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BRONCHIOLITIS OBLITERANS FOLLOWING LUNG TRANSPLANTATION: EARLY DETECTION USING CT

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What this paper adds: We systematically evaluated inter- and intraobserver agreement for qualitative CT scoring of a variety of abnormalities, including a composite CT_{BO}-score in a lung transplant recipient patient population with predominantly mild abnormalities. The composite CT score predicts the course of the FEV_1 over the next year. Our findings indicate a potential role for a composite CT score as well as an air trapping score alone in predicting the clinical course of lung transplant recipients.

Key words: CT, FEV_1, BO/BOS, lung transplant

ABSTRACT (word count 198)

Background: CT scanning may enable earlier diagnosis of chronic lung allograft dysfunction than FEV_1. Our aims were to determine intra- and interobserver agreement of composite and air trapping CT-scores, to examine the association of FEV_1 with composite and air trapping CT-score and to relate baseline composite CT-score to changes in FEV_1 and changes in composite CT-score over one year.

Methods: Lung function and baseline post-transplant CT and subsequent annual follow-ups were analyzed in 38 lung transplant recipients. Scans were randomly scored by two observers for: bronchiectasis; mucous plugging; airway wall thickening; consolidation; mosaic pattern; and air trapping, and re-scored after one month. CT-scores were expressed on a 0-100 scale and correlated to FEV_1 as a percentage of the post-transplant baseline value.

Results: The mean interval [SD] between baseline and follow-up CT was 11.2[4.7] months. Inter- and intraobserver agreement was good for both the composite and air trapping CT-score. There was a significant association between FEV_1 and composite CT-score, whereby each unit worsening in baseline composite CT-score predicted a 1.55% and 1.37% ($p<0.0001$) and a 1.25 and 1.12 unit ($p<0.0001$) worsening over the following year in FEV_1 and composite CT-score for observer 1 and 2, respectively.

Conclusion: Our findings indicate a potential role for a composite CT scoring system in the early detection of BO.

INTRODUCTION

Long term survival after lung transplantation is limited by the development of chronic allograft dysfunction which manifests as bronchiolitis obliterans (BO). BO consists of heterogeneously-distributed areas of obliterated respiratory and terminal bronchioles that leads ultimately to a decline in forced expiratory volume in one second (FEV_1), graft failure and recipient death (1-4). It is thought that earlier diagnosis and more timely treatment of BO could improve long term survival (1-3, 5, 6), however, the heterogeneous distribution of BO within the transplanted lungs renders invasive diagnosis by transbronchial biopsy unreliable, with reported sensitivities as low as 17%-28% (3, 7, 8). Therefore, in an attempt to identify BO earlier a functional surrogate for this structural abnormality, bronchiolitis obliterans syndrome (BOS), has been defined as a progressive decline in FEV_1 (9). Unfortunately identifying patients using BOS criteria still may not identify the subjects early enough in the development of airflow limitation due to the distribution of the BO process. Recently investigators have turned their attention to computed tomography (CT) scoring systems because it is thought that direct evaluation of anatomic markers may allow for earlier detection of BO compared to indirect measurements such as FEV_1.

There are, however, limitations to CT scoring systems predominately due to sensitivity and specificity for disease progression as well as the high inter and intra-observer variability of the score itself. For example, it has been suggested that air trapping is the most sensitive and specific CT abnormality for the early detection of BOS (10-14), while exhibiting the highest interobserver agreement (14-16). However, more recent work has not always confirmed these findings (17) and there is no consensus on how to score air trapping. For example, Bankier et al evaluates gas trapping as 0-20%, 20-40%, 40-60%, 60-80% or 80-100% of the lobe involved (14, 16) while, Siegel et al score the lobes as 0%, 1-25%, 26-50%, 51-75%, 76-100%) (13). Furthermore, scores for mosaic pattern of attenuation, airway wall thickening and bronchiectasis are individually less sensitive and specific than scores for air trapping (10-14, 17) and the intra- and interobserver agreement individual scores for bronchiectasis, airway wall thickening and mosaic pattern have not been evaluated in lung transplant recipients. Therefore, given the variety of CT abnormalities seen in BO/BOS, it may be that a composite CT-score ($CT_{BO\text{-}score}$) will be more sensitive and specific than a CT air trapping score ($CT_{AT\text{-}score}$) alone for the early detection of BO.

The aims of the present study were to determine the intra- and interobserver agreement of a CT_{BO}-score and a CT_{AT}-score, to determine the cross-sectional relationship between CT_{BO}-score and CT_{AT}-score with FEV_1, and to relate CT_{BO}-score at baseline to changes in FEV_1 and changes in CT_{BO}-score over the course of one year. Our hypotheses were: 1) CT_{BO}-score and CT_{AT}-score would show significant associations with FEV_1 in lung transplant recipients and 2) the CT_{BO}-score at baseline would predict changes in FEV_1 and changes in CT_{BO}-score over the course of one year.

METHODS

Subjects

For this study, we included the baseline CT scan (first scan following transplantation) and the first annual surveillance CT (follow-up) on 38 consecutive subjects who received a single or double lung transplant at our centre since 2000. CT scans were excluded when performed for the diagnosis of acute clinical events, when there were incidental CT findings of acute disease (e.g. pneumonia), or when the recipient had coincident clinical or bronchoscopic evidence of an acute event (acute rejection, infection). We did not routinely perform bronchial provocation testing on our lung transplant recipients. None of the subjects included in this study had clinical manifestations of asthma post-transplant, and none had

significant bronchodilator responses according to ATS criteria on spirometry. The study was approved by the clinical ethics review board of the University of British Columbia.

CT scans

All CT scans were performed on a GE Lightspeed Ultra scanner (General Electric Medical System, Milwaukee, WI, USA). Inspiratory images were acquired at suspended inspiration from lung apex to base using 1.25 mm slice thickness at 10-mm intervals. Expiratory 1.25 mm thick images were acquired at end-exhalation at the level of the aortic arch, the carina and 2-cm above the hemi-diaphram. Images were acquired using 150 mA, 120 kVp, 1 second scan time, reconstructed using a high spatial frequency algorithm ("Bone") and an appropriate field of view. For the first part of the study, each baseline CT scan was assigned a random identification number, blinded for patient characteristics and reviewed using a medical imaging workstation (Leonardo Workstation, Siemens AG Medical Solutions, Erlangen, Germany). For the second part of the study, each pair of baseline plus follow-up scans was assigned another random identification number, blinded for patient characteristics and reviewed as per baseline.

Spirometry

Spirometry was performed according to ATS guidelines (18). For the purposes of this study, FEV_1 was expressed as a percentage of the average of the two best FEV_1 values obtained after lung transplantation (9). BOS was defined according to the International Society of Heart and Lung Transplantion guidelines with BOS stage 0 as an FEV_1 above 80% of post transplant baseline. BOS stages 1, 2 and 3 were 66-80%, 51-65% and below 50% of post-transplant baseline, respectively (9).

CT scoring

To establish the CT scoring system, two observers (PAD, JDD) independently scored the baseline CT scans in a random and blinded fashion. To test for intra-observer variation, one observer re-scored all baseline CT scans after one month.

Our CT scoring system is presented in Table 1 and illustrative examples are provided in Figure 1. The CT scans were viewed using display settings of: Window, -500 Hounsfield Units (HU) and Level, 1500 HU. Inspiratory scans were evaluated for: severity and extent of central and peripheral bronchiectasis; extent of central and peripheral mucus plugging; severity and extent of central and peripheral airway wall thickening; extent of consolidation; and extent of mosaic pattern. Expiratory scans were evaluated for the extent of air trapping. Each of the 5 lobes (including the lingula as a sixth "lobe") were evaluated separately using the inspiratory CT image while six lung zones (upper, middle, lower and left, right) were scored using the expiratory images. In single lung transplant recipients, only the lobes of the transplanted lung were scored.

Table 1: CT_{BO} scoring system for one lobe*

Lobe	**Score**			
CT abnormality	0	1	2	3
1. Bronchiectasis				
- Central lung (extent)	Absent	<33%	33%-67%	>67%
- Peripheral lung (extent)	Absent	<33%	33%-67%	>67%
- Size of largest	Absent	B<2V	B=2-3V	B>3V
- Size of average	Absent	B<2V	B=2-3V	B>3V
2. Mucous plugging				
- Central (extent)	Absent	<33%	33%-67%	>67%
- Peripheral (extent)	Absent	<33%	33%-67%	>67%
3. Airway wall thickening				
- Severity	Absent	Mild	0.5-1V	>1V
- Central lung (extent)	Absent	<33%	33%-67%	>67%
- Peripheral lung (extent)	Absent	<33%	33%-67%	>67%
4. Consolidation (extent)	Absent	<33%	33%-67%	>67%
5. Mosaic pattern (extent): inspiratory CT scan finding	Absent	<33%	33%-67%	>67%
6. Air trapping (extent): expiratory CT scan finding	Absent	<33%	33%-67%	>67%

For bronchiectasis peripheral is 1 to 2 cm from costal/diaphragmatic pleura or abutting the mediastinal pleura; B = diameter bronchial lumen, V = diameter of accompanying pulmonary artery. Central mucus = plugging in identifiable bronchi. Peripheral mucus = centrilobular nodules and tree in bud. Airway wall thickening: Mild = greater than 2 mm in hilum, 1 mm centrally and 0.5 mm peripherally. *Scores for each abnormality were calculated according to Brody et al (19). Figure 1 shows images corresponding to the scoring system abnormalities.

Abnormalities were defined according to recommendations of the nomenclature committee of the Fleischner society. To score peripheral bronchiectasis and airway wall thickening, “peripheral” was defined as less than 2 cm from costal and diaphragmatic pleura. Visible airways abutting the mediastinal pleura were scored as bronchiectasis. Peripheral mucus plugging was evaluated using the radiological appearance of “centri-lobular nodules” or “tree-in-bud” pattern rather than using a peripheral location. Central mucous plugging was scored if mucus was seen in identifiable bronchi. Mild airway wall thickening was defined as an airway wall thickness greater than 2 mm in the hilum, 1 mm in the central and 0.5 mm in the peripheral lung. Mild bronchiectasis was defined as a bronchial lumen diameter greater than the diameter of the adjacent pulmonary artery or as a lack of tapering between bronchial generations.

Scores for bronchiectasis, mucus plugging, airway wall thickening, air trapping and a composite CT_{BO}-score were calculated similar to Brody et al (19). In brief, for each lobe a bronchiectasis score, mucous plugging score and airway wall thickening score were calculated by combining the abnormalities and severity of the abnormalities in the central and peripheral lung. Next, the lobe scores for bronchiectasis, mucous plugging, airway wall thickening, consolidation, mosaic pattern and air trapping were summed to produce a total maximum of 108, 54, 36, 18, 18 and 18, respectively. The composite score was calculated by adding the component scores together for a total maximum of 252. The maximum total scores and maximum component scores were expressed on a scale from 0-100 for statistical analysis.

For the second part of the study, after 3 months the baseline CT scans were combined with the follow-up CT scans, randomized and scored using the above scoring system to assess the predictive value of the scoring system for disease progression. The readers did not have

information on which scans were baseline and which were follow-up. The scores from this reading were also used to evaluate the intra-observer agreement.

Statistical analysis

Intra- and interobserver agreement of scores for CT components, CT_{AT}-score and CT_{BO}-score were calculated using intraclass correlation coefficients. An intraclass correlation coefficient of greater than 0.8 represents good agreement.

Linear regression was used to model the association between CT-score and FEV_1 measured at baseline. The regression analysis was conducted for CT_{BO}-score and CT_{AT}-score and for each observer separately. The regression coefficient was a measure of association, showing the average decrease in CT score for every additional percent change in FEV_1. The analysis was repeated for follow-up measurements and was conducted for observer 1 and observer 2 separately. The linear regression was also used to model the association between baseline CT_{BO}-score and FEV_1 at follow up and baseline CT_{BO}-score and CT_{BO}-score at follow up. Finally, the linear regression was used to model the association between baseline CT_{AT}-score and FEV_1 at follow up and baseline CT_{AT}-score and CT_{AT}-score at follow up. The analysis was conducted for observer 1 and observer 2, separately.

A p value less than 0.05 was considered significant and all data are presented as mean±SD (range) unless indicated otherwise.

RESULTS

Study population

The mean age at transplantation of the 38 lung transplant recipients that were included in the present study was 43.7±13.1 (12.7-64.6) years. The interval between transplantation and baseline CT was 44±33 (2-120) months and the interval between baseline and follow-up CT was 11.2±4.7 (2.3-17.4) months. At the time of the baseline CT, 22, 10, 4 and 2 patients were in BOS stage 0, 1, 2 and 3, respectively, by spirometric criteria. One patient did not have a follow-up CT scan and another was excluded from follow-up analysis because of biopsy-proven acute rejection. Other subject characteristics are given in Table 2.

Table 2: Characteristics of the study population

Type of transplantation	
- Single lung (n)	21
- Double lung (n)	16
- Heart lung (n)	1
Diagnosis	
- Cystic fibrosis (n)	13
- Emphysema / COPD (n)	11
- A1-antitrypsine deficiency, IPF and LAM (n)	3 for each
- PAH, idiopathic obliterative bronchiolitis (n)	2 for each
- Langerhans cell histiocytosis, sarcoidosis (n)	1 for each
Spirometry	
FEV_1 at baseline CT (% of baseline post-transplant)	82±18 (34-100)
FEV_1 at follow-up CT (% of baseline post-transplant)	77±21 (27-100)
CT Scores	
CT_{AT}-score at baseline CT (unit)	47±23 (0-100)
CT_{AT}-score at follow-up CT (unit)	51±23 (0-100)
CT_{BO}-score at baseline CT (unit)	7±4 (1-16)
CT_{BO}-score at follow-up CT (unit)	7±5 (0-24)

Data given are mean±SD (range) or absolute numbers. CT data are given for observer 1. COPD, IPF, LAM and PPH stand for chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis, lymphangioleiomyomatosis and pulmonary arterial hypertension, respectively. CT, AT, BO and FEV_1 stand for computed tomography, air trapping, bronchiolitis obliterans and forced expiratory volume in one second, respectively.

Inter- and intraobserver agreement

The interobserver and intraobserver agreement for CT_{AT}-score, CT_{BO}-score and other component scores are shown in Table 3. An intraclass correlation coefficient above 0.80 was considered to represent good agreement. The interobserver agreement was above 0.80 for the $CT_{AT\text{-}score}$ and the bronchiectasis CT score. However the CT_{BO}-score and consolidation, mucous plugging, airway wall thickening and mosaic pattern component scores were below 0.80. The intraobserver agreement after one month was good for the $CT_{AT\text{-}score}$ and the CT_{BO}-score, but was below 0.80 for mucous plugging, airway wall thickening and mosaic pattern component scores (Table 3).

Table 3: Intra- and interobserver agreement of CT abnormalities including air trapping and composite CT_{BO}-score

	Interobserver agreement	Intraobserver agreement
CT_{AT}-score	0.86	0.97
CT_{BO}-score	0.78	0.94
Bronchiectasis-score	0.84	0.94
Consolidation-score	0.78	0.90
Mosaic pattern-score	0.68	0.72
Airway wall thickening-score	0.61	0.72
Mucous plugging-score	0.12	0.39

Data are intraclass correlation coefficients. An intraclass correlation coefficient of greater than 0.8 represents good intra- and interobserver agreement. CT = computed tomography. AT = air (gas) trapping. BO = bronchiolitis obliterans.

Relationship between baseline FEV_1 and CT_{BO}-score or CT_{AT}-score

There was a significant association between FEV_1 and both CT_{BO}-score and CT_{AT}-score measured at baseline (Figure 2), with a higher (more damage) CT-score corresponding to a lower (worse) FEV_1 value. The baseline CT_{BO}-score increased by 0.2 ($p=0.0001$, observer 1) and 0.26 ($p<0.0001$, observer 2) and the baseline CT_{AT}-score increased by 0.55 ($p=0.02$, observer 1) and 0.55 ($p=0.02$, observer 2) for each percentage decrease in baseline FEV_1 (Figure 2). The follow-up CT_{BO}-score increased by 0.25 ($p<0.0001$, observer 1) and 0.27 ($p<0.0001$, observer 2) and the follow-up CT_{AT}-score increased by 0.36 ($p=0.002$, observer 1) and 0.63 ($p<0.0001$, observer 2) for each percentage decrease in follow-up FEV_1.

We divided the subjects into a group without BOS (FEV_1>80% baseline) and a group with BOS (FEV_1 below 80% baseline). We arbitrarily set a CT score > 5 as abnormal. In the patients without BOS, 12 out of 22 had a CT score >5 (55% of patients with normal FEV_1 had an abnormal CT score). Air trapping alone was present in 19 of the 22 subjects without BOS (86%). In the subjects with BOS, 13 of 16 had an abnormal CT score > 5 (81%) and air trapping alone was present in 16 (100%).

Relationship between baseline CT_{BO}-score and changes in CT_{BO}-score and FEV_1

There were significant associations between baseline CT_{BO}-score with both FEV_1 and CT_{BO}-score measured after one year. The average FEV_1 at follow-up decreased by 1.55

percent of baseline (observer 1) or 1.37 (observer 2) for every additional unit in CT_{BO}-score at baseline ($p<0.0001$). The average CT_{BO}-score at follow-up increased by 1.25 units (observer 1) or 1.12 (observer 2) for every additional unit in CT_{BO}-score at baseline ($p<0.0001$).

Relationship between baseline CT_{AT}-score and changes in CT_{AT}-score and FEV_1

There were significant associations between baseline CT_{AT}-score with both FEV_1 and CT_{AT}-score measured after one year. The average FEV_1 at follow-up decreased by 0.27 percent of baseline (observer 1) or 0.24 (observer 2) for every additional unit in CT_{BO}-score at baseline ($p=0.0003$ and $p=0.0004$, respectively). The average CT_{BO}-score at follow-up increased by 0.74 units (observer 1) or 0.68 (observer 2) for every additional unit in CT_{BO}-score at baseline (both $p<0.0001$).

DISCUSSION

The aims of the present study were to determine the intra- and interobserver agreement of the CT_{BO}-score and CT_{AT}-score, to determine the cross-sectional association between CT_{BO}-score and CT_{AT}-score with FEV_1 and to relate CT_{BO}-score at baseline to changes in FEV_1 and changes in CT_{BO}-score over the course of one year. Our hypotheses were 1) that CT_{BO}-score and CT_{AT}-score would show significant associations with FEV_1 and 2) that the CT_{BO}-score at baseline would predict changes in FEV_1 and CT_{BO}-score over the course of one year. This study was not designed to determine if the CT_{BO}-score is more useful than the CT_{AT}-score.

Similar to previous studies (14, 16), our data show good interobserver and intraobserver agreements for the CT_{AT}-score. However, also similar to a previous study (13), the intraclass correlation coefficient for the composite CT_{BO}-score in our study was borderline. This was related to the relatively low level of interobserver agreement in scoring mucous plugging, airway wall thickening and mosaic pattern. A number of factors may be responsible for the disagreements in scoring of airway wall thickening and mosaic pattern. Firstly, the majority of our cohort was within the mild (BOS-0 and BOS-1) stages of airflow obstruction. Therefore, the CT scans showed only subtle abnormalities which makes scoring more difficult. Not surprisingly, there is better interobserver agreement in cystic fibrosis studies where the abnormalities are more pronounced, although in those studies the scores for airway wall thickening and mosaic pattern were also not very reproducible (15, 20). Secondly, although both observers had substantial expertise with chest CT interpretation and scoring, they had limited experience in reading CT scans of lung transplant recipients. However, this situation may accurately reflect the typical clinical setting, where chest CT scans are often read by radiologists with limited experience in lung transplant CT interpretation. Interobserver agreement may be improved by observers in large transplant centers that are more experienced in CT scan evaluation of lung transplant recipients. Alternatively it may be best to combine these subjective scoring systems with a computerized analysis of lung parenchyma (21, 22) and airways (23, 24), which could allow the synthesis of the clinical impression with objective quantitative values.

The most important findings of this study are that both CT_{BO}-score and CT_{AT}-score are significantly associated with FEV_1. In addition, both the CT_{BO}-score and the CT_{AT}-score predicts the clinical course of a patient over the year following the CT scan. A 1% higher CT_{BO}-score at baseline predicts a 1.55% faster worsening in FEV_1 and a 1.25% faster worsening in CT_{BO}-score over the coming year (observer 1). A 1% higher CT_{AT}-score at baseline predicts a 0.27% faster worsening in FEV_1 and a 0.74% faster worsening in CT_{BO}-score over the coming year (observer 1). This finding suggests that both the composite CT_{BO} score and the CT_{AT}-score could potentially identify BO earlier than FEV_1. Based on our study, one cannot determine if the CT_{BO}-score is more useful than the CT_{AT}-score, and

therefore it would be prudent for future longitudinal studies evaluating the usefulness of subjective CT interpretation in BO to include a composite CT score as well as an air trapping CT score alone.

Nevertheless, these results support the concept that CT is a valuable tool in the evaluation and follow-up of lung transplant recipients. Lung function is currently the "gold-standard" for detecting lung allograft dysfunction, but is only an indirect measurement and can only give a global assessment of the pulmonary condition. The major advantage of CT is that it is a direct measure of lung structure and allows for the identification of structural abnormalities associated with chronic allograft dysfunction, including as bronchiectasis, airway wall thickening, mucus in small and large airways and air trapping due to small airway abnormalities. Furthermore, CT imaging allows for the detailed analysis of the regional distribution of pathologic processes such as BO. This is particularly pertinent in single lung transplant recipients, where physiologic measures such as FEV_1 are confounded by the contribution from the native lung. Even in double lung-transplant recipients, lung function tests may be insensitive in a situation of heterogeneous distribution of damage, especially when abnormalities are located in the most peripheral airways. For these reasons, we suggest that CT could identify BO earlier than FEV_1, at a time point when alteration of immunosuppression may result in improved clinical outcomes. Therefore, the use of clearly defined CT parameters (particularly a composite CT score that quantifies numerous lung components), possibly in combination with quantitative CT measures, may have an important role as a standardized outcome for research trials involving BO.

In the present study we did not analyze our data utilizing the BOS 0p stage. Because FEV_1 declines later in the disease process this new category (BOS0-p) was added based on forced expiratory flows between 25 and 75 % of forced vital capacity (FEF_{25-75}) (3). However, its prognostic usefulness has been debated (17, 25) with variable positive and negative predictive values reported. In view of this uncertainty, our statistical analysis was based on using FEV_1 as a continuous variable rather than bins based on BOS stages, and hence this did not effect our analysis.

Potential limitations of our study include the relatively small study population, the short follow-up and the variation in timing of the baseline CT scan. A larger number of patients followed over a longer time frame would be useful to help characterize the potential role of CT for the early detection of chronic lung allograft dysfunction. Such a study could also aim to determine the optimal interval between CT scans to detect BO earlier than FEV_1. Finally our analysis may be limited by the fact that only three expiratory CT images were obtained and it may be advantageous in future studies to increase this number.

In conclusion, we systematically evaluated inter- and intraobserver agreement for qualitative CT scoring of a variety of abnormalities, including a composite CT_{BO}-score in a patient population with predominantly mild abnormalities. Both the composite CT_{BO}-score and the CT_{AT}-score had a good or almost good inter- and intraobserver agreement. Our findings indicate a potential role for a composite CT score as well as an air trapping score alone in lung transplant recipients.

Figure 1: Representative CT images demonstrating the CT_{BO}-scoring system abnormalities

Legend: A collection of trans-axial 1.25 mm CT sections in different patients viewed at lung window and level setting (width 1500 HU, level –500 HU) showing: (A) Bronchiectasis (arrows) identified by the absence of normal bronchial diameter tapering. (B) Peripheral mucous plugging demonstrated as multiple centri-lobular nodules (arrows). (C) Dilated bronchus with associated wall thickening (arrow). (D) Lingular consolidation (arrow) demonstrated as an area of increased density obscuring the underlying pulmonary vasculature. (E) Generalised mosaic pattern in both upper lobes shown by areas of decreased attenuation and vessel size (straight arrow) compared to regions of normal attenuation and normal vessel size (curved arrow). (F) Expiratory image showing areas of air trapping (arrows).

Figure 2: Association between FEV_1 at baseline CT scan and CT_{BO}-score (A) and CT_{AT}-score (B) at baseline CT scan

Legend: The air trapping score showed a greater and stronger association (slope 0.55 for CT_{AT}-score versus 0.20 for CT_{BO}-score). However the association of the CT_{AT}-score with FEV_1 appeared to be less precise than for the BO score (p-value 0.02 versus 0.0001, respectively). Data given are for observer 1 first observation.

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CONFLICT OF INTEREST

PdJ, JDD, HOC, CSB, PDP, JRM and RDL have no competing interest in the content of this manuscript to declare.

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ETHICS

The study was approved by the institutional ethical review board of the University of British Columbia.

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