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Featured Article

The effect of pre-operative diagnosis on patient reported outcomes in patients undergoing colorectal operations: A prospective study

Jennifer A. Yonkus [a], Cornelius A. Thiels [b], Pamela Skaran [a], Kellie L. Mathis [a], Juliane Bingener [a, *]

[a] Department of Surgery, Mayo Clinic, 200 First Street SW, Rochester, MN, 55902, USA
[b] Department of Surgery, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY, 10065, USA

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ABSTRACT

Introduction: Patient Reported Outcomes (PROs) capture peri-operative fatigue, pain, and quality of life and influence outcomes in gastrointestinal surgery. We compared peri-operative PROs in patients undergoing colorectal operations for neoplastic versus non-neoplastic processes.
Methods: Patients undergoing colectomy were enrolled prospectively. Demographics and PROs were gathered preoperatively and on post-operative day (POD) 2, 7, 14, and 30 using the validated Linear Analog Self-Assessment (LASA). Severe pain was defined as pain $\geq$5, severe fatigue as $\geq$7, a quality of life deficit as QOL $\leq$5.
Results: We included 192 patients, median age 54 years, 44% female, 88 (46%) for neoplasia. Morbidity was 38%, mortality 3%. Pre-operatively, non-neoplasia patients reported significantly more pain, fatigue, and QOL deficits than neoplasia patients. Severe pain at POD 2 was a positive predictor for complications (p-value$<$ 0.05).
Conclusion: In patients undergoing colorectal surgery, diagnosis influences peri-operative PROs; early severe pain and fatigue may predict complications.

Background

Patient reported outcomes are being used with increasing frequency in the peri-operative setting.[1–5] Modern PROs are non-arduous clinical tools that are easily interpreted. They enable providers to provide low cost, non-invasive predictors of surgical outcomes through simple questionnaires which can be administered at bedside. Patient reported outcomes elucidate patients' perception of recovery, which historically facilitated metrics such as length of stay (LOS) and lack of complications fail to address. Therefore, patient reported outcomes may serve as a better method of assessing patient recovery from an operation when compared to these historical metrics.[6]

The use of PROs is still early in its incorporation in the peri-operative setting and many subtleties need to be assessed for optimal application. Certain patient populations may present with baseline differences in PRO scores which must be taken into consideration. Elucidating these differences through further research on PROs in the peri-operative setting and their correlation with surgical outcomes will enhance the ability of providers to apply PRO in the peri-operative period. The aim of our research is to analyze the differences in PROs in patients undergoing colorectal operations with neoplastic versus non-neoplastic indications for surgery.

Methods

Patients age $\geq$18 scheduled to undergo minimally invasive (MIS) or open colectomy or proctectomy from the dates of May 1, 2016 to August 1, 2018 were eligible for enrollment in this Mayo Clinic Institutional Review Board-approved prospective clinical study. Inclusion was limited to patients with American Society of Anesthesiologists (ASA) classification 1–4 and those willing to consent for the study. Patients with ASA classification 5, patients who were unable or unwilling to consent, had acute psychiatric illness, were undergoing urgent or emergent surgery, and cancer patients undergoing planned palliative surgery without curative intent were excluded. Analysis included patients who had undergone neo-adjuvant chemo- or chemo-radiotherapy.

* Corresponding author. Department of Surgery, Mayo Clinic 200 First Street Southwest, Rochester, MN, 55905, USA.
E-mail addresses: bingenercasey.juliane@mayo.edu, yonkus.jennifer@mayo.edu (J. Bingener).

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Demographics, primary diagnosis, comorbidities, and receipt of neoadjuvant therapies were prospectively collected at enrollment. Patient-reported quality of life (QOL), fatigue, and pain were collected by a dedicated study coordinator pre-operatively and on POD 2, 7, 14, and 30 and complications were noted. Providers and care teams were not aware of results of surveys during the study time frame. Neoplastic indications included cancer diagnosis confirmed by pathology or polyp with suspicion of cancer that was endoscopically unresectable, colorectal polyposis syndromes and other neoplastic disease processes. Non-neoplastic indications for surgery included inflammatory bowel disease, diverticulitis, or other conditions or infections not suspicious for neoplasia. All collected data was prospectively maintained in a secured REDCap database.

PROs were reported on a scale from 0 to 10 using the Linear Analog Self-Assessment (LASA) tool, which is a validated brief assessment that collects patient-reported outcomes including pain, fatigue, and QOL. The LASA tool has been validated in multiple patient populations.[7–9] Severe fatigue was defined as a rating of $\geq$7, severe pain was defined as a rating of $\geq$5, and a deficit in QOL was defined as a rating of $\leq$5. The cut-off for severe fatigue is based on NCCN guideline definition of severe fatigue being equal to 7–10 in oncologic patients and QOL cut-off of $\leq$5 are based on a previous study which evaluated LASA findings in multiple studies to determine clinically meaningful differenced in QOL.[10,11] The primary outcome was the effect of the patient's pre-operative diagnosis on PROs with a secondary outcome of association of peri-operative PROs with complications. Patient complications were classified based on the Clavien-Dindo system with major complication defined as complications with Clavien-Dindo grade $\geq$ III. Examples of events categorized as Clavien-Dindo grade $\geq$ III included intra-abdominal infection/fluid collections requiring drain placement or aspiration, return to operating room (ROR) for anastomotic leak, wound dehiscence, bleeding requiring invasive intervention or ROR, septic shock, and death. Clavien-Dindo grade II complications included superficial wound infection, urinary tract infection, blood transfusion in a hemodynamically stable patient, ileus, hypertensive urgency, atrial fibrillation with RVR in a stable patient, and nausea/vomiting.

Association of PROs with total complications and major complications was based on cumulative complications by POD 30. Timing of complications was recorded in the following time frames: POD 0–2, POD 3–7, POD 8–14, POD 15–30. Linear regression was used to assess for differences in trends of patient recovery. Fisher's exact testing was used where appropriate to assess for association between groups. Logistic regression was performed to assess associations of overall QOL, pain, and fatigue reported pre-operatively and at POD 2, POD 7, and POD 14 with any complication and major 30-day complication (Clavien-Dindo $\geq$ III). GraphPad Prism 8.2.0 was used for statistical analysis.

Results

A total of 192 patients met inclusion criteria and underwent one of two types of operations; colectomy ($n = 151$) or proctocolectomy ($n = 41$). Patients were divided into those undergoing an operation for neoplastic ($n = 88$) or non-neoplastic indication ($n = 104$). Thirty day follow-up for complications was completed for 96% of patients ($n = 185$). Percent of patients completing PROs pre-operatively, at POD 2 and POD 30 was 100% ($n = 192$), 97% ($n = 187$), and 83% ($n = 160$), respectively. Characteristics of the cohort and subgroups can be found in Table 1. In summary, the median age of the entire cohort was 54 (IQR 45–67) years old. Patients in the neoplastic group were older and this difference was statistically significant ($p<0.05$; Table 1). Forty-four percent of all patients were women, ($n = 84$). There was no significant difference between patients with an oncologic indication for surgery and in the non-neoplastic group regarding sex, obesity, defined as BMI $\geq$30 or ASA score of 3 or 4. Seventy-four patients (84%) in the neoplastic group carried the diagnosis of invasive cancer and amongst these; thirty-one were sequenced in a neoadjuvant fashion (42%). Patients who underwent neoadjuvant therapy demonstrated no significant difference in severe pain, severe fatigue, or QOL pre-operatively or at POD 2, 7, or 30, when compared to those who did not receive neoadjuvant therapy. Amongst the entire cohort 72% of patients underwent a minimally invasive procedure. There was no significant difference in the proportion of minimally invasive versus open procedures between the two groups (p-value = 0.75). Ostomy placement was needed in 36 patients (40%) in the neoplastic group and 56 (53%) in the non-neoplastic group. This difference was not statistically significant (p-value = 0.08). There was no significant difference in the number of patients undergoing colectomy versus proctocolectomy between groups. Median length of stay (LOS) was 3 days and was similar between groups.

The majority of patients, 54% ($n = 104$) underwent colorectal operations for non-neoplastic purposes, while the remaining 46% ($n = 88$) had neoplasia indication for surgery. Non-neoplastic indications included inflammatory bowel disease (52%, $n = 54$), diverticulitis (34%, $n = 35$), and other chronic inflammatory conditions (14%, $n = 15$). Other non-neoplastic chronic inflammatory diagnosis included fistulae, mesh erosion, stricture, pelvic/abdominal abscess, invasive endometriosis, and sacral ulcer. The indications for surgery in the neoplastic group were colon cancer (42%, $n = 37$), rectal cancer (35%, $n = 31$), rectosigmoid cancer (5%, n = 4) polypoid lesions (14%, $n = 12$), and other or neoplastic indication (5%, $n = 4$).

The median perioperative pain, fatigue, and QOL values for the entire cohort and the subgroups are depicted in Fig. 1. In the total cohort, 34% of patients ($n = 66$) reported severe pre-operative pain, 30% ($n = 56$) severe pre-operative fatigue and 17% ($n = 33$) poor pre-operative QOL. At POD 2 47% ($n = 87$) experienced severe pain, 31% ($n = 58$) severe fatigue, and 28% ($n = 53$) poor QOL. By POD 30, the proportion of patients experiencing severe pain and fatigue in the total cohort had improved with now 21% of patients ($n = 34$) having severe pain, 18% ($n = 29$) severe fatigue. The proportion of patients experiencing a QOL deficit was not significantly improved by POD 30 and was reported by 16% ($n = 26$) of patients. Amongst those in the non-neoplastic group, 44% ($n = 46$) of patients had severe pre-operative pain and 42% ($n = 44$) had severe fatigue, while 23% ($n = 20$) of patients in the neoplastic group had severe pre-operative pain and 14% ($n = 12$) had severe fatigue. At POD 2, 53% ($n = 54$) of non-neoplastic patients had severe pain compared to 39% ($n = 33$) of patients in the neoplastic group. In the non-neoplastic group 32% ($n = 33$) reported severe fatigue and 29% ($n = 25$) in the neoplastic group. By POD 30 21% ($n = 18$) of non-neoplastic patients reported severe pain and 12% ($n = 10$) reported severe fatigue. At POD 30, patients with neoplastic diagnosis demonstrated less improvement in PROs than patients with non-neoplastic diagnosis with 21% ($n = 16$) with persistent severe pain and 25% ($n = 19$) with severe fatigue. The difference in pre-operative pain, pre-operative fatigue, and POD 30 fatigue was statistically significant between the two groups (Table 2). On linear regression analysis, there was no difference between the change in severe pain between the two groups (p-value = 0.62), severe fatigue (p-value = 0.08), or QOL (p-value = 0.22).

Amongst the entire cohort, 38% ($n = 73$) of patients experienced a complication by POD 30 and 10% ($n = 19$) patients experienced a severe complication by POD 30. Several patients experienced a complication at multiple time points for a total of 105

Table 1
Overall cohort characteristics.

	Neoplastic indication ($n = 88$)	Non-Neoplastic indication ($n = 104$)	Total ($n = 192$)	p-value
Median Age, (IQR)	58 (51–72)	50 (36–62)	54 (45–67)	<0.05
Percent Female, % (n)	40 (35)	47 (49)	44 (84)	0.381
Percent BMI ≥30, % (n)	40 (35)	40 (42)	40 (77)	>0.999
ASA category, I/II, % (n)	56 (49)	56 (58)	56 (10)	>0.999
III/IV, % (n)	44 (39)	44 (46)	44 (85)	
Ostomy, % (n)	41 (36)	54 (56)	48 (92)	0.083
Colectomy, % (n)	85 (75)	73 (76)	79 (151)	0.052
Proctocolectomy, % (n)	15 (13)	27 (28)	21 (41)	
Minimally Invasive, % (n)	70 (62)	73 (76)	72 (138)	0.748
Open, % (n)	30 (26)	27 (28)	28 (54)	

IQR interquartile range, *MIS* minimally invasive surgery, *ASA* American Society of Anesthesiologists Score, *BMI* body mass index, *LOS* length of stay.

complications of any type and 23 major complications. During the study period the mortality rate of the entire cohort was 3% ($n = 5$). The majority (82%, $n = 86$) of all complications occurred after POD 2 as did the majority of severe complications (91%, $n = 21$). The bar graph in Fig. 2 demonstrates the timing of all complications and major complications at POD 0–2, POD 3–7, POD 8–14, and POD 15–30.

Peri-operative PROs were assessed for association with any complication and major complication that occurred throughout the 30-day post-operative time frame. Within the entire group, pre-operative severe pain or fatigue was not predictive of any complication; however POD 2 severe pain was a positive predictor for the occurrence of any complication (p-value < 0.05). For the entire group, POD 30 severe pain and severe fatigue were also associated with any complication. In the non-neoplastic group 37% ($n = 38$) of patients experienced a complication and 9% ($n = 9$) experienced major complication. In this group, severe fatigue at POD 2 was associated with any complication (p-value < 0.05) and with the occurrence of major complications (p-value < 0.05). Severe fatigue at POD 7 was also associated with major complications (p-value < 0.05). In the neoplastic group 40% ($n = 35$) of patients experienced a complication and 11% ($n = 10$) suffered major complication. In this group, severe pain on POD 2 remained associated with the occurrence of any complication (p-value < 0.05) and a major complication (p-value = 0.04).

Discussion

In this study we demonstrated that patients undergoing colorectal operations for inflammatory bowel disease and other non-oncologic conditions are significantly more likely to report severe pre-operative pain and fatigue, and worse overall QOL when compared to patients with neoplastic diagnosis, including a portion of patients that underwent chemotherapy and/or radiation. Therefore, this must be taken into consideration when interpreting patient reported outcomes in the peri-operative setting. While we and others have shown that patient reported outcomes can provide valuable information in the management of patients undergoing major gastrointestinal operations, they may differ depending on the patient population. Fortunately, in both groups, patient reported outcomes improved after surgical intervention and these patients did not demonstrate significant differences in the trends of improvement. Optimal application of PROs in the future will likely be based on trends in recovery as opposed to absolute values reported at as single point in time since this is variable based on pre-operative diagnosis.

One of the most beneficial applications of PROs in the peri-operative setting is the potential for bedside application to predict those at risk of complications. While the overall number of patients in our study who experienced complications was not very large ($n = 74$ for any complication, $n = 19$ for major complications), POD 2 measures were obtained before the majority of complications was discovered. Our data suggests that patients experiencing severe pain on POD 2 were at risk for complications. Using this information can assist providers in identifying patients who may need additional attention and guide patient care, for example, if a patient reports severe pain on POD 2 and otherwise has equivocal signs for a potential problem, consideration may be given to further investigation, compared to a patient who does not have severe pain. This association remained true for both oncologic operations and non-oncologic surgical patients undergoing colorectal operations. Therefore, using severe pain at POD 2 for all patients undergoing colorectal operations can be used as an additional tool to predict patients who are likely to develop complications of both any complication as well as major complications. Early severe post-operative fatigue on POD 2 is also associated with complications in certain patients. In our cohort we were able to demonstrate this in patients undergoing operation for non-neoplastic indications. By POD 30, severe pain, severe fatigue, and poor QOL are likely a result of a complication rather than an early warning sign, since the majority of the complications occurred between POD 2 and POD 30.

The differences in peri-operative PROs were significant between patients undergoing operations for neoplastic processes when compared to those undergoing operations for non-neoplastic operations. The reason for these differences may be due to the chronicity of disease in patients with IBD. Additionally, the inflammatory nature inherent to these diseases may lead to symptoms with a more significant impact on patient QOL than neoplastic processes. Patients in the non-neoplastic group were younger and may have different expectations for their QOL based on interaction with age matched peers and, therefore, may report worse PROs. However, Singh et al. suggest that age is not associated with differences in QOL in observational studies but was worse with increasing age in treatment studies in cancer patients.[11] An innovative, yet feasible future for PRO tools would include creations of clinical calculators using this data to shift treatment paradigms. As these tools become created and made available to providers, pre-operative diagnosis and indication for operations must be taken into consideration.

A critical component of using and applying PRO tools in the clinical setting is selection of appropriate and timely surveys. Patients are less likely to comply with lengthy surveys, especially patients who are experiencing poor QOL or are in a palliative care situation where they are placing an emphasis on life quality. Spending a lengthy amount of time on surveys may not be appealing to this patient population. However, concise, validated analog bedside tools can replace lengthy symptom specific studies and provide valuable clinical information. The validated measures

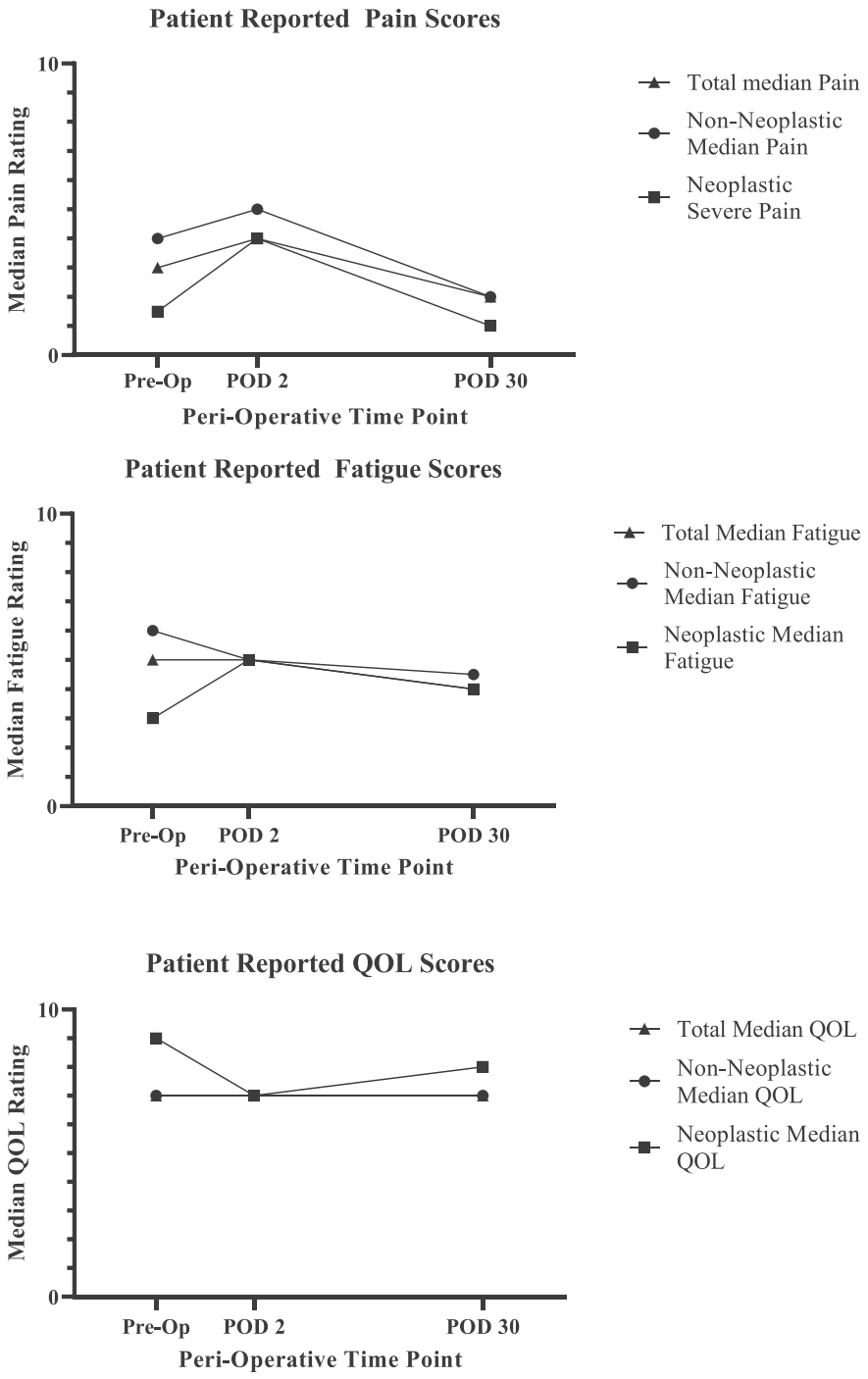

Fig. 1. Peri-operative PRO of Pain, Fatigue, and QOL*Pre-Op* pre-operative assessment date, *POD* post-operative day, *QOL* quality of life.

used here are 3 analog items, measured 1–10, with the pain measurement already integrated in daily clinical practice. While overall QOL is more often referred to as a perioperative outcome in surgical studies, less attention has been paid to fatigue, the inverse of vitality, which may be a more sensitive measure than overall QOL and more responsive to change in the perioperative setting, possibly denoting stages in recovery. Overall QOL in PRO is a composite concept and is often less responsive to small changes than fatigue, pain, and physical or social functioning. The lack of sensitivity of QOL is supported by the finding in our study showing that QOL demonstrated the least amount of change throughout the study period.

This study team was not involved in the care of patients and data was not collected by the provider, therefore, did not provide the PROs to providers in real time, limiting opportunities for bias. Future directions will be to assess whether provider knowledge of PROs affects care in a meaningful way that impacts patient care leading to improved surgical outcomes. Although this study is

Table 2
Comparison of peri-operative pain, fatigue, and QOL.

	Neoplastic Indication	Non-neoplastic Indication	Total	*p*-value
Pre-Operative	($n = 88$)	($n = 104$)	($n = 192$)	
Severe Pain, % (n)	23 (20)	44 (46)	34 (66)	<0.05
Severe Fatigue, % (n)	14 (12)	42 (44)	30 (56)	<0.05
Poor QOL, % (n)	5 (4)	28 (29)	17 (33)	<0.05
POD 2	($n = 87$)	($n = 100$)	($n = 187$)	
Severe Pain, % (n)	39 (33)	53 (54)	47 (87)	0.06
Severe Fatigue, % (n)	29 (25)	32 (33)	31 (58)	0.75
Poor QOL, % (n)	28 (24)	28 (29)	28 (53)	>0.99
POD 30	($n = 76$)	($n = 84$)	($n = 160$)	
Severe Pain, % (n)	21 (16)	21 (18)	21 (34)	>0.99
Severe Fatigue, % (n)	25 (19)	12 (10)	18 (29)	0.04
Poor QOL, % (n)	13 (10)	19 (16)	16 (26)	0.39

POD post-operative day, *QOL* quality of life.

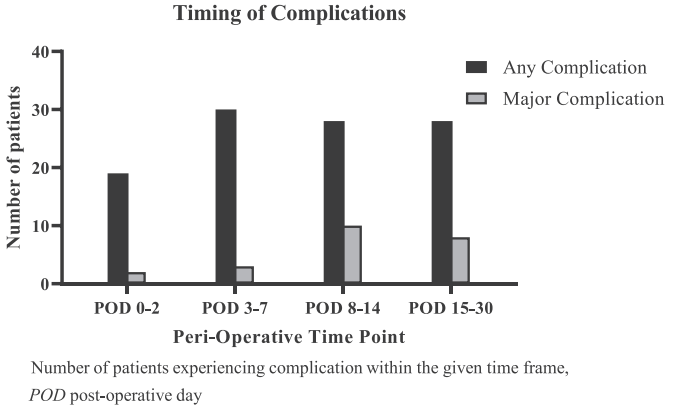

Fig. 2. Timing of complications amongst entire cohortNumber of patients experiencing complication within the given time frame, *POD* post-operative day.

strengthened by its prospective nature it is limited by small sample size. An additional limitation of this study, which is inherent in many prospective PROs studies, is patient drop-out and incomplete follow-up. Our study was strengthened by a low drop-out rate by the end of the 30-day period with 96% of patients still followed at the end of the 30-day period. However, there was a drop in the completion rate of surveys. The data was also limited to patients undergoing colorectal operations and the association of PROs with complications cannot be projected onto other patient populations and requires further study. As standardized PRO use becomes more common in the care of surgical patients we believe that association between these metrics and the patient's burden of disease, experienced as consequence of the diagnosis or a complications will become evident.

Conclusion

Patient reported outcomes vary amongst patients undergoing colorectal operations dependent on pre-operative indication for surgery and should be considered when caring for patients in the peri-operative setting. Early severe post-operative pain can be used to predict patients who are more likely to have complications and can be used to tailor care plans. Further investigation of patient reported outcomes in the peri-operative setting to confirm our findings are needed.

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Declaration of competing interest

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