordance with the PRISMA. A literature search without language restrictions was carried out in the electronic databases MEDLINE-PubMed and EMBASE until December 2020. The search terms were: "oligodendroglioma", "anaplastic oligodendroglioma", "astrocytoma", "anaplastic astrocytoma" "oligodendroglial tumours", "diffuse glioma" "extracranial metastasis" "oligodendroglioma metastatic to", "astrocytoma metastatic to", "extraneural metastases" "primary brain tumours", "metastatic oligodendroglioma", "metastatic astrocytoma". Screening of article titles and abstracts was independently performed by three investigators using Rayyan QCRI reference manager web application[20]. Some references for Journal articles also were searched from (*RCA*), an artificial intelligence technology-based open citation analysis database (https://www.referencecitationanalysis.com, Baishideng Publishing Group Inc., Pleasanton, CA, United States).

Inclusion criteria and data extraction

The full texts of the articles fulfilling the initial screening criteria were retrieved and reviewed (Supplementary Table 1); disagreement was resolved *via* consensus. Inclusion criteria were: Case reports, case series, and literature reviews reporting on patients with a history of oligodendroglioma or astrocytoma that subsequently metastasized outside the CNS. Articles with limited data were included if they at least reported the histologic diagnosis of primary and metastatic tumors (Table 1; Supplementary Table 1). We included articles mentioning different tumor histotypes only if findings of each case were further detailed. We excluded articles reporting metastatic disease not histologically

Table 1 Clinical-pathological features of the study populations

Clinical features	Oligodendroglioma (%)	Astrocytoma (%)
Patients	90 (100)	67 (100)
Sex		
Male	52 (58)	39 (58)
Female	32 (35)	27 (40)
Undisclosed	6 (7)	1 (2)
Age in yr	1.5-74.0 (mean: 44.5; median: 46)	0-82.0 (mean: 31.0, median: 26)
Location		
Frontal lobe	34 (38)	7 (11)
Parietal lobe	8 (9)	2 (3)
Temporal lobe	5 (6)	11 (16)
Spine	1 (1)	6 (9)
NA	22 (24)	2 (3)
Other sites	20 (22)	39 (58)
Surgery		
Yes	79 (88)	48 (71)
No	2 (2)	16 (24)
Multiple surgeries		
Yes	44 (49)	24 (36)
No	35 (39)	41 (61)
Radiotherapy		
Yes	60 (67)	49 (73)
No	14 (15)	15 (22)
Chemotherapy		
Yes	33 (37)	16 (23)
No	37 (41)	48 (72)
VA/VP shunt		
Yes	3 (3)	20 (30)
No	26 (29)	34 (50)
Metastatic sites		
Bone	48 (53)	30 (44)
Bone marrow	30 (33)	6 (8)
Lymph nodes	27 (30)	24 (30)
Cervical	16 (17)	14 (17)
Retroperitoneal	3 (3)	2 (3)
Axillary	2 (2)	-
Other	6 (7)	7 (10)
Lung	10 (11)	11 (17)
Liver	8 (9)	8 (11)
Scalp	8 (9)	8 (11)
Pleura	5 (6)	6 (8)
Parotid gland	5 (6)	3 (4)

Breast	3 (3)	-
Chest wall	3 (3)	1 (1)
Peritoneum	3 (3)	10 (14)
Kidney	-	3 (4)
Retroperitoneum	2 (2)	1 (1)
Soft tissues	1 (1)	11 (15)
Pericardium	1 (1)	-
Pancreas	1 (1)	1 (1)
Spleen	1 (1)	-
Thymus/mediastinum	1 (1)	1 (1)
Adrenal gland	1 (1)	-
Muscles	3 (3)	2 (3)
Intra-CNS metastases/recurrence		
Yes	43 (48)	37 (55)
No	19 (21)	26 (39)
Non-conclusive	1 (1)	3 (6)
Time from the diagnosis to metastatic spread	0-324 (mean: 53.7; median: 36)	0-276 (mean: 31.0; median: 13)

NA: Not available; VA/VP: Ventriculo-atrial/ventriculo-peritoneal; CNS: Central nervous system.

confirmed and those concerning only animal models or cell cultures. Articles reporting extracranial metastases from primary glioblastomas were also excluded. Finally, from the included articles we extracted data on: Author and publication year, country, type of paper, sex and age of the patients at metastatic spread, tumor histotype and grade, synchronous or metachronous malignancies, intracranial recurrence, intra-axial spreading, tumor progression, time between the diagnosis and the onset of metastases, sites and number of metastases, tumor progression of the primary neoplasm preceding extracranial extra-CNS spread, prior surgeries, prior radiotherapy and/or chemotherapy, ventriculo-atrial or VP shunt placement, *IDH1/2* mutation and 1p/19q codeletion in both the primary and metastatic tumors.

Statistical analysis

Statistical analysis was performed using open-source software R 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria) with RStudio 1.4.1106 environment (RStudio Inc, Boston, Massachusetts, United States). The statistical correlation between chemotherapy or radiotherapy and the presence of multiple extra-CNS metastases was analyzed using χ^2 and Fischer exact test. Kaplan-Meyer method was used to investigate the correlation between metastasis-free time and metastatic sites, presence/absence of intracranial recurrence, and the occurrence of multiple metastases. A *P*-value less than 0.05 was considered statistically significant. No institutional review board approval was needed, as no ethical issue is raised by literature reviews.

RESULTS

The results are summarized in Table 1 and detailed in Supplementary Table 1. A total of 2675 articles were identified after duplicate removal. After an initial screening on titles and abstracts, we considered 267 articles as potentially relevant to our study. We excluded 3 articles with unavailable full text and 83 reporting only intracranial or spinal drop metastases; 51 articles were excluded due to language restrictions. A PRISMA flow diagram of the literature screening and article exclusion is shown in Figure 1.

The 130 articles included were case series, case reports, and literature review articles reporting data on a total of 90 patients (52 males, 32 females, and 6 with undisclosed sex) with extra-CNS metastases from oligodendroglial tumors and 67 patients with extra-CNS metastatic astrocytoma (39 males, 27 females, and 1 with undisclosed sex) (Table 1; Supplementary Table 1). Age at metastatic spread ranged between 1.5 years to 74.0 years (mean: 44.7; median: 46) in patients with oligodendrogliomas and between 8 mo and 84.0 years (mean: 31.3; median: 26) in patients with astrocytoma.

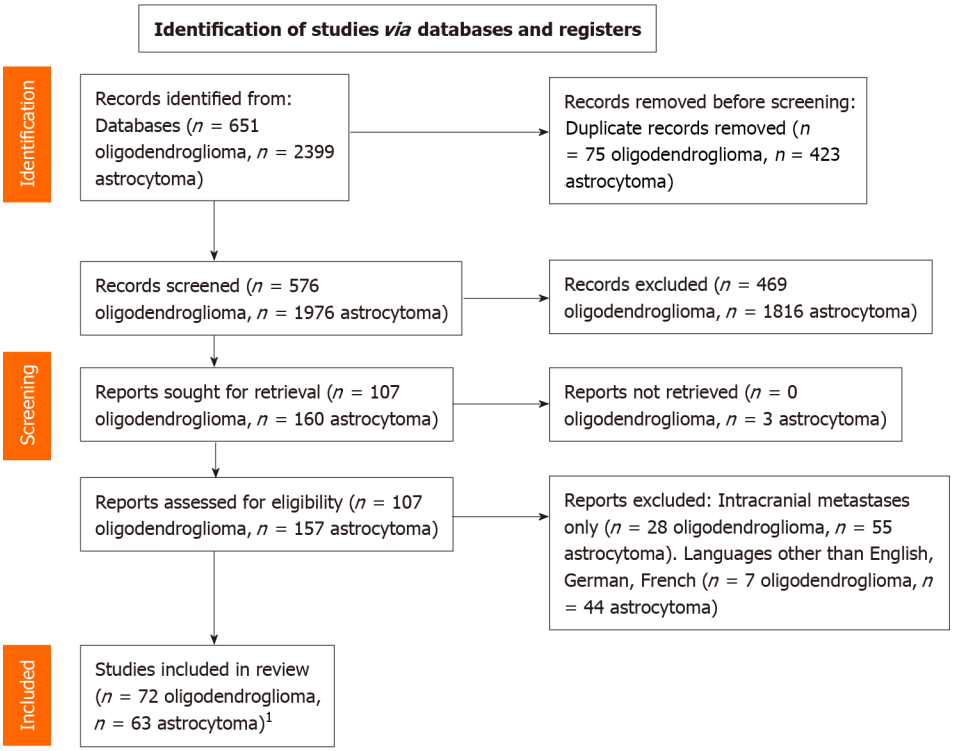

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Figure 1 PRISMA flow diagram. [1]Three articles included in the systematic review reported cases of extraneural metastases from both oligodendrogliomas and astrocytomas.

Among patients with metastatic oligodendrogliomas, 11 (12%) progressed from grade II to III in the intracranial relapse or in the metastasis, and 1 anaplastic oligodendroglioma recurred as a secondary glioblastoma; 2 cases diagnosed as oligoastrocytomas at the initial diagnosis were reported as oligodendrogliomas at recurrence. Twenty-one astrocytic tumors also displayed tumor progression, and 15 patients received a diagnosis of secondary glioblastoma at the time of recurrence or at microscopic evaluation of the metastasis. Time from the initial diagnosis to metastatic spread of oligodendrogliomas ranged from 0 to 325 mo (mean: 54; median: 36) and from 0 to 276 mo for astrocytic tumors (mean: 31; median: 13) (Table 1). One patient with oligodendroglioma and 10 patients with astrocytic tumors were found with extraneural metastatic disease at the time of the first diagnosis.

Two patients with oligodendroglioma and 8 patients with astrocytic tumors did not undergo any surgical resection before metastatic spread. In 7 cases a diagnostic stereotactic biopsy was performed without open craniotomy; the remaining cases received an autoptic diagnosis. Sixty-three (70%) patients with oligodendroglioma and 51 (76%) patients with astrocytoma received radiation therapy, chemotherapy, or both before metastases occurred, while 12 patients with oligodendroglioma and 8 with astrocytoma did not receive any adjuvant therapy. Twenty patients with astrocytoma underwent VP shunt placement, while among patients with oligodendroglioma, only three required VP shunt placement. Forty-three patients with oligodendroglioma (48%) and 37 patients with astrocytomas (55%) had at least one intracranial recurrence and/or intra-CNS metastatic disease before extra-CNS metastases.

Among oligodendrogliomas, metastases were mainly localized at the bone (n = 48), bone marrow (n = 30), and lymph nodes (n = 27), with cervical stations being the most affected (n = 16). Metastases to the scalp were present in 8 cases. The most common visceral metastatic sites were the lung (n = 10), liver (n = 8), and pleural cavity (n = 5). Kidneys were always spared (Table 1). The most common extra-CNS metastatic sites of astrocytoma were instead bone (n = 30) and lymph nodes (n = 24), and in more than half of the cases the cervical nodal stations were affected (n = 14). The scalp was involved in 8 cases and the soft tissues in 11 cases. Visceral metastases were localized to the lungs (n = 11), liver (n = 8), and kidney (n = 3) (Table 1).

There was a significantly shorter metastasis-free time in patients with astrocytoma than in those with oligodendrogliomas (P = 0.0042), and median time from the diagnosis of the primary tumor to metastatic spread was 36 mo [95%confidence interval (CI): 29-48] in patients with oligodendroglioma and 13 mo in patients with astrocytic tumors (95%CI: 15-41) (Figure 2). There was no significant correlation between timing of metastatic spread and metastatic sites (bone and lymph nodes *vs* visceral metastases) for both oligodendrogliomas (P = 0.98) and astrocytomas (P = 0.93).

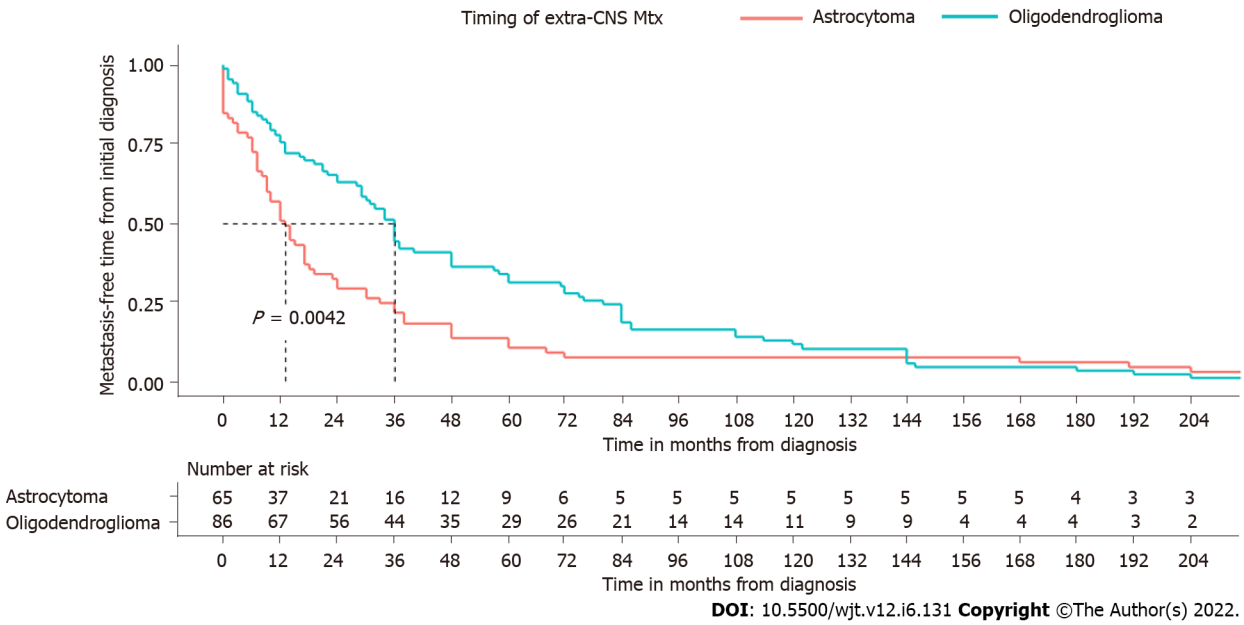

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Figure 2 Survival analysis of patients with extra-central nervous system metastases of oligodendroglioma and astrocytoma. CNS: Central nervous system; Mtx: Metastasis.

Considering: (1) Surgical procedures; (2) Radiotherapy/chemotherapy; and (3) VP shunt as risk factors for extracranial metastatic spread, in the astrocytoma cohort, 7 patients had extra-CNS metastases without any recognized risk factor, 6 patients displayed only one risk factor, 29 of them had two risk factors, and only 3 patients received all the above-mentioned treatments. All patients with metastatic oligodendroglioma had instead at least one risk factor for extracranial metastatic spread.

Patients with intracranial recurrence or intra-CNS dissemination of oligodendroglioma had a significantly longer extra-CNS free-time interval (median: 59.8 mo; 95%CI: 36-84) than those who had no local recurrences (median: 24.0 mo; 95%CI: 9-37) (P = 0.014) (Figure 3). The same correlation was present when considering patients with astrocytomas. There is indeed a significant correlation between the presence of intracranial metastases and a longer time before extra-CNS metastatic spread (P = 0.04) (Figure 3).

DISCUSSION

In this study, we reviewed the literature on oligodendrogliomas and astrocytomas with extra-CNS metastases. Based on the present review, extra-CNS metastasis of these tumor entities may occur, independently from the grade of the primary neoplasm. Indeed, the reported cases of extra-CNS metastases were roughly similar in lower and higher grade oligodendrogliomas. This distinction appears to be less sharp taking into account extraneural metastases from astrocytomas since in many articles the tumor grade is not specified, while terms such as "low grade", "aggressive" or "malignant" are used as substitutes of the grading system. Indeed, it should be noted that the criteria for tumor grading changed substantially over the past decades. As an example, the tumor reported by James and Pagel[21] in 1951 as oligodendroglioma showed areas of necrosis and moderately conspicuous mitotic activity, which are nowadays considered diagnostic criteria of a higher grade oligodendroglioma. These limitations are partly shared by many transplantation registry data, whose reports cover a wide timespan and in the past were often incomplete, not providing data on donors' tumor histotypes or the interval between performed treatments and donation[22,23]. According to the Disease Transmission Advisory Committee, recurrence-free survival can be used as a surrogate for transmission risk and donors, with a history of neoplasm diagnosed 5 or more years earlier and with a probability of cure of > 99% are considered at low risk for tumor transmission, while neoplasms with a probability of cure between 90% and 99% are considered at intermediate risk of transmission[24].

According to this literature review, while the extraneural spread of PBT appears to be an earlier event in astrocytic tumors, in oligodendrogliomas it can occur after more than 10 years from the primary diagnosis in a non-negligible number of patients. Indeed, the interval between diagnosis and metastatic spread varied widely among patients, and many of them underwent multiple treatments that have possibly interfered with the natural history of the tumor[25]. Therefore, the possibility of metastatic spread even after many years should be carefully considered when selecting eligible donors for organ transplantation. In light of these findings, taking into account that diffuse gliomas preferentially

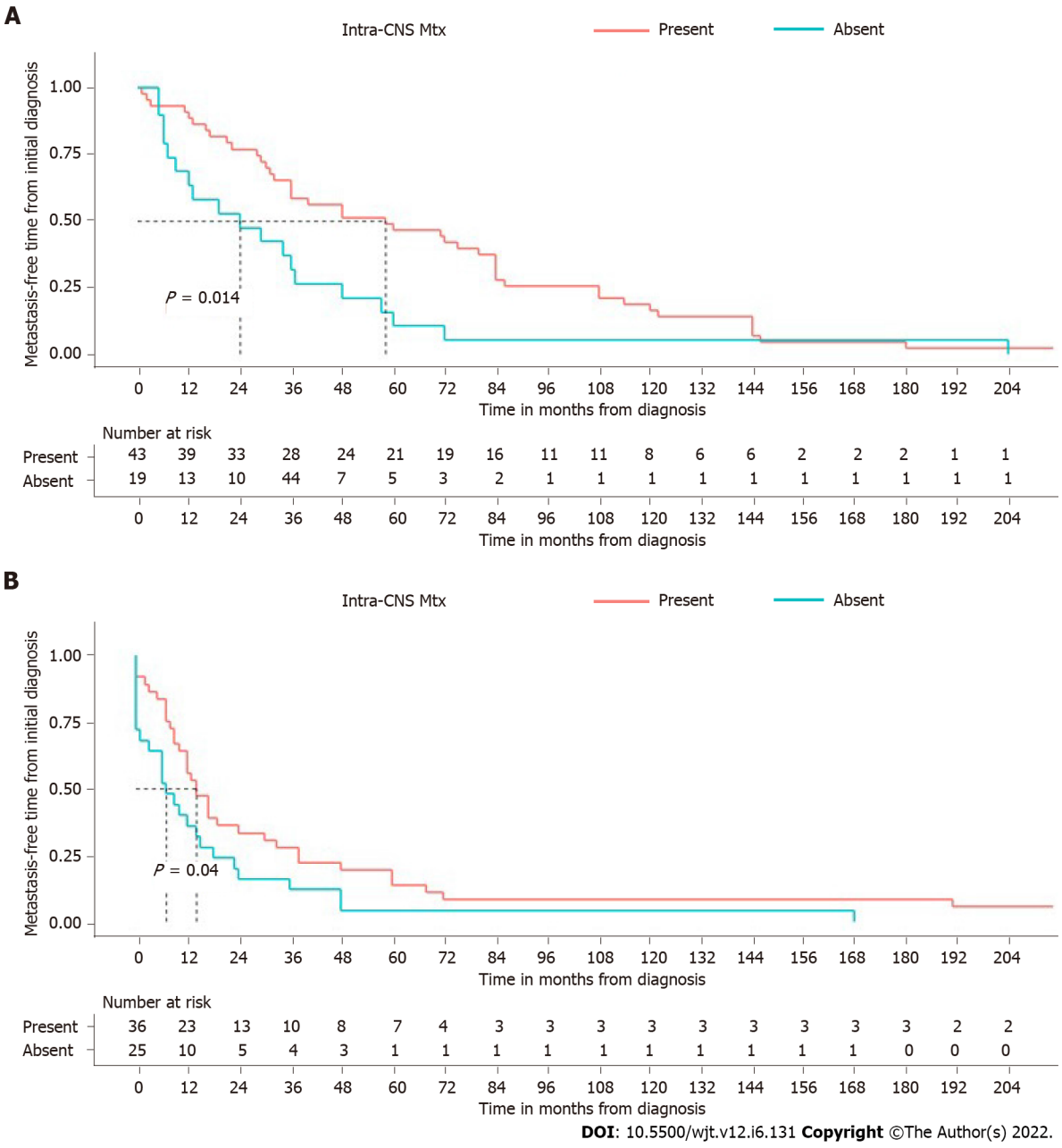

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Figure 3 Time from initial diagnosis to metastatic spread in patients with and without intra-central nervous system recurrences/metastases. A: Oligodendrogliomas; B: Astrocytomas. CNS: Central nervous system; Mtx: Metastasis.

metastasize to the bone and cervical lymph nodes, we suggest that protocols for potential donors with a present or past history of oligodendroglioma should include ultrasound imaging of the head and neck and/or computerized tomographic scan of the skeleton. A minority of patients also had metastases in transplantable organs such as lungs, liver, and pancreas, while metastases to kidney and heart were not reported in oligodendrogliomas, suggesting that these organs are relatively spared from metastatic spread. This is in accordance with two studies on donors with glioblastoma that described a better outcome in recipients of kidneys than in those with lung or liver grafts and worse outcomes in patients with liver metastases compared to those with other extracranial metastatic sites[9,26].

Of note, patients with intracranial tumor relapse had a significantly longer interval between the initial diagnosis and the metastatic spread. Additionally, we found that patients who had multiple surgeries for intra-CNS relapses or metastases developed extra-CNS disease after a longer time interval than those who had a single surgery. We may speculate that patients with intracranial relapses or metastases have tumors with a lower biological aggressiveness and that acquire "visceral" metastatic potential only in a later stage.

The present review has several limitations. First, we did not include in the literature search articles reporting extracranial metastases from primary glioblastomas, currently classified as grade IV tumors according to the WHO[18]. Moreover, the selected literature covers a wide timespan, and inevitably the

changes in the classification of tumor entities and in grading systems represent a limitation to every systematic review on this topic. It should be noted, indeed, that most of the articles included in this review were published before the 2016 update of the WHO classification of CNS tumors and do not always include data on 1p19q codeletion and *IDH1/2* mutations[18].

CONCLUSION

In conclusion, despite the relatively low propensity to metastasize outside the CNS of oligodendrogliomas and astrocytomas, findings in this review confirm the theoretical possibility of tumor transmission when transplanting organs from these donors and that a long interval between tumor diagnosis and donor death does not exclude the possibility of metastases. Tumor grade does not seem to be the main feature influencing the metastatic potential, with the caveat that recent diagnostic advances may add useful information in the future. Kidneys and hearts seem to be relatively resistant to metastases compared with lungs and livers. Finally, we suggest that imaging of the skeleton and cervical lymph nodes could be helpful to identify metastatic disease in donors with a past or present history of these gliomas.

ARTICLE HIGHLIGHTS

Research background

Under extended criteria, patients with a history of primary brain tumor can be eligible for organ donation. Tumor histotype and tumor grade are considered the main risk factors of tumor transmission, and previous surgeries, chemo-/radiotherapy, and ventriculo-peritoneal shunt placement concur to increase the transmission risk.

Research motivation

Most of the literature on the extraneural metastatic spread of diffuse gliomas is based on case reports and case series, and there is a lack of systematic appraisal of patterns of metastatic spread- and on factors concurring to increase the risk of extraneural spreading.

Research objectives

We aimed to collect and analyze the existing literature on extraneural spreading of oligodendroglial and astrocytic tumors in order to identify clinical or pathological factors that could help clinicians to assess the risk of tumor transmission from donors with a history of these gliomas and guide decision making in organ transplantation.

Research methods

We performed a systematic review of the literature in accordance with the PRISMA guidelines. A literature search without language restrictions was performed in the electronic databases MEDLINE-PubMed and EMBASE, searching for articles, case reports, and case series reporting data on extra-central nervous system metastases of oligodendrogliomas and astrocytomas.

Research results

Elapsed time from the initial diagnosis to metastatic spread ranged from 0 to 325 mo and from 0 to 276 mo for oligodendrogliomas and astrocytic tumors, respectively. The most common metastatic sites were bone and lymph nodes for both tumors, while the most common visceral sites were the lungs and the liver in patients with oligodendrogliomas and lungs, liver, and kidneys in patients with astrocytomas. Among patients with astrocytomas, 7 did not undergo surgery, chemo-/radiotherapy or ventriculo-peritoneal shunt placement before the onset of metastases.

Research conclusions

A long interval between the tumor diagnosis and the donor's death does not exclude the possibility of extraneural spreading of these tumors. Bone and lymph nodes are the most common metastatic sites; the lungs and the liver are instead the preferential visceral sites of metastatic spread. Follow-up imaging of the skeleton and cervical lymph nodes could be useful to identify metastatic disease in donors with a history of these gliomas.

Research perspectives

The diagnostic advances made recently in tumor classification and targeted follow-up protocols could improve the knowledge on the factors involved in extraneural spreading of gliomas, with repercussions on the tumor transmission risk assessment of potential donors.

FOOTNOTES

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REFERENCES

1 **Kauffman HM**, Bennett LE, McBride MA, Ellison MD. The expanded donor. *Transplant Rev* 1997; **11**: 165-190 [DOI: 10.1016/S0955-470X(97)80037-7]
2 **López-Navidad A**, Caballero F. Extended criteria for organ acceptance. Strategies for achieving organ safety and for increasing organ pool. *Clin Transplant* 2003; **17**: 308-324 [PMID: 12868987 DOI: 10.1034/j.1399-0012.2003.00119.x]
3 **Eccher A**, Girolami I, Motter JD, Marletta S, Gambaro G, Momo REN, Nacchia F, Donato P, Boschiero L, Boggi U, Lombardini L, Cardillo M, D'Errico A, Neil D, Segev DL, Zaza G. Donor-transmitted cancer in kidney transplant recipients: a systematic review. *J Nephrol* 2020; **33**: 1321-1332 [PMID: 32535833 DOI: 10.1007/s40620-020-00775-4]
4 **Eccher A**, Girolami I, Marletta S, Brunelli M, Carraro A, Montin U, Boggi U, Mescoli C, Novelli L, Malvi D, Lombardini L, Cardillo M, Neil D, D'Errico A. Donor-Transmitted Cancers in Transplanted Livers: Analysis of Clinical Outcomes. *Liver Transpl* 2021; **27**: 55-66 [PMID: 32746498 DOI: 10.1002/lt.25858]
5 **Warrens AN**, Birch R, Collett D, Daraktchiev M, Dark JH, Galea G, Gronow K, Neuberger J, Hilton D, Whittle IR, Watson CJ; Advisory Committee on the Safety of Blood, Tissues and Organs, UK. Advising potential recipients on the use of organs from donors with primary central nervous system tumors. *Transplantation* 2012; **93**: 348-353 [PMID: 22258288 DOI: 10.1097/TP.0b013e31823f7f47]
6 **European Directorate for the Quality of Medicines & HealthCare**. Guide to the Quality and Safety of Organs For Transplantation. Strasbourg: Council of Europe, 2018
7 **Subramanian A**, Harris A, Piggott K, Shieff C, Bradford R. Metastasis to and from the central nervous system--the 'relatively protected site'. *Lancet Oncol* 2002; **3**: 498-507 [PMID: 12147436 DOI: 10.1016/s1470-2045(02)00819-7]
8 **Armanios MY**, Grossman SA, Yang SC, White B, Perry A, Burger PC, Orens JB. Transmission of glioblastoma multiforme following bilateral lung transplantation from an affected donor: case study and review of the literature. *Neuro Oncol* 2004; **6**: 259-263 [PMID: 15279719 DOI: 10.1215/S1152851703000474]
9 **Jimsheleishvili S**, Alshareef AT, Papadimitriou K, Bregy A, Shah AH, Graham RM, Ferraro N, Komotar RJ. Extracranial glioblastoma in transplant recipients. *J Cancer Res Clin Oncol* 2014; **140**: 801-807 [PMID: 24595597 DOI: 10.1007/s00432-014-1625-3]
10 **Jonas S**, Bechstein WO, Lemmens HP, Neuhaus R, Thalmann U, Neuhaus P. Liver graft-transmitted glioblastoma multiforme. A case report and experience with 13 multiorgan donors suffering from primary cerebral neoplasia. *Transpl Int* 1996; **9**: 426-429 [PMID: 8819282 DOI: 10.1007/BF00335707]
11 **Buell JF**, Trofe J, Sethuraman G, Hanaway MJ, Beebe TM, Gross TG, Alloway R, First MR, Woodle ES. Donors with central nervous system malignancies: are they truly safe? *Transplantation* 2003; **76**: 340-343 [PMID: 12883189 DOI: 10.1097/01.TP.0000076094.64973.D8]
12 **Penn I**. Transmission of cancer from organ donors. *Ann Transplant* 1997; **2**: 7-12 [PMID: 9869872]

13 **Kauffman HM**, Cherikh WS, McBride MA, Cheng Y, Hanto DW. Deceased donors with a past history of malignancy: an organ procurement and transplantation network/united network for organ sharing update. *Transplantation* 2007; **84**: 272-274 [PMID: 17667822 DOI: 10.1097/01.tp.0000267919.93425.fb]

14 **Chui AK**, Herbertt K, Wang LS, Kyd G, Hodgeman G, Verran DJ, DeLeon C, Sheil AG. Risk of tumor transmission in transplantation from donors with primary brain tumors: an Australian and New Zealand registry report. *Transplant Proc* 1999; **31**: 1266-1267 [PMID: 10083564 DOI: 10.1016/s0041-1345(98)01989-7]

15 **Pokorna E**, Vítko S. The fate of recipients of organs from donors with diagnosis of primary brain tumor. *Transpl Int* 2001; **14**: 346-347 [PMID: 11692220 DOI: 10.1007/s001470100334]

16 **Watson CJ**, Roberts R, Wright KA, Greenberg DC, Rous BA, Brown CH, Counter C, Collett D, Bradley JA. How safe is it to transplant organs from deceased donors with primary intracranial malignancy? *Am J Transplant* 2010; **10**: 1437-1444 [PMID: 20486904 DOI: 10.1111/j.1600-6143.2010.03130.x]

17 **Lee MS**, Cho WH, Ha J, Yu ES, Jeong YS, Oh JS, Lee JR, Lee JM. Safety of Donation From Brain-dead Organ Donors With Central Nervous System Tumors: Analysis of Transplantation Outcomes in Korea. *Transplantation* 2020; **104**: 460-466 [PMID: 31596740 DOI: 10.1097/TP.0000000000002994]

18 **Louis DN**, Ohgaki H, Wisteler OD, Cavenee WK, Ellison DW, Figarella-Branger D, Perry A, Refeinberger G, von Deimling A. WHO Classification of Tumors of the Central Nervous System. Revised 4th ed. Lyon: IARC, 2016: 16-74

19 **Liwnicz BH**, Rubinstein LJ. The pathways of extraneural spread in metastasizing gliomas: a report of three cases and critical review of the literature. *Hum Pathol* 1979; **10**: 453-467 [PMID: 381159 DOI: 10.1016/s0046-8177(79)80051-9]

20 **Ouzzani M**, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. *Syst Rev* 2016; **5**: 210 [PMID: 27919275 DOI: 10.1186/s13643-016-0384-4]

21 **James TG**, Pagel W. Oligodendroglioma with extracranial metastases. *Br J Surg* 1951; **39**: 56-65 [PMID: 14858828 DOI: 10.1002/bjs.18003915312]

22 **Nalesnik MA**. Donors With Central Nervous System Cancer: Proceed With Vigilance. *Transplantation* 2020; **104**: 458-459 [PMID: 31596741 DOI: 10.1097/TP.0000000000002995]

23 **Penn I**. Questions about the use of organ donors with tumors of the central nervous system. *Transplantation* 2000; **70**: 249-250 [PMID: 10919617]

24 **Nalesnik MA**, Woodle ES, Dimaio JM, Vasudev B, Teperman LW, Covington S, Taranto S, Gockerman JP, Shapiro R, Sharma V, Swinnen LJ, Yoshida A, Ison MG. Donor-transmitted malignancies in organ transplantation: assessment of clinical risk. *Am J Transplant* 2011; **11**: 1140-1147 [PMID: 21645251 DOI: 10.1111/j.1600-6143.2011.03565.x]

25 **Perry A**. Metastatic Oligodendroglioma: A Mini-Epidemic? *Adv Anat Pathol* 2004; **11**: 325 [DOI: 10.1097/01.pap.0000146222.25928.b7]

26 **Cunha MLVD**, Maldaun MVC. Metastasis from glioblastoma multiforme: a meta-analysis. *Rev Assoc Med Bras (1992)* 2019; **65**: 424-433 [PMID: 30994843 DOI: 10.1590/1806-9282.65.3.424]

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