Original Article

Perioperative factors predicting delayed enteral resumption and hospital length of stay in cytoreductive surgery with hyperthermic intraperitoneal chemotherapy: Retrospective cohort analysis from a single centre in India

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ABSTRACT

Background and Aims: Cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (CRS-HIPEC) is an extensive procedure associated with significant morbidity, delay in return of gastrointestinal function and discharge from hospital. Our aim was to assess perioperative factors influencing enteral resumption (ER) and length of stay in the hospital (LOS) in CRS-HIPEC. **Methods:** A retrospective analysis was conducted in a major tertiary cancer centre. Sixty-five patients who underwent CRS-HIPEC between July 2014 and March 2019 were included in the study. The perioperative data were collected from patient records. The primary outcome measure was day of oral resumption of 500 ml of clear fluids and secondary outcome was the LOS. Univariate and multivariate logistic regression analysis was done for the various continuous and categorical perioperative variables for both ER and LOS to elicit the magnitude of risk for both outcomes. **Results:** Univariate logistic regression revealed that peritoneal carcinomatosis index score (PCI), duration of surgery, blood loss and postoperative ventilation influenced both ER and LOS. Serum albumin, plasma usage and total peritonectomy affected only the LOS but not ER. Multivariate analysis showed that duration of surgery ($P = 0.006$) and quantum of intravenous fluid infused ($P = 0.043$) were statistically associated with ER, while serum albumin level ($P = 0.025$) and postoperative ventilation ($P = 0.045$) were independently predictive of LOS. **Conclusion:** CRS-HIPEC is an extensive surgery and multiple factors are associated with ER; of these, duration of surgery and intraoperative fluid therapy are significant factors. Low serum albumin and prolonged postoperative ventilation are associated with increased LOS.

Key words: Cytoreductive surgery, hyperthermic intra-peritoneal chemotherapy, length of stay, logistic regression, serum albumin

INTRODUCTION

Cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (CRS-HIPEC) is a long and complex surgery comprising of extensive tumour debulking followed by perfusion of heated chemotherapeutic agent into the peritoneal cavity.[1] It is the standard treatment in patients with Pseudomyxoma Peritonei (PMP) and mesotheliomas as well as those with low volume metastasis from colonic, gastric and ovarian cancers.[2] The anaesthetic concerns pertaining

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to CRS-HIPEC are manifold. Preoperatively, it includes optimisation of comorbid conditions, nutrition and prehabilitation. Intraoperatively it involves meticulous haemodynamic, temperature, coagulation and electrolyte management.[3] Postoperatively apart from surgical complications, requirement of ongoing haemodynamic management, need for postoperative ventilation, initiation of enteral fluid and length of hospital stay are the prime concerns.

Length of stay in the hospital (LOS) is associated with a number of perioperative factors. Timing to enteral resumption (ER) plays a key role in LOS.[4] Early feeding is associated with reduced risk of postoperative infectious complications and shorter LOS.[5] Following major abdominal surgery, the return of gastrointestinal function is delayed and commencement of oral feeds depends on it. In patients who have undergone major abdominal surgeries like Whipple's pancreaticoduodenectomy[6] and colectomy,[4] oral liquids were started by 5-8 days and 4-5 days, respectively. CRS-HIPEC being a much more extensive procedure, there is a reluctance to start early enteral feeds. Unlike LOS, factors associated with time to ER in CRS-HIPEC have not been characterised. ER is directly associated with LOS in multiple studies, and return of gastrointestinal function has been described as a research priority.[7] Hence we sought to identify perioperative factors associated with delay in time to ER as our primary objective and LOS as the secondary objective.

METHODS

This single centre retrospective study analysed data of 65 patients who underwent CRS and HIPEC surgery between July 2014 and March 2019.Before commencement of the study, approval was obtained from the institutional ethics committee. The study was conducted as per the principles of Helsinki Declaration of 1975, as revised in 2013. All consecutive patients who underwent CRS-HIPEC were included. Patients who despite being posted for CRS-HIPEC, did not receive HIPEC were excluded. Any missing data were excluded from the analysis for that variable. The data was collected from records, both electronic and patient files, and included preoperative, intraoperative and postoperative parameters.

All patients had been assessed preoperatively and received general anaesthesia with thoracic epidural analgesia. All patients had a completeness of cytoreduction (CC) score of CC_0 or CC_1. Induction and intraoperative management were similar in all patients. Monitoring included electrocardiogram, invasive blood pressure, pulse oximetry, nasopharyngeal temperature and respiratory gas analysis. A central line was inserted and continuous cardiac output monitoring with FloTrac (EV1000 Edwards Lifesciences Corp, Irvine, CA, USA), was used. Laparotomy was performed with an extended midline incision and the peritoneal carcinomatosis index (PCI) was assessed by the surgeon followed by cytoreduction. Fluid replacement was based on stroke volume variation and stroke volume index trends. Our transfusion trigger was a haemoglobin of 9 g dl^{-1} and was based on the allowable blood loss. Mean arterial pressure was maintained, within 10–15% of the patient's baseline, with fluids and vasopressors. Temperature was maintained by convective and fluid warmers during the CRS phase and by maintaining normothermia during HIPEC phase by active cooling. HIPEC was performed using the closed technique in all patients and the chemotherapeutic agents used were either Cisplatin, Oxaliplatin or Mitomycin C. All patients were shifted to the intensive care unit (ICU) after surgery. Patients meeting standard extubation criteria had been extubated on table. Patients who were haemodynamically unstable and on more than one ionotrope, had persistent acidosis or surgery had lasted >10 hrs were ventilated electively.

Pre-operative parameters collected were demographic characteristics like age, sex, weight, height and laboratory values like pre-operative albumin and haemoglobin values, history of smoking, co morbidities and American Society of Anesthesiologists (ASA) grade.

Intra-operative parameters collected were: 1. PCI (It is calculated by the surgeon to assess the extent of peritoneal involvement) 2. If total peritonectomy or 3. Omentectomy done 4. Patients needing bowel resection with anastomosis 5. Need for stoma 6. Gastroepiploic artery if preserved 7. Intra-operative blood loss (sum of suction loss and weighed pads) 8. Duration of surgery 9. Amount of intravenous fluid infused (crystalloids + colloids) 10) Blood/fresh frozen plasma (FFP) replaced. 11. The need for intraoperative vasopressors and the number of vasopressors used was coded as either the use of more than one vasopressor or if it was needed for greater than 24 hours postoperatively.

Postoperative parameters obtained were 1. The use of vasopressors for >24 hrs, 2. Postoperative ventilatory

support ≥24 hours 3. The day of initiation of 500 ml of clear water 4. LOS 5. Total parenteral nutrition days (TPN) 6. Ambulation.

The data was analysed using Statistical Package for Social Sciences (SPSS) Statistics for Windows, version 16.0 (SPSS Inc., Chicago, Ill., USA) software. Descriptive statistics was used to analyse the categorical and continuous variables. Qualitative variables were expressed as counts and percentage while quantitative variables were expressed as median and range. Univariate logistic regression analysis was done for the various continuous and categorical variables for ER and LOS and a '*P*' value of ≤0.05 was considered significant. The significant prognostic factors that emerged in the univariate analysis, both continuous and categorical were subjected to multivariate logistic regression to elicit the magnitude of risk for ER and LOS with 95% confidence interval.

RESULTS

Out of the 65 patients included in the analysis, most were females with median age of 51. Twenty-eight patients had pseudomyxoma peritonei, 17 patients had colorectal cancer, 16 had ovarian cancers and 4 were due to other causes. During HIPEC, 43 received mitomycin C, 8 received oxaliplatin and 14 received cisplatin. The various demographic and perioperative parameters in the study are in Table 1. Factors like ASA, comorbidities, age did not have any significant effect on ER or LOS. On univariate logistic regression analysis of continuous variables, factors that were found to be significantly associated with ER were PCI ($P = 0.003$), duration of surgery ($P < 0.001$), blood loss ($P = 0.011$) and intravenous fluid replacement ($P = 0.002$). Variables associated with LOS were serum albumin level ($P = 0.005$), PCI score ($P < 0.001$), duration of surgery ($P < 0.001$), blood loss ($P = 0.001$), intravenous fluid replacement ($P = 0.006$), and FFP transfusion ($P = 0.009$) [Table 2]. Categorical variables associated with ER were need for use of vasopressor ($P = 0.021$) and ventilator ($P = 0.038$) while for LOS it was need for peritonectomy ($P < 0.001$) and ventilator ($P = 0.001$) [Table 3]. On multivariate logistic regression, only duration of surgery ($P = 0.006$) and intravenous fluid administration ($P = 0.043$) surfaced as independent prognostic predictors for ER after adjusting for other factors [Table 4]. The analysis showed a 75% probability of {OR1.75 (95%CI 1.17-2.620)} increase in time to ER for every hour delay in surgery and a 42% probability of increase in time to ER with every litre of incremental intravenous fluid infused during the surgery {OR1.42 (95%CI 1.012-2.004)}.

Table 1: Demographic details of patients

Perioperative variables	
Pre-operative variables	
Median age (range)	51 years (22-72)
Female:male ratio	46:19
ASA° I/II/III/IV *n* (%)	0/58 (89.2)/7 (10.7)/0
HTN/°°DM/HTN &DM/Hypothyroid/ Malnourished/ˇIHD/Smoking status/ascites (*n*)	7/14/5/6/5/1/2/7
Median Haemoglobin in g dl^{-1} (range)	11.20 (7-14.5)
Median Serum Albumin in g (range)	3.5 (1.7-4.7)
Median BMI* Kg m^{-2} (range)	25.11 (14.17-34.08)
Intraoperative variables	
Median PCI† (range)	15 (0-39)
Median duration of surgery (range)	9 h (5-20)
Median Infusion of fluid (range)	5.5 l (2.5-19.5)
Median Blood loss (range)	1000 ml (100-6500)
Median Blood transfusion (range)	500 ml (0-4000)
Median Fresh Frozen Plasma transfusion (range)	600 ml (0-2100)
Postoperative variables	
Post-operative vasopressor use *n* (%)	38 (58.5)
Median time to enteral resumption (range)	6 days (1-18)
Patients on TPN†† *n* (%)	32 (49.2)
Median Postoperative TPN days	6 (2-27)
Median days on Nasogastric tube (*n*=50)**	4 (1-54)
Median days for Mobilisation (*n*=32)**	5 (2-54)
Postoperative Ventilation *n* (%)	21 (32.3)
Median Length of stay (range)	15 days (9-58)

*Body mass index; †Peritoneal Carcinomatosis Index, °American Society of Anesthesiologists, ˣBMI <18.5 Kg/m^2. °°Diabetes Mellitus; ˇischaemic Heart disease,**missing data, ††Total parenteral nutrition

The factors independently associated with LOS without being significantly associated with ER were pre-operative albumin levels and the need for postoperative ventilation. Analysis showed that for every gram increase in preoperative serum albumin level there was a 80% probability of decreased length of stay {OR0.208 (95% CI 0.05-0.818)}($P = 0.025$).The patients who were ventilated for more than a day had six-fold risk of prolonged hospital stay than those who were not ventilated or extubated early {OR6.32 (95% CI 1.04-38.35)} ($P = 0.045$) [Table 5].The significant multivariate continuous variables were divided into quartiles for better clarity [Table 6]. It was found that there were 16 patients with serum albumin of <3.05 gms%, for 20 patients surgery lasted more than 12 hours, and 19 patients needed fluid greater than 9.5 litres.

DISCUSSION

We sought to identify factors influencing delay in time to ER and LOS in CRS-HIPEC patients. The factors

Table 2: Factors predicting ER* and LOS† by univariate analysis (continuous variables)

Parameter	*ER		†LOS	
	Odds ratio (95% ‡CI)	*P*	Odds ratio (95% ‡CI)	*P*
Age (years)	0.979 (0.93-1.028)	0.390	1.014 (0.966-1.064)	0.570
Serum Albumin (g dl^{-1})	0.788 (0.382-1.625)	0.519	0.275 (0.112-0.676)	0.005
§PCI score	1.072 (1.024-1.123)	0.003	1.103 (1.04-1.164)	<0.001
Duration (hours)	1.602 (1.261-2.035)	<0.001	1.605 (1.25-2.05)	<0.001
Bloodloss (liters)	1.824 (1.147-2.900)	0.011	5.775 (1.995-16.71)	0.001
?IVF (liters)	1.545 (1.178-2.027)	0.002	1.436 (1.108-1.859)	0.006
·FFP transfusion (ml)	1.001 (1.000-1.002)	0.152	1.005 (1.001-1.008)	0.009

*Enteral Resumption; †Length of stay; ‡confidence interval; §peritoneal carcinomatosis index; ?intravenous fluid; ·Fresh frozen plasma

Table 3: Factors predicting ER and LOS with their odds ratio and *P*, *n*=65 (categorical variables)

Parameters	*n*=65	*ER ≤6 days *n*=37 (57%)	ER >6 days *n*=28 (43%)	Univariate †OR (95% §CI)	*P*	‡LOS ≤15 *n*=30 (46%)	LOS >15 *n*=35 (54%)	Univariate †OR (95% §CI)	*P*
Total peritonectomy	No, *n*=34 (%)	23 (68)	11 (32)	1.00?		23 (67)	11 (33)	1.00?	
	Yes, *n*=31 (%)	14 (44)	17 (56)	2.5 (0.9-6.95)	0.070	7 (23)	24 (77)	7.1 (2.3-21.5)	<0.001
Total omentectomy	No, *n*=10 (%)	8 (80)	2 (20)	1.00?		4 (40)	6 (60)	1.00?	
	Yes, *n*=55 (%)	29 (53)	26 (47)	3.5 (0.6-18.4)	0.126	26 (47)	29 (53)	0.7 (0.18-2.9)	0.671
Bowel anastomosis	No, *n*=23 (%)	15 (65)	8 (35)	1.00?		14 (61)	9 (39)	1.00?	
	Yes, *n*=42 (%)	22 (52)	20 (48)	1.7 (0.59-4.8)	0.320	16 (38)	26 (61)	2.5 (0.9-7.1)	0.08
Stoma	No, *n*=56 (%)	31 (55)	25 (45)	1.00?		25 (45)	31 (55)	1.00?	
	Yes, *n*=9 (%)	6 (67)	3 (33)	0.6 (0.14-2.7)	0.525	5 (56)	4 (44)	0.6 (0.15-2.6)	0.544
Vasopressor use	No, *n*=27 (%)	20 (74)	7 (26)	1.00?		16 (59)	11 (41)	1.00?	
	Yes, *n*=38 (%)	17 (45)	21 (55)	3.5 (1.2-10.3)	0.021	14 (37)	24 (63)	2.4 (0.9-6.8)	0.077
Ventilation	No, *n*=44 (%)	29 (66)	15 (34)	1.00?		27 (61)	17 (39)	1.00?	
	Yes**, *n*=21 (%)	8 (38)	13 (62)	3.1 (1.06-9.2)	0.038	3 (14)	18 (86)	9.5 (2.4-37.3)	0.001

*Enteral resumption; †Odds ratio; ‡length of hospital stay; §confidence interval; ?Reference category, Vasopressor usage >24 h or intraoperative use of ≥2 vasopressors. **Intubated and Ventilated ≥24 h

Table 4: Factors predicting enteral resumption: Multivariate logistic regression analysis

Parameters	Multivariate odds ratio (95%*CI)	*P*
†PCI score	0.96 (0.887-1.042)	0.342
Duration (hours)	1.75 (1.17-2.620)	0.006
Blood loss (liters)	0.85 (0.45-1.60)	0.629
‡IVF (liters)	1.42 (1.012-2.004)	0.043
Vasopressor use		
No	1.00§	
Yes?	1.522 (0.39-5.936)	0.546
Ventilated		
No	1.00§	
Yes·	0.545 (0.107-2.78)	0.466

*Confidence interval; †Peritoneal carcinomatosis index; ‡Intravenous Fluid ; §Reference category. ?Vasopressor usage >24 h or intraoperative use of ≥2 vasopressors · Intubated and Ventilated ≥24 h

associated with both ER and LOS in our cohort by univariate analysis like PCI, duration of surgery, blood loss, IVF replacement and need for ventilation were all inter-related and show the extent of surgery. Newton *et al*. in their paper have discussed several factors which influence morbidity in CRS-HIPEC and PCI figures prominently.[8]

On multivariate analysis, the factors associated with ER in our cohort were duration of surgery and IVF used while hypoalbuminemia and postoperative ventilation led to delay in LOS. Of the many definitions for postoperative ileus, one is the presence of a nasogastric tube or nil per os (NPO) on postoperative day (POD) 4 or later,[4] but this is for abdominal surgeries. Among patients who have undergone CRS-HIPEC, oral liquids commenced variably ranging from day one to eleven,[9] with some studies quoting a time between 6 to 8 days before oral intake.[10] Our median day of enteral resumption was 6 days. In a survey conducted on knowledge and attitudes on nutritional support in CRS-HIPEC, 77.36% of respondents preferred to wait till five days before initiation of enteral feeds in the post-operative period.[11] Recent guidelines from the society of onco-anaesthesia in India also suggest that majority of the patients do not tolerate enteral feed in the first postoperative week, and hence parenteral nutrition may be initiated.[3] Many factors cause postoperative ileus like fluid infusion rate intra-operatively, use of nasogastric decompression, use of opioids and operative approach.[12]

A recent review on patients undergoing CRS-HIPEC defines ileus as inability to tolerate oral intake after seven days of surgery.[13] They reported paralytic ileus in 31/247 patients (12.6%). Median day of ER

Table 5: Factors predicting length of hospital stay: Multivariate logistic regression

Parameters	Odds ratio (95%*CI)	*P*
Preoperative Serum Albumin (g dl^{-1})	0.208 (0.05-0.818)	0.025
†PCI score	0.981 (0.87-1.104)	0.746
‡IVF (liters)	1.15 (0.77-1.72)	0.485
Duration (hours)	1.145 (0.72-1.83)	0.567
Fresh Frozen Plasma (milliliters)	1.003 (0.99-1.007)	0.170
Blood Loss (litres)	1.93 (0.41-9.2)	0.408
Total Peritonectomy		
No	1.00§	
Yes	1.62 (0.20-13.02)	0.646
Ventilated		
No	1.00§	
Yes?	6.32 (1.04-38.35)	0.045

*Confidence interval; †Peritoneal carcinomatosis index: ‡Intravenous Fluid; §Reference category; ?Intubated and Ventilated ≥24 h

Table 6: Significant multivariate variables as quartiles

Variables	*n*	Median ER* (range)	Median LOS† (range)
Pre-operative albumin (g dl^{-1})			
1.7-3.05	16	6 (3-18)	17 (11-38)
3.06-3.50	21	8 (3-10)	15 (10-58)
3.51-3.95	12	5 (2-13)	14 (9-31)
3.96-4.7	16	5 (1-10)	14 (9-29)
Duration (hours)			
<7 h	15	5 (1-8)	12 (9-30)
7.0-8.99	16	5 (2-10)	13.5 (10-48)
9.0-11.99	14	6 (3-18)	15 (10-58)
12-20.00	20	9 (6-18)	20.5 (13-54)
Fluid administered (litres)			
2.5-4.49	15	6 (1-18)	13 (9-26)
5-5.49	13	5 (2-13)	14 (9-48)
5.5.-7.49	18	6 (3-10)	14.5 (10-58)
7.5-19.5	19	8 (5-18)	19 (12-54)

*Enteral resumption; †Length of stay

in our subset was six days and by that benchmark, 43% of our patients had an ileus. This figure is more comparable to a study by Eng *et al*.[14] where 74/133 (55.6%) patients had ileus. This study had a similar median PCI (13), and duration of surgery (8.5 hours). {Our median PCI was 15 and duration of surgery 9 hours}. In our cohort, operative factors like total peritonectomy, bowel resection and anastomosis or omentectomy had no association with ER. Eng *et al*. too found the number of organs resected or PCI had no impact on the morbidity in a multivariate analysis. We found that duration of surgery ($P = 0.006$) which is related to the extent of cytoreduction and intravenous fluid infusion ($P = 0.043$) were significantly associated with ER. Interestingly, they also found that among other factors, mean intraoperative fluid rate 15.7 ml/kg/hr was predictive of an increased comprehensive complication index (our mean fluid infusion was 14.7 ml/kg/hr).

Liberal intraoperative fluid infusion as a culprit in delaying ER has been reported in other abdominal surgeries and CRS-HIPEC.[15-17] Colantonio *et al*.[18] found that the use of goal directed therapy improves outcome in terms of incidence of major abdominal and systemic postoperative complications and length of hospital stay, compared to standard fluid therapy in CRS-HIPEC. In our cohort, we used protocolised goal directed fluid therapy with EV-1000 monitor and used dynamic indicators for fluid therapy.

There is no clarity if the type of fluid will have an impact on ER. Colloids have an apparent benefit, however this study is not in CRS-HIPEC where the fluid losses and replacement are much more.[16] A recent retrospective audit finds colloids to be associated with increased morbidity in CRS-HIPEC while albumin was associated with better outcome.[19] We used crystalloids like Ringers lactate and balanced salt solution and colloids like gelatin, blood and blood products as needed. We did not use human albumin routinely in all patients.

Opioids are implicated in sluggish bowel movements but none of our patients received intravenous opioids All our patients received an epidural containing a local anaesthetic, with the addition of an opioid for analgesia. According to a recent Cochrane review, local anaesthetic with an opioid only accelerated the return of bowel movements.[20] Study on the effects of norepinephrine (NE) on the microcirculatory flow of the bowel found that treatment of hypotension with low doses of NE had no ill effects on the microcirculation or oxygen tension.[21] While the effect of NE on mucosal blood flow of gut is neutral, a dose-dependent inhibition of gastrointestinal motility occurs through the effect on alpha receptors.[22] In our patients we did notice that those who received vasopressors for more than 24 hours had delayed ER on univariate analysis.

Duration of surgery was an important predictor of ER. Operative time has been implicated as a major predictor of morbidity in a recent review of 889 patients.[23] Longer duration of surgery with HIPEC is associated with increased sympathetic stimulation. The sympathetic nervous system, which is generally inhibitory to the gastro intestinal tract, becomes hyperactive and this causes decreased release of the neurotransmitter acetylcholine and leads to increased inhibition of motility.[24]

In a study on outcome trends in CRS-HIPEC it was found that operative time, morbidity and LOS

improved over a study period of eight years. We did not compare our surgical duration over time as the numbers were small.[23] Total peritonectomy which is an indicator of the extent of surgery was associated with LOS in our subset of patients but was not identifiable as an independent risk factor for prolonged LOS. Only pre-operative serum albumin levels and need for post-operative ventilation were independently associated with LOS in our cohort of patients.

Pre-operative albumin has been documented as a predictor of outcome including morbidity and LOS in gastrointestinal surgery.[25] A recent review auditing CRS-HIPEC patients for factors associated with LOS also found pre-operative albumin of less than 3.0 g dl^{-1} as an independent predictor.[26] There are studies implicating low albumin levels to increased morbidity which translates to increased LOS.[23] Serum albumin is a modifiable factor and preoperative protein supplementation can be advocated. Baseline nutrition is a good predictor of LOS and should be modified where feasible.[27]

LOS was also associated with postoperative ventilation in our cohort. In a review of anaesthesia and postoperative ventilation, it was found that patients needing postoperative ventilation usually have a longer LOS.[28] Kajdi *et al*. in their retrospective analysis found need for ventilation was associated with operative time and increased postoperative morbidity translating to increased LOS.[29]

This being a retrospective study is subject to observed and unobserved confounding, nevertheless all surgeries were performed by only two surgeons and perioperative management of patients were standardised hence the data were more comparable without too many confounding factors. Some data, both intraoperative and postoperative were missing, thus compromising completeness of statistical data and hence were removed from the analysis. Yet another limitation of the study was that data on postoperative infective and surgical complications were excluded which could be confounders for both ER and LOS, but these were beyond the scope of the study as only anaesthetic parameters were mainly analysed. A major limitation of the study was that it was retrospective and numbers were small. As this study involved a single centre, it could compromise its generalisability. As our experience increases and the surgical duration decreases it might be possible to fast-track patients undergoing CRS-HIPEC by instituting personalised haemodynamic management and initiating early ER. Further prospective studies are needed to determine whether preoperative optimisation of serum albumin and judicious application of elective postoperative ventilation will reduce LOS.

CONCLUSION

CRS-HIPEC is an extensive surgery and multiple factors are associated with ER, of these duration of surgery and intraoperative fluid therapy are significant factors. Low serum albumin and prolonged postoperative ventilation are associated with increased LOS.

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Conflicts of interest

There are no conflicts of interest.

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