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Title	Time trends in organ donation after neurological determination of death: a cohort study
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Reviewer 1	Dr. Danielle Paciulli
Institution	Stony Brook University, Center for Medical Humanities, Compassionate Care and Bioethics, Stony Brook, NY
General comments (author response in bold)	The article discusses how brain injury directly correlates to how many organs can be procured and transplanted. This is done following the neurological termination of death (NDD). 1. On page 3 line 44, the Author needs to review what "marginal" means in terms of organ transplantation. Because this commentary is for a general medical and science audience, it may be unclear to someone what the author is saying about organs being procured. **We have removed the word "marginal" and changed the sentence to provide more explanation: "When injured and poorly functioning organs are transplanted, graft function in recipients may be delayed or even permanently impaired".** 2. On page 7 line 41, the author discusses consent rates for organ donation from patients who can be categorized into ABI, TBT and stroke. The author fails to state what was the significance for figuring out these percentages. A sentence after could provide much clarity for the general audience explaining the relevance in that there was no change over time. **This was a study of consenting NDD organ donors, rather than all patients with a diagnosis of NDD.** As such, it was important to demonstrate that temporal changes in the relative proportions of donors with various diagnoses were not attributable to systematic differences or changes in consent rates depending on the underlying cause of NDD. **We have added an explanatory sentence to the Interpretation section.** 3. On page 9 line 3-15, the author makes a correlation that organs from ABI were transplanted less frequent compared from TBI or stroke. The author should elaborate this point as to why finding this out is significant and possibly novel. **This point is discussed in the Interpretation section, second and third paragraphs, as well as the concluding paragraph.** 4. Page 12 Line 34: The author states that "…there was a consistent trend towards improved early and long-term kidney function in recipients of allografts from donors with TBI compared with ABI or stroke." The author needs to expand more as to why this is true. **This sentence has been modified slightly in the revised manuscript: "Although there was a consistent trend towards lower creatinine concentrations in recipients of kidneys from TBI donors compared with ABI or stroke in the immediate post-transplant period, the differences were not statistically significant after one year".**
Reviewer 2	Dr. James Lin
Institution	Mattel Children's Hospital, Department of Pediatrics, Los Angeles, CA
General comments (author response in bold)	The authors present a well-done study that reports the changing demographics of organ donation after neurologic determination of death (NDD). This descriptive manuscript presents data from 2 sources: a retrospective chart review of organ donations in Southern Alberta and data obtained from the Canadian Institute of Health Information (CIHI). This dual data sources can be somewhat confusing, especially when examining the Tables and Figures in isolation. However, overall the presentation is succinct and clear. I have a few specific comments and questions as follows: Page 5, 1st full paragraph beginning line 20: 1. Was a primary outcome defined for this study? **We have modified the last sentence of the Introduction section to read: "to determine whether the distribution of causes responsible for NDD has changed (primary outcome), and if so, whether this has had an impact on organ quality, transplantation rates and recipient outcomes".** 2. Were these laboratories and imaging studies performed as part of routine donor evaluations, according to individual clinician practices, or something else?

	To clarify, we have added the sentence "These tests are performed routinely in all NDD organ donors". 3. Please provide some indication in the manuscript of how complete data collection was. **For some outcomes (e.g. etiology of NDD, number of organs transplanted per donor), there was no missing data.** **For laboratory tests, data was available for 96-99% of donors, with the exception of troponin T (available in 88%) and ejection fraction (available in 66%). This information has been included in a footnote in Table 1 of the revised manuscript.** Page 9, line 24 and page 10, line 6: 4. Are these time periods exclusive or inclusive of each other? In other words, {<30, 31-60, >60} or {<30, >30 (including >60), >60}. Similarly, {30-44, 45-60, >60}, or {>30 (including >45), >45 (including >60), >60}? **To avoid lack of clarity, we have modified the wording in the revised manuscript.**
Reviewer 3	Dr. Dana Baran
Institution	McGill University Health Centre, Royal Victoria Hospital, Montréal, Que.
General comments (author response in bold)	This study is a retrospective overview of organ donation trends and outcomes in Southern Alberta for the period of 2003-2014. The study cohorts include 226 NDD donors classified as ABI, TBI, or stroke, and 143 kidney transplant recipients. 1. Overall, the study is well done and provides an interesting snapshot of donor trends in Southern Alberta. It confirms the overall trend toward fewer TBI donors and more donors with ABI in the Canadian donor population (as has been reported worldwide). The increasing and very high percentage of ABI donors in Southern Alberta in most recent years (80% in 2013) is unusual, however, and does not reflect the overall Canadian experience. The authors should mention this and comment on why this might be the case. **We appreciate the Reviewer's comments.** **As mentioned in our response to the Editors (see above), we do not agree that there has been worldwide reporting of more NDD donors over time with ABI, at least not in peer-reviewed literature. As such, our findings are more novel (rather than just confirmatory) than the Reviewer has suggested.** **As shown in our Results, Canadian data demonstrate a threefold increment in organ donation from NDD donors with ABI between 2000-2005 and 2012-2013 (Figure 2). This is consistent with the increment we observed in Southern Alberta (Figure 1; ≈ 20-30% in 2003-2005 to > 50% in more recent years). We agree that 80% is an unusually high number, but this was just one (uncharacteristic) year. It is possible that the decline in NDD following TBI has been greater in Southern Alberta than in other Canadian regions, but this interpretation would speculative, and we would rather not comment in the manuscript.** **We have added the following sentence to the Interpretation section: "There may be regional differences, but overall trends were consistent across Canada."** **It is important to remember that in our analysis, a donor with TBI, stroke, overdose, etc. would have been categorized as having ABI if they also had a prolonged cardiac arrest in addition to their underlying cause of death. As mentioned in the Methods, CORR/CIHI data does not permit more than one cause of death to be listed. As such, it is to be expected that there would be more ABI donors in our local cohort, which involved more detailed medical record review than CORR/CIHI data. This is a limitation of the CORR/CIHI data, which underestimates the prevalence of cardiac arrests in NDD organ donors. In the Results section, we list causes of cardiac arrests; overdoses and traumatic injuries were among the most common causes, and could easily have been categorized differently in CORR/CIHI data (as "other" and "TBI", respectively). In fact, when NDD occurs after an overdose, it is almost always in large part because there has first been a cardiac arrest as a complication of the overdose. For example, a narcotic overdose causes apnea, which in turn causes hypoxemia, which in turn causes a cardiac arrest, which in turn causes cerebral edema and herniation. The narcotics themselves do not directly cause cerebral edema and progression to NDD.** **Please also see our first response to Reviewer 4, where we elaborate further on this issue.** 2. The authors go on to provide the data on organs transplanted per donor, pointing out that the organ yield from ABI donors is less than that from TBI or stroke donors. This is largely driven by the inability to successfully procure lungs, heart, and pancreas (the organs that are likely to suffer the most "irreversible" damage from ischemia

following prolonged cardiac arrest). The authors should emphasize this since intervention directed to increasing organs transplanted per donor will have to focus on these particular organs more so than on livers or kidneys. The type of intervention is also intrinsically different, ranging from extending the time between diagnosis of NDD and organ procurement to allow for better organ resuscitation to ex vivo treatment of organs such as the lungs to increase the number of transplantable organs from all organ donors not just ABI donors.

We thank the Reviewer for these insightful comments.

We would point out that the proportion of NDD donors in whom kidneys and liver could be procured/transplanted in our region was more than 10% (absolute increase) higher with TBI than with ABI (Table 1). For kidneys, the same effect was observed nationally using CIHI data (Table 3). As such, we believe that efforts to increase the number of organs procured per donor should focus also on kidneys and livers, even if the overall proportion of donors from whom they are procured is much higher than with lungs, heart and pancreas.

In the Interpretation section, we have added the sentence: "Acceptance of hearts, lungs and pancreas is significantly lower than that of kidneys and livers; it is for these organs where there is the greatest potential for increased utilization".

We agree that in some NDD donors, delaying organ procurement can result in improved organ function over time. However, in other cases, donors may deteriorate, such that other organs may be threatened by time delays. A detailed discussion of these issues is beyond the scope of this paper (particularly with the word count restrictions). As we have stated in our closing paragraph: "Future research should develop additional strategies aimed at optimizing organ usage in NDD donors"

3. The authors also collect some pre-procurement data on organ function that indicates that ABI NDD donors are more likely to have evidence of organ ischemia which is not surprising. This would be easier to interpret if data on the time between NDD diagnosis and procurement were available but this would admittedly be hard to obtain.

We agree with the Reviewer that higher ALT levels in ABI donors are likely to be due to "ischemic hepatitis" or "shock liver". In many cases, the higher creatinine concentrations in ABI donors were likely due to ischemia-induced acute tubular necrosis. Higher troponin T concentrations are likely attributable to the combination of ischemia and CPR-induced cardiac trauma. In the case of lungs, the explanation for lower PaO2/FIO2 among ABI donors is less obvious and not necessarily due to ischemic injury to the lungs.

We do not have data for the time interval from NDD diagnosis to procurement, although it could be obtained (if the Editor(s) wish). This time frame is typically 24-36 hours. There is no reason to believe there would have been any systematic differences in time to procurement based on the cause of death; as such, we do not believe this would improve the manuscript.

Beyond this descriptive Albertan data (number and type of donors over time, type and number of organs procured, functional parameters), the paper addresses two other issues: outcome in a subgroup of patients who received kidney transplants in Alberta, and a comparison of donor data with overall Canadian data.

4. With regard to outcome data, I find the analysis rather weak given problems with definitions and the paucity of information about the peri-transplant period and the recipients. For example, the definition of DGF is only partly conventional (need for dialysis after transplant), and the inclusion of another group of patients with slow decline in creatinine muddies the waters.

The need for dialysis in the first week post-transplant is a very common definition for delayed graft function (DGF) that is consistently used in clinical trials. Recent examples that used precisely this definition include Nieman et al, N Engl J Med 2015; Chapal et al, Trials 2015; Orban et al, Transplantation 2015; Wszola et al, Transpl Int 2013; and Hermayer et al, J Clin Endocrin Metab 201 (there are many more). We therefore regard this definition "conventional".

However, one of the limitations of this definition is that there is some subjectivity in deciding whether dialysis is truly necessary (i.e. not all transplant nephrologists have the same "threshold"). As such, we have also included a second, alternative definition of DGF. This particular definition ("functional DGF") was chosen based on the cited manuscript by Moore et al (Transplantation 2010), which concluded "this study confirms the utility of fDGF as an early marker of subsequent inferior allograft outcomes, suggesting superiority over the traditional (often subjective) dialysis based definition". We regard the use of an additional analysis, using an alternative definition for DGF, as further strengthening our study, and do not agree that it "muddies the waters". Of note, use of the alternative definition did not alter the results

	in a major way (Table 2), although it found an even higher rate of DGF with kidney allografts from ABI donors. In our opinion, it would detract from the study to remove this analysis. The early creatinine data up to the time of discharge is really uninterpretable without more information. How many kidneys in each group were perfused before transplant and what were the cold ischemia times? **We agree with the Reviewer that conclusions based on early creatinine values should not be overstated. Indeed, we have been careful to avoid doing so. However, we do not see any down side to providing this complementary information in Table 2 to supplement the data regarding DGF.** **As requested, we have clarified in the Methods section that machine perfusion was not used at our center during the time period of interest.** **Cold ischemic times have been added to Table 2. Median cold ischemic time was 11.5 (6.7-16) hours in ABI donors, 12 (8-16) hours in TBI donors, and 13 (10-18) hours in donors with stroke (differences non-significant).** How many of the patients in each group were peritoneal vs hemodialysis patients (the former start with a serum creatinine that often exceeds 800-1000 micromoles/l and the creatinine therefore takes more time to drop post-transplant), when were the creatinine measurements taken (for those on dialysis, this is especially problematic), etc. **We have added a footnote to Table 2 stating that creatinine values were measured each morning after transplantation.** **Relative proportions of transplant recipients receiving hemodialysis, peritoneal dialysis or pre-dialysis is not information that we have readily available, but it could be obtained with additional chart review if the Editor(s) wishes. However, there is no clear reason why there should be any systematic difference in mode of renal replacement therapy in recipients based on the cause of death in donors.** In the end, the harder endpoints of creatinine at one year and death/return to dialysis in the short term are not different among the groups. **We agree with the Reviewer that creatinine at one year, in particular, is a more important outcome than creatinine values during the immediate post-transplant period. We have been careful not to overstate conclusions based on these results. Nevertheless, as discussed above, there is really no downside to presenting this information in Table 2, as it supplements the other information, in particular the data about DGF.** I do not believe this outcome data adds much to the paper since it only confirms that the best type of donor is a young TBI donor (or standard criteria donor in other terminology) which is already well-known. There is so much missing information on the peri-transplant period and the recipients that I think the best thing to do is to remove this outcome data and summarize only the final conclusion on creatinine at one year and death/return to dialysis in the text. **We believe the Reviewer is overstating the degree to which it is "well-known" that "the best type of donor is a young TBI donor".** **As the Reviewer will be aware, it is entirely possible for NDD donors post cardiac arrest or post stroke to also be "standard criteria donors" (the usual definition of an expanded criteria donor is age > 60 OR 2/3 of the following criteria: history of hypertension, elevated creatinine, cause of death cerebrovascular accident). Indeed, as shown in Table 1, 12% of ABI donors, 12% of TBI donors and 38% of donors with stroke were "expanded criteria donors".** **In the manuscript, we have reviewed the (limited) existing literature comparing outcomes in transplant recipients based on the cause of NDD in donors. The Reviewers' statement that the "best type of donor is a young TBI donor" may be a widespread perception amongst donation/transplantation clinicians, but it is not well established in peer-reviewed literature.** **We have clearly demonstrated that NDD donors in whom the cause of death was ABI have a greater degree of organ injury than donors with other diagnoses. The obvious next question is whether or not this has important implications in recipients. As such, it is important that our paper provide such an analysis.** **In the Interpretation, we have explicitly stated "Despite the high rate of DGF with prolonged cardiac arrests, few patients required dialysis after one year. In addition, although there was a consistent trend towards lower creatinine concentrations in recipients of kidneys from TBI donors compared with ABI or stroke in the immediate post-transplant period, the differences were not statistically significant after one year".** 5A. With regard to the Canadian comparison, this section has inherent limitations that are acknowledged by the authors. First of all, they cannot be sure that they are

	comparing the same donors since the CIHI database does not classify donors in the same way. **We agree with the Reviewer that it is unfortunate that the CIHI database does not have the type of detail, granularity and precision that we are able to provide with Southern Alberta data.** **Had we not included national data, the main criticism of our study would have been that it lacks generalizability. The addition of CIHI data therefore greatly strengthens our findings (as pointed out by Reviewer 4). Despite the differences in assignment of diagnostic categories, it is remarkable that the overall national findings are largely consistent with our local experience.** **We have performed an additional analysis, as requested by Reviewer 4, comparing categorization of donors in our dataset compared with diagnoses submitted by our regional organ donation agency to CORR/CIHI (see below). This analysis demonstrates: (1) Good agreement between the two classifications (kappa 0.78); (2) As expected, underestimation of the importance of cardiac arrests / anoxic brain injury in the CORR/CIHI set (because some patients with TBI, CVA and "other" conditions also sometimes have cardiac arrests as a concomitant cause of death). This difference in methodology actually accounted for all of the discrepancies (kappa score was 1.00 for the remainder of donors).** 5B. This aside, all Quebec data is missing and this represents a substantial number of NDD donors (Quebec consistently has the highest number of deceased donors per million population in Canada, followed closely only by Ontario). At the very least, the authors should mention the number of total NDD donors missing in their analysis for lack of Quebec data. They could also easily get some of the missing donor data directly from Transplant-Quebec. **We have responded to this issue in our initial comments to the Editorial Board. We would have obviously preferred to include Quebec data. It is indeed unfortunate that Commission D'Access a L'Information would not initially approve release of Quebec data. If the Quebec Privacy commission does not approve release of Quebec CIHI data, it is not reasonable to expect this same data to be available through Transplant Quebec.** **Since being provided with this review, we have re-contacted CIHI and learned that Commission D'Access a L'Information has now provided approval for release of data from 2000-2011 (but still not 2012-2013). Available data has been included in our revised manuscript. Of note, trends from Quebec were consistent with those observed elsewhere in Canada. Addition of these data did not change our conclusions.** Minor points: 6. p.6, line 15 - would remove the comment about "prolonged ischemia" which of course can be deleterious and leave only "brief cardiac arrest." **The manuscript refers to "prolonged hypoxemia" rather than "prolonged ischemia". We therefore do not see any reason to change the sentence.** 7. p.11, line 8 - would add that the six patients were from "all groups combined." **The sentence has been modified accordingly in the revised manuscript.**
Reviewer 4	Damon Scales
Institution	Sunnybrook Health Sciences Centre, Department of Critical Care Medicine, Toronto, Ont.
General comments (author response in bold)	Kramer and colleagues have conducted a cohort study examining trends in rates of donation after neurological determination of death (brain death) in Southern Alberta. They conclude that the relative proportion of these patients with traumatic brain injury as the primary neurological injury has decreased over time, whereas relatively more patients have become organ donors after brain death due to anoxic brain injury during recent years. They also observed different patient characteristics among these 2 groups – with generally greater injury severity for patients dying from anoxic brain injury, and fewer organs procured. This study provides valuable regional and national information about a very important aspect of our healthcare system. Organ transplantation has been shown to have dramatic impact on improving health of recipients, yet waiting lists remain unacceptably long. Studies like this one are important for policy and decision makers who plan and organize organ donation organizations, and also for clinicians who treat organ donors and transplant recipients. Major comments: 1. A major strength of the methodology is that it includes an analysis of Alberta local granular health data and chart review for the primary analysis, and then a national analysis using CIHI data to complement these findings. This is an excellent addition – and helps increase generalizability to a larger region. However, it appears that the

	classification of causes of brain death for the primary study (i.e. conducted in Southern Alberta) and this secondary analysis (i.e. conducted using CIHI) involve different approaches. Is it possible to also provide results using the CIHI approach, but restricted to the Southern Alberta region that is the focus of the primary analysis? This would reinforce that these 2 analyses that use different approaches to coding and data measurement yield complementary findings. **We thank the Reviewer for this suggestion.** **The causes of death in NDD donors in the CORR/CIHI database are provided by individual organ donation agencies and assigned by organ donation coordinators.** **We were able to obtain the diagnoses submitted to CORR/CIHI by the Southern Alberta Organ and Tissue Donation Agency.** **The kappa statistic comparing categorization of the causes of NDD in the two datasets was 0.77 (0.71-0.84). All "discrepancies" were for donors with a primary diagnosis of TBI, CVA, or "Other" (mostly overdoses) who also had a prolonged cardiac arrest, and were therefore categorized differently in our local analysis as having ABI.** **This issue was anticipated in advance, as discussed in detail in our Methods section, and demonstrates why the CORR/CIHI database underestimates the importance of anoxia as a cause of NDD in Canada. We have provided these data in the revised Results section and discussed them further in the revised Interpretation section.** 2. One of the key findings is that anoxic brain injury has become a much more common cause of brain death during the past decade in this region. The authors hypothesize in the Discussion that this trend is largely related to a reduction in overall rates of TBI. Is there any way to present these trends in overall TBI requiring ICU (i.e. the cohort at risk for brain death) in the Southern Alberta using the available databases? Similarly, can they provide any trends in overall rates of ICU admission for cardiac arrest survivors during the same time frame, that would help explain why rates of brain death after anoxic brain injury have also increased? An alternative explanation is that more patients with cardiac arrest are being treated with extended life support (in keeping with guideline recommendations to provide targeted temperature management and postponing neurological prognostication) – which in turn could postpone early withdrawal of life sustaining therapies and allow more of these patients to progress to brain death. **In the Interpretation section, we have referenced two papers to justify our statement that "A reduction in donors with TBI is likely due to a declining incidence of severe TBI, as well as a smaller proportion of patients that progress to NDD1, 22". One of these papers provides exactly the data that the Reviewer is suggesting (data from Southern Alberta demonstrating fewer ICU admissions for severe TBI and a smaller proportion of TBI patients that progress to NDD) (Kramer et al, CMAJ 2013). We have modified the wording in the revised manuscript to make this clearer.** **This same paper also demonstrated a slight increment in the overall number of cardiac arrest survivors (and a growing proportion of all brain injured patients) in Southern Alberta over time.** **Accordingly, we have added the following text to the Interpretation section: "Previous work from our region demonstrates that cardiac arrest victims account for a growing proportion of brain-injured patients admitted to intensive care units1. Moreover, as suggested in consensus guidelines, clinicians may be delaying withdrawal of life-support to a greater degree, which in turn may provide more time for progression to NDD23-24.** Minor comments: 3. Abstract: "Nationally this figure remained stagnant despite increments for each individual cause of death" – it is unclear to which number you refer (TBI vs ABI). Please clarify. **The wording has been changed to "Nationally, organs per donor remained stagnant despite increments for each individual cause of death"** 4. Abstract: there are several sentences that reference findings, yet no numbers or actual results are presented. Either delete these sentences, or provide the relevant data. **The Abstract was written this way to comply with word count restrictions. We have modified the Abstract as much as possible. However, to provide comparisons of all of the laboratory values (creatinine, ALT, troponin T, PaO2:FIO2) and urine output would result in us substantially exceeding the 250 word limit.** 5. Abstract: final sentence: strategies to maximize organ usage should be pursued. Surely this is true! However – I am uncertain that your results lead directly to this conclusion. **This sentence has been removed.**

	6. Methods: I appreciate that one specialist adjudicated all deaths (and was blinded), and in particular classified cause of death as cardiac (versus other). The methodology would be strengthened if another reviewer also blindly adjudicated. I would just cite this as a limitation in your Discussion. **A short paragraph with limitations has been included in the revised manuscript, which mentions this limitation.** 7. Methods: The secondary outcomes are clearly described, but we are left assuming that primary outcome is cause of brain death. Please state this explicitly. **We have explicitly indicated in the revised document that the primary outcome was the distribution of causes responsible for NDD over time.** 8. Methods: please explain how you actually identified an organ donor using CIHI coding. **The Canadian Organ Replacement Registry (CORR) is management by CIHI. Organ donor data is provided directly from all provincial organ donation agencies. This has been mentioned in the revised Methods section.** 9. Methods: are assumptions satisfied for conducting linear regression to analyze cause of NDD and number of organs transplanted per donor? I worry that the outcome – number of organs transplanted – has a very narrow range, likely spanning about 0 to 5 or 6, with clustering around 4 in most patients. **Thank you for pointing this out. The Editorial Board has asked us to instead use ordinal regression. We have done so in the revised manuscript. The results were not altered significantly in the revised analysis.** 10. Results: when describing reduction in numbers of organs transplanted per donor (or any other trends) – please provide significance testing for these changes (page 9) **The text in the section the Reviewer is referring to has been modified to read as follows: "The peak number of organs transplanted per donor was 4.5-4.6 in 2005-2006, compared with 3.4-3.8 in 2012-2014. However, the reduction in number of organs transplanted per donor over time was not statistically significant (p=0.34)".** 11. Discussion: re donor management goals. I am not sure why your observations suggest that consistent achievement of these may be less realistic for donors with ABI. Can you explain/clarify? **We have added the following explanatory sentence to the Interpretation section: "For example, despite routine adherence to Canadian guidelines17, significantly fewer donors with ABI achieved PaO2/FIO2 > 300 mmHg or urine output > 0.5 ml/kg/hour (both of which are DMGs)[40-41]".**