Incidence of Oxaliplatin Hypersensitivity Reaction Among Colorectal Cancer Patients: a 5-Year Retrospective Study

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Abstract

Purpose

We explored the clinical data of colorectal cancer patients treated with oxaliplatin-based regimen to determine the incidence, severity, and risk factors of oxaliplatin-related hypersensitivity reaction (HSR).

Method

This retrospective study investigated 245 colorectal cancer patients (1,690 treatment cycles) receiving care at King Chulalongkorn Memorial Hospital, Thai Red Cross society between January 1, 2015, and December 31, 2019. The patients' demographic data, laboratory data, and clinical features suggesting hypersensitivity reactions to oxaliplatin were reviewed. The Fisher's Exact test and unpaired t-test were used to determine the differences among patients with and without oxaliplatin HSR. The potential risk factors for oxaliplatin HSR were analyzed for statistical significance by logistic regression.

Results

A total of 245 colorectal cancer patients (1,690 treatment cycles) were included in this study. The incidence of oxaliplatin HSR was 37.96%, according to the NCI-CTCAE v.5, (grade 1, grade 2, and higher grades were 27.35% (67 patients), 6.53% (16 patients), and 4.08% (10 patients), respectively). The proportion of male patients and patients with history of prior exposure to platinum-based chemotherapy were statistically higher in the HSR group. The eosinophil count and serum creatinine level were also significantly greater in the HSR group. On the contrary, the total lymphocyte count and serum albumin level were significantly lower in the HSR group. The multivariate logistic regression found 5 risk factors with significant difference. Male gender, prior exposure to platinum-based chemotherapy, and elevated eosinophil count were associated with increased risk of oxaliplatin HSR, whereas elevated monocyte count and elevated serum albumin were protective factors for the development of oxaliplatin HSR.

Conclusion

Colorectal cancer patients treated with oxaliplatin-based regimen with male gender, prior exposure to platinum-based chemotherapy, and elevated eosinophil count have a greater risk of oxaliplatin related hypersensitivity reactions.

Introduction

Colorectal cancer (CRC) is the fourth most common cancer in the world and the second leading cause of cancer death in the world. CRC treatment is presently a public health priority and oxaliplatin represents a key chemotherapeutic agent.[2, 22]

Oxaliplatin is a third-generation platinum compound with a 1,2-diaminocyclohexane carrier ligand, has been approved both for treatment of metastatic colorectal cancer and adjuvant treatment in combination with 5-fluorouracil (5-FU) and leucovorin (LV) or capecitabine.[8, 23] The adverse reactions of oxaliplatin include nausea, vomiting, diarrhea, neutropenia, thrombocytopenia, peripheral neuropathy, and hypersensitivity reaction (HSR).[13, 20] HSR to oxaliplatin has been less frequently described than cisplatin or carboplatin. At the first use, the incidence of HSR to oxaliplatin was very rare, but after expanded use of oxaliplatin in clinical practice, we are now encountering a significant increase of oxaliplatin-HSR. Recent reports have shown that the rate of HSR to oxaliplatin has varied from 8.9–23.8%.[7, 11, 18, 28] HSR to oxaliplatin should be of concern, due to its unpredictability, it is potentially life-threatening and the subsequent treatment withdrawal. Identifying patients with risk of oxaliplatin-HSR is a key clinical issue and several studies have shown supporting risk factors, with various results.[11, 16, 26, 29] In this retrospective study, we explored the incidence, severity, and risk factors of oxaliplatin-HSR.

Method

We conducted a retrospective review of the medical records of colorectal cancer patients treated with oxaliplatin-based regimen at King Chulalongkorn Memorial Hospital, Thai Red Cross society between January 1, 2015, and December 31, 2019. All patients received intravenous dexamethasone 8 mg and ondansetron 8 mg as premedication. HSR was assessed and classified according to the National Cancer Institute Common Criteria (NCI-CTCAE v5.0)[6] and was noted by attending healthcare in the medical records. The following data were collected: gender, age, type of cancer, treatment regimen, oxaliplatin dose administration, the baseline laboratory data, the number of cycles administered when the episode occurred, and the severity of HSR. In addition, the management, the response to treatment, the mode of prevention used during rechallenging and the final decision (oxaliplatin continuation or withdrawal) were reviewed. This study was approved by the Institutional Review Board (IRB), Faculty of Medicine, Chulalongkorn University (IRB no. 323/61).

Data analysis

Statistical analysis was performed using the SPSS software, version 22 (IBM Corp., Armonk, NY, USA). After collecting the data, we imputed the missing data by using multiple regression. Quantitative data are reported as means and standard deviation, and qualitative data are shown as numbers and percentage. Incidence was defined as the number of cases divided by the total number of patients included in the study. The correlations between HSR to oxaliplatin and several background factors were statistically analyzed using Fisher's exact test or the unpaired t-test. In statistical testing, two-sided p -values ≤ 0.05 were considered statistically significant.

The risk factors examined included gender, age, body mass index, ECOG performance status, preexisting allergies (allergy for specific food or drug) and pre-exposure to platinum chemotherapy. The results from laboratory test data were obtained for 1 month prior to the day of administration of oxaliplatin regimen, which were also analyzed, including serum creatinine, serum glutamic-oxaloacetic transaminase (SGOT), serum glutamate-pyruvate transaminase (SGPT),

alkaline phosphatase (ALP), serum albumin, white blood cell (WBC) count, neutrophil count, lymphocyte count, monocyte count, and eosinophil count. To determine risk factors potentially associated with HSR to oxaliplatin, those factors were collected and subjected to univariate and multivariate logistic regression. All variables with a p -values < 0.2 were included in the initial multivariate model. Multivariate analysis with backward stepwise elimination was then conducted to develop the final model. Goodness of fit for each stepwise model was compared with Hosmer and Lemeshow test. A p -value of < 0.05 was considered significant.

Results

We retrospectively analyzed the records of 245 colorectal cancer patients (1,690 treatment cycles) who treated with oxaliplatin-based regimens. The median age was 61 years (range 33–88 years), and 142 (57.96%) were male. Approximately 70% of patients had received capecitabine plus oxaliplatin regimen (CapeOx). The background characteristics of colorectal cancer patients who had positive and negative experience of oxaliplatin-HSR and the baseline laboratory data were listed in Table 1.

Table 1
Patient characteristics (n=245)

Parameter	Number of patients (%)		p-value
	Patient without HSR (n=152) [Max,Min]	Patient with HSR (n=93) [Max,Min]	
Age (years), mean $\pm$ SD	59.34 $\pm$ 11.38 [81,33]	59.96 $\pm$ 11.19 [88,40]	0.677
Gender: Male/Female	79 (52.0)/73 (48.0)	63 (67.7)/30 (32.3)	0.015*
Body surface area (m ²), mean $\pm$ SD	1.62 $\pm$ 0.19 [2.23,1.12]	1.64 $\pm$ 0.15 [2.01,1.27]	0.370
ECOG Performance Status			
0	1 (0.7)	0 (0.00)	0.574
1	133 (87.5)	79 (84.9)	
2	18 (11.8)	14 (15.1)	
Metastasis, yes	88 (57.9)	46 (49.5)	0.198
Prior exposure to platinum-based chemotherapy, yes	18 (11.8)	23 (24.7)	0.009*
History of drug hypersensitivity, yes	13 (5.3)	12 (4.9)	0.275
Underlying medical condition, yes	97 (63.8)	55 (59.1)	0.499
Regimen			
mFOLFLOX	15 (9.9)	16 (17.2)	0.059
CapeOx	104 (68.4)	66 (71.0)	
FLOX	33 (11.8)	11 (11.8)	
Purpose			
Adjuvant	81 (53.3)	70 (75.3)	0.001*
Palliative	71 (46.7)	23 (24.7)	
Dose (mg), mean $\pm$ SD	177.36 $\pm$ 45.78 [250,65]	183.06 $\pm$ 37.51 [250,100]	0.290
Dose per body surface area (mg/m ²), mean $\pm$ SD	108.71 $\pm$ 23.70 [135.80, 43.62]	111.58 $\pm$ 21.55 [142.86,55.87]	0.342
Cumulative dose (mg), mean $\pm$ SD	1160.53 $\pm$ 471.58 [2040,125]	1234.11 $\pm$ 465.85 [2400,180]	0.235
Total infusion course, median	8 [12, 1]	7 [12, 1]	0.844 ^b
WBC count ($\times 10^3/\mu\text{L}$)	6.95 $\pm$ 2.26 [14.74,2.19]	6.78 $\pm$ 2.05 [14.07,3.99]	0.329
Neutrophil count (cells/mm ³)	4468.09 $\pm$ 1922.92 [12087,1473]	4414.39 $\pm$ 1764.801 [11017,1828]	0.827
Total lymphocyte count (cell/mm ³)	1690.83 $\pm$ 914.56 [6222,131]	1459.30 $\pm$ 639.54 [3185,356]	0.033*

* $P < 0.05$, ^a Fisher's Exact Test

mFOLFLOX: oxaliplatin plus leucovorin and 5-Fluorouracil every 2 weeks

XELOX: Intravenous oxaliplatin 130 mg/m² (day 1) followed by oral capecitabine 1,000 mg/m² twice daily (day 1, evening, to day 15, morning)

WBC white blood cell

FLOX: 5-Fluorouracil plus oxaliplatin on weeks 1,3,5 of 8-week cycle

SGOT: Serum glutamic-oxaloacetic transaminase

SGPT: Serum glutamate-pyruvate transaminase

eGFR: estimated glomerular filtration rate

Parameter	Number of patients (%)		p-value
	Patient without HSR (n=152) [Max,Min]	Patient with HSR (n=93) [Max,Min]	
Monocyte count (cell/mm ³)	479.01±192.56 [995.80,37.98]	444.97±210.39 [1210.02,24.00]	0.196
Eosinophil count (cell/mm ³)	142.41±134.24 [716,0]	189.45±170.32 [961,0]	0.017*
Serum albumin (g/dL), n=171	3.76±0.46 [4.5,2] n=98	3.59±0.54 [5, 2] n=73	0.024*
Alkaline phosphatase (U/L)	90.89±94.71[869,20]	96.91±98.82 [573,21]	0.635
Serum creatinine (mg/dL)	0.78±0.19 [1.3,0.3]	0.84±0.28 [2.2,0.5]	0.073
- more than 1 mg/dL	14 (9.2)	20 (21.5)	0.007*
eGFR (mL/min)	83.84±27.22 [199.84,26.22]	83.23±26.29 [137.67,15.86]	0.863
*P< 0:05, ^a Fisher's Exact Test			
mFOLFLOX: oxaliplatin plus leucovorin and 5-Fluorouracil every 2 weeks			
XELOX: Intravenous oxaliplatin 130 mg/m ² (day 1) followed by oral capecitabine 1,000 mg/m ² twice daily (day 1, evening, to day 15, morning)			
WBC white blood cell			
FLOX: 5-Fluorouracil plus oxaliplatin on weeks 1,3,5 of 8-week cycle			
SGOT: Serum glutamic-oxaloacetic transaminase			
SGPT: Serum glutamate-pyruvate transaminase			
eGFR: estimated glomerular filtration rate			

There were no statistical differences of age, body surface area, dosage regimen, performance status, total infusion course, and a history of drug hypersensitivity between the patients without HSR (control group) and with HSR (case group). Compared with women, men had a higher susceptibility to HSR ($p=0.015$). Those patients who had been exposed to platinum compound prior to this episode of treatment also had higher HSR reports ($p=0.009$). Baseline biochemical examination of blood showed that the percentage of lymphocytes, eosinophiles and serum albumin were statistically different between the 2 groups ($p=0.044$, 0.012 , 0.024 respectively).

Incidences of hypersensitivity reaction

During the 5-year follow-up, 93 patients experienced oxaliplatin-HSR. According to NCI-CTCAE v.5, the incidence rate of grade 1, grade 2 and higher grade was 27.3% (67 patients), 6.5% (16 patients) and 4.1% (10 patients), respectively. (Table 2) Oxaliplatin hypersensitivity appeared on a median of 3 infusions (1-11). In addition, out of 23 patients (9.39%) who developed oxaliplatin-HSR at first and second infusion course, 10 (43.48%) had been exposed to platinum agents prior to this episode of treatment. The most common HSR were mild cutaneous reactions such as flushing, urticaria, itching and small area erythema, largely on palms and soles. Some patients presented more severe reactions with facial swelling, dyspnea, wheezing, stomach cramp, diarrhea, or changes of blood pressure. (Table 2) Eleven patients were diagnosed anaphylaxis, with acute and severe symptoms during the infusion or started within 30 minutes after complete infusion. Ten of these were grade 3 HSR, in which the oxaliplatin infusion was immediately discontinued when the reaction occurred and was promptly handled before being admitted into the hospital. (Table 3)

Table 2
Severity and manifestations of oxaliplatin hypersensitivity reactions
(n=245)

	Number of patients (%)
Incidence of hypersensitivity	93 (37.96)
Severity	
Grade 1	67 (27.35)
Grade 2	16 (6.53)
Grade 3/4	10 (4.08)
Symptom	
Cutaneous reactions	58 (23.67)
Peripheral neuropathy	53 (21.63)
Anaphylaxis	11 (4.49)
Digestive symptoms	20 (8.16)
Respiratory symptoms	17 (6.94)
Blood pressure rising	6 (2.45)
Fever/Chill	4 (1.63)/6 (2.45)
Palpitation	3 (1.22)
Blood pressure lowering	2 (0.82)
Cycle number at event, median (range)	3 (1-11)
Grade 2, median (range)	4 (1-11)
Grade 3, median (range)	2.5 (1-6)

Table 3
Characteristics of the ten patients with grade 3/4 oxaliplatin hypersensitivity

No.	Gender	Age (years)	Prior platinum exposure	Metastasis	Regimen	Purpose	Dose per BSA (mg/m ²)	Cycle number at event	Onset of HSR (minutes)	Total cycle	Treatment	Managem
1	F	59	N	N	CapeOx	A	130	5	50	5	1. CPM 10 mg, Dexamethasone 5 mg IV STAT 2. Hold 30 minutes then slow infusion about 6 hours	Discontin and adju single capecitabi then re-evaluation
2	M	59	N	N	CapeOx	A	130	2	90	6	1. Discontinue 2. Hyoscine-N-butyl bromide 20 mg IV STAT and hydration	1. Add loperamid mg Sig. 2 cap CMT day 2. Add CPI mg IV pre 3. Rechallenge with prolo infusion ti hours), fin complete 1 6 cycles
3	F	60	Y	N	mFOLFLOX	A	85	2	20	12	1. Hold and reduce rate of administration to 80 mL/hr 2. CPM 10 mg, Dexamethasone 5 mg IV STAT 3. Adrenaline 0.3 mg IM	12 step desensitiz protocol, f complete 1 12 cycles
4	F	62	Y	Y	FLOX	P	80	2	120	4	1. Adrenaline 1 mg IM and hydration	1. 12 step desensitiz protocol w mild HSR through desensitiz 2. Patient requested discontinu after the 4 cycle
5	M	47	N	N	mFOLFLOX	A	85	3	110	8	1. Discontinue 2. Dexamethasone 10 mg IV STAT 3. Adrenaline 0.5 mg IM	1. 12 step desensitiz protocol, t grade-2 H through th cycle 2. Discont after the 8 cycle
6	M	45	Y	N	CapeOx	A	100	2	15	3	1. Hold 2. Adrenaline 0.3 mcg IM and hydration 3. Admit and rechallge oxaliplatin 20-40 mL/hr	1. Rechallenge with prolo infusion ti hours), gra HSR was occurred s discontinu 2. Skin tes Positive

A=Adjuvant, P=Palliative, CMT=chemotherapy

No.	Gender	Age (years)	Prior platinum exposure	Metastasis	Regimen	Purpose	Dose per BSA (mg/m ²)	Cycle number at event	Onset of HSR (minutes)	Total cycle	Treatment	Managem
7	M	47	Y	N	FLOX	P	85	1	90	6	1. Hold and oxygen therapy 2. Adrenaline 0.5 mg IM and Dexamethasone 10 mg IV 3. Admit and then slow infusion about 4 hours	1. Skin tes Negative 2. rechalle (2nd cycle with prolo infusion ti hours), bu HSR. 2. 12 step desensitiz protocol (: -6th cycle)
8	M	56	N	N	mFOLFLOX	A	80	6	80	6	1. Hold 2. Symbicort™ (160/4.5) 4 puffs and oxygen therapy 3. CPM 10 mg IV 4. Continue infusion rate 80 mL/hr	Discontin according therapeuti plan
9	M	44	N	N	CapeOx	A	90	6	120	6	1. Hyoscine-N-butyl bromide 20 mg IV and CPM 10 mg IV STAT	Discontin according therapeuti plan
10	F	73	Y	Y	CapeOx	P	120	3	120	3	1. Loperamide 2 mg 2 capsules STAT 2. Hydration	Discontin [Hand foo syndrome grade 3]
A=Adjuvant, P=Palliative, CMT=chemotherapy												

Risk factors for hypersensitivity reaction

To investigate the potential risk factors for the development of oxaliplatin HSR, we initiated logistic regression model, in which the following factors were included: (1) age, (2) gender, (3) metastasis, (4) prior platinum exposure, (5) history of drug hypersensitivity, (6) neutrophil count, (7) lymphocyte count, (8) monocyte count, (9) eosinophil count, (10) serum albumin, (11) serum creatinine, (12) oxaliplatin infusion number, and (13) total dose of oxaliplatin. Though the univariate analysis, in total 8 factors had *p*-values < 0.2 which met the criteria for inclusion in multivariate analysis (Table 4).

Table 4
Univariate analysis and multivariate analysis for candidate risk factors for oxaliplatin hypersensitivity [N=245]

Factors	Univariate analysis				Multivariate analysis			
	B	Adjusted OR	95%CI	p-value	B	Adjusted OR	95%CI	p-value
Age	0.005	1.005	0.982-1.028	0.675				
Gender, male	0.663	1.941	1.132-3.326	0.016*	0.966	2.628	1.450-4.763	0.001
Metastasis, yes	-0.034	0.712	0.424-1.196	0.199				
Prior platinum exposure, yes	0.894	2.446	1.238-4.834	0.010*	0.818	2.265	1.079-4.755	0.031
History of drug hypersensitivity, yes	0.460	1.584	0.69-3.637	0.278				
Neutrophil count (cell/mm ³)	0.0002	0.99998	0.9998-1.0002	0.826				
Total lymphocyte count (cell/mm ³)	0.0004	0.9996	0.9992-0.9999	0.037*				
Monocyte count (cell/mm ³)	-0.001	0.999	0.998-1.000	0.197	-0.002	0.998	0.996-0.999	0.007
Eosinophil count (cell/mm ³)	0.002	1.002	1.000-1.004	0.020*	0.003	1.003	1.001-1.005	0.004
Serum albumin (g/dL)	-0.787	0.455	0.258-0.804	0.007*	-1.111	0.329	0.170-0.638	0.001
Serum creatinine (mg/dL)	1.128	3.090	0.984-9.707	0.053				
Oxaliplatin infusion number (times)	0.028	1.028	0.929-1.138	0.589				
Total dose of oxaliplatin (mg)	0.0003	1.000	1.000-1.001	0.234				
Constant					3.419			
*p < 0.05								

After backward stepwise elimination method, 5 final factors were selected: gender, prior platinum exposure, eosinophil count, monocyte count and serum albumin. The odds ratio (95% CI) from the multivariate model was presented in Table 4. We established the incidence of hypersensitivity in colorectal cancer patients treated with this oxaliplatin base regimen(Y) model:

$$Y = 3.419 + [0.966 \times (\text{Gender; if male} = 1)] + [0.818 \times (\text{if prior platinum exposure})] + [0.003 \times (\text{number of eosinophil count})] - [0.002 \times (\text{number of monocyte count})] - [1.111 \times (\text{serum albumin})]$$

Discussion

Hypersensitivity reactions to oxaliplatin result in the withdrawal of the chemotherapy or reducing the number of therapeutic options. The incidence of oxaliplatin HSR is growing as a consequence of the increasing use of oxaliplatin in colorectal cancer. The incidence of oxaliplatin HSR in this study was 37.96%, relatively higher than the rates described in previous studies (8.9–23.8%)[1, 4, 7, 9–11, 28], suggesting racial effects and dosage effects. The MOSAIC trial, a large, randomized phase 3 trial in Western countries, showed 10.3% of 1,100 patients who received 5-fluorouracil with oxaliplatin experienced HSR.[18] The report from Japanese patients indicated that 22.9% of 108 patients experienced hypersensitivity.[24] Additionally, the dose of oxaliplatin in the MOSAIC trial was 85 mg per square meter or was reduced to 75 mg per square meter in the event of persistent neuropathy[1], but the average dose of oxaliplatin in this study was 110 mg per square meter. Interestingly, grade 3/4 HSR in this study was similar to the previous study.[1, 24] Ten patients experienced grade 3/4 HSR to oxaliplatin and 6 patients were reintroduced to oxaliplatin. The reintroduction of oxaliplatin was done after skin testing to oxaliplatin or using a 12-step desensitization protocol, developed by the Dana–Farber Cancer Institute and the Brigham and Women's Hospital.[5, 14]

The identification of risk of developing HSR is an important issue for the prevention and related management of serious events. The risk factors to platinum drugs related HSR, especially carboplatin and cisplatin were examined. Only a few studies were focused to identify potential risk factors for oxaliplatin-related HSR.[15] This study emphasized the risk factors to recognize patients at risk of oxaliplatin-related HSR. Logistic regression analysis found five significant factors, three risk factors (male, prior platinum exposure, eosinophil count) and two protective factors (monocyte count, serum albumin).

Okayama et al., reported that male patients and eosinophil count in peripheral blood were independent variables for oxaliplatin-related HSR,[19] which were similar to our finding. Eosinophil, one of the immunologic cells, absolutely characterizes drug HSR especially drug eruptions, consequently in patients with high eosinophil counts, this may be a component in mechanisms of HSR to oxaliplatin.[12, 19] This is contrary to Parel et al., Seki et al., and Kim et al., studies which suggested that female was higher risk of oxaliplatin-related HSR,[10, 21, 24] explained by a possible role of hormonal influences. Several studies have also reported no correlation between gender and HSR.[25, 28] Our study demonstrated that prior platinum exposure was the independent risk factor which was distinguished from previous studies.

On the other hand, we found that lower monocyte count and serum albumin was significantly associated with the incidence of oxaliplatin-related HSR. Seki et al., also suggested that female, preexisting allergies, lower LDH level, higher neutrophil count and lower monocyte count were associated with the incidence of HSR.[24] Serum albumin is commonly utilized as a marker of nutritional status. Malnutrition degrades both the innate and adaptive immune system.[3] Low serum albumin level increases vascular permeability and increases interstitial volume, which potentiates immediate HSR.[27] However, Nishihara et al., reported that serum albumin level above 4.1 g/dL was the potential risk associated with the incidence of oxaliplatin-related HSR. Oxaliplatin may also act as a

happen, binding to macromolecular carrier proteins, such as albumin.[17] A reason for the variation of risk factors was the ethnic differences between the participants in this study. Finally, we found that treatment regimen and oxaliplatin dose was not associated with an increased risk of oxaliplatin-related HSR.

This retrospective study was conducted to clarify the risk factors for oxaliplatin-related HSR in Southeast Asia and demonstrated the management of severe oxaliplatin-related HSR in real situation. Limitations of this study include its retrospective design and incomplete clinical data. Some medical records were insufficient, and hypersensitivity symptoms were not actively followed. Further prospective studies are needed to refine this oxaliplatin-related hypersensitivity prediction model to be more precise and develop the final model as a guide to prevent oxaliplatin-related HSR.

Conclusion

Oxaliplatin-related hypersensitivity is a significant potential adverse reaction. The incidence was approximately 38%, with grade 3/4 events in 4%. In this study, males, prior platinum exposure, eosinophil count, monocyte count, and serum albumin were the independent risk factors which were associated with the incidence of oxaliplatin-related hypersensitivity.

Declarations

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Conflicts of interest/Competing interests: None to declare

Availability of data and material: The datasets generated during or analysed during the current study are not publicly available due to data policy of Chulalongkorn Memorial Hospital but are available from the corresponding author on reasonable request.

Code availability: IBM® SPSS® version 22 licensed provided by Chulalongkorn University via splm.it.chula.ac.th.

Authors' contributions: All authors contributed to the study conception and design. Material preparation and data collection were performed by Sirinoot Palapinyo. The data analysis was performed by Sirinoot Palapinyo and Nutthada Areepium. The first draft of the manuscript was written by Sirinoot Palapinyo, and all authors commented and edited on previous versions of the manuscript. All authors read and approved the final manuscript. The content has not been published elsewhere.

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Consent to participate: Not applicable

Consent for publication: Not applicable

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