Nonphysician Clinicians in the Follow-Up of Resected Patients with Colorectal Cancer

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Keywords

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Abstract

Background/Aims: The 5-year postoperative follow-up for patients undergoing curative treatment for colorectal cancer (CRC) is labour intensive. We assessed the added value of a dedicated nonphysician clinician (NPC) in the follow-up of patients after resection for CRC. **Methods:** Patients were divided into 2 groups as defined by the number of follow-up visits in the first year, including intensive ($\geq 3\times$) and minimal ($\leq 2\times$). Involvement of an NPC, diagnosis of disease recurrence and the course of the disease were determined. **Results:** Of the 681 patients, 79.9% belonged to the “intensive” and 21.1% to the “minimal” group. Involvement of an NPC resulted in a higher adherence to follow-up (84.3 vs. 73.9%, $p = 0.001$). Overall, patients in regular follow-up less often had multifocal recurrence (47.1 vs. 73.7%, $p = 0.04$), and a better survival after recurrence (SAR; hazard ratio [HR] 3.604, $p < 0.001$). The “intensive” group had a significantly better overall survival compared to the “minimal” group (HR 1.71, $p = 0.013$). **Conclusion:** Adherence to surveillance programs after resection for CRC is better in hospitals with a dedicated NPC. Overall, patients’ adherence to follow-up resulted in

less multifocal disease recurrence at the time of diagnosis as compared to patients presenting with symptoms and a better 3-year SAR.

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Introduction

Colorectal cancer (CRC) is the third most common malignancy worldwide with over 1.2 million new cases surfacing annually and is therefore a major cause for higher rates of morbidity and mortality [1]. The main cause of death is metastatic disease [2]. Of all patients, 20–25% will present with metastatic disease at the time of diagnosis and another 20–25% will develop metastatic disease after curative treatment [2]. Therefore, patients undergoing curative treatment for CRC are followed for at least 5 years after surgery to detect recurrence. The 2 main components of the follow-up are blood carcinoembryogenic antigen measurement (CEA) and radiological imaging of the liver with CT imaging or ultrasound [3, 4]. As the success of resection of liver metastases is increas-

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Table 1. Dutch surveillance program after curative resection of colorectal cancer

	1st year	2nd year	3th year	4th year	5th year
3 months	CEA	CEA			
6 months	CEA US/CT	CEA US/CT	CEA US/CT	CEA	CEA
9 months	CEA	CEA			
12 months	CEA US/CT Colonoscopy	CEA US/CT	CEA US/CT	CEA US/CT	CEA US/CT

ing with 5-year overall survival (OS) rates as high as 40–60%, early detection of liver lesions is warranted [5, 6].

Interestingly, although multiple follow-up regimens have been suggested in literature with differences in both frequency of follow-up and components used at various time points, the intensity and components of the follow-up are still a matter of debate [7, 8]. A recent systematic review concluded that intensive follow-up strategies were associated neither with improved cancer-specific survival, nor with a higher detection rate for tumour recurrences after curative treatment of CRC [9]. The FACS-trial, the most recent randomized controlled trial comparing multiple follow-up strategies with the same intensity but different components, suggested that follow-up should include at least one of the 2 components, CEA or imaging [3].

The follow-up visits of patients with CRC is labour intensive because of both the administrative and logistic work that is required for a well-defined format. Therefore, nonphysician clinicians (NPCs) are increasingly employed to organize the follow-up of these patients. However, until now, no literature has been published assessing the added value of an NPC in the follow-up.

This study is the first of its kind to assess the added value of a dedicated PA in the follow-up of patients with CRC.

Method

All aspects of the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines were followed, and the paper was written accordingly [10].

Patient Selection

Patients were selected from the MATCH-study, an ongoing registration cohort including patients who undergo curative resection for primary CRC in 7 centres in the Rotterdam region, the Netherlands (Institutional Review Board number MEC-2007-

088). Patients with colon cancer included in the first 5 years of the MATCH-study (July 1, 2007–July 1, 2012) were selected for this study if they were willing to give written informed consent.

Follow-Up

The surveillance of patients after curative colon resection in the Netherlands is performed by gastrointestinal surgeons, alone or in collaboration with specialized NPCs. Patients treated with adjuvant chemotherapy are referred to the surgeon for follow-up as well. The surveillance program includes visits to the outpatient clinic every 3–6 months in the first 3 years and yearly visits up to 5 years after surgery. CEA blood levels are checked every 3 months in the first 3 years and every 6 months in years 4 and 5. Imaging of the liver (ultrasound or CT) is performed every 6 months in the first 2 years and on a yearly basis up to 5 years after surgery. A colonoscopy check is performed 1 year after surgery; thereafter the colonoscopy surveillance guidelines are followed (Table 1) [11, 12].

Follow-up visits were scored using patient charts and an electronic appointment history log. A follow-up visit consisted of an appointment with a surgeon or a trained NPC specialized in oncology. Additional, CEA testing with an abdominal ultrasound or abdominal CT scanning was performed.

Patients were divided into groups based on the number of visits in the first year using the national guideline for the follow-up of patients after curative surgery for CRC, in which 4 visits with a minimum of 2 visits in the first year is advised [13]. Patients with 3 or more visits in the first year were classified as “intensive” and patients with 2 or fewer visits were classified as “minimal.” The involvement of an NPC in the follow-up was scored per centre (i.e., all patients from centres in which an NPC was present were categorized in the NPC group).

Information about whether disease recurrence was found in symptomatic or asymptomatic patients was registered. Recurrence was found either because of a regular follow-up visit or as a result of additional imaging in the context of complaints. Furthermore, the number of metastatic sites, the treatment modality, as well as the curative or palliative intent of the treatment plan was studied.

Statistical Analysis

Summary data for the study groups was presented as frequencies and percentages. Continuous variables were presented as mean values with SDs. The difference in distribution between

groups was determined using a χ^2 -test. Differences in continuous variables were determined using a Student *t* test. The univariable and multivariable survival analyses were performed using Cox regression models with centre included as strata to adjust for centre heterogeneity. Kaplan-Meier estimates were used to visualize overall effects. Disease-free survival (DFS) was defined as the time elapsed between the date of surgery and either the date of any recurrence of disease or the date of the last follow-up visit at which a patient was considered to have no recurrence. OS was defined as the time elapsed between the date of surgery and either the date of death or the date of the last check in the Municipal Personal Records Database at which a patient was censored. Survival after recurrence (SAR) was defined as the time elapsed between the date of recurrence of disease and either the date of death or the date of the last check in the Municipal Personal Records Database at which a patient was censored. All statistical analyses were performed using SPSS version 21 (IBM, Armonk, NY, USA). Significance was determined by a *p* value <0.05.

Results

Patient Characteristics

A total of 870 patients were enrolled in the MATCH-study from July 1, 2007 to July 1, 2012. Of these patients, 71 patients died within the first year after surgery and 118 patients were lost to follow-up in the first year, resulting in a study sample size of 681 patients.

The baseline characteristics are summarized in Table 2. Most of the patients were in the “intensive” group (79.9%). The mean age of the total population was 69.3 years. Just over half of the patients were male (54.0%). Although the distribution of the ASA classification did not differ between the 2 follow-up groups, significantly more patients in the “intensive” group underwent a laparoscopic procedure compared to the “minimal” group (56.1 vs. 44.1%, *p* = 0.01, respectively). Radicality was similar in both groups (both >99%). Just over half of the patients had a left-sided tumour (53.3%). Significant differences were seen in the distribution of both tumour stage and tumour grade between the 2 groups, with fewer stage III patients (19.5 vs. 29.2%, *p* = 0.046) and more moderately differentiated tumours (77.6 vs. 67.4%, *p* = 0.04) in the “intensive” group. The majority of tumours showed no angioinvasive growth (91.5%). The percentage of patients receiving adjuvant therapy was 24.0% for the whole group, and was significantly related to the then existing tumour stage (stage I 6.2%, stage II 14.5% and stage III 70.3%, *p* = 7×10^{-49}). Most patients had no recurrence of disease within the follow-up period (87.5%).

Nonphysician Clinicians

An NPC was involved in the follow-up of 394 (57.9%) patients after curative resection in 4 of the 7 participating centres during the full study period. Patients with a follow-up in an outpatient clinic with an NPC did not significantly differ from patients followed up in an outpatient clinic without an NPC for any of the basic characteristics except for ASA (*p* = 0.002) and tumour grade (*p* = 0.00002; Table 3). Patients visiting an outpatient clinic working with an NPC were more often stratified to the “intensive” group compared to patients visiting an outpatient clinic without an NPC (84.3 vs. 73.9%, *p* = 0.001).

Survival

In total, 85 (12.5%) patients had recurrence of disease after curative surgery of the primary colon cancer. The median follow-up for DFS in the entire group was 34.3 months (interquartile range 20.1–45.8 months). Univariable cox regression analysis showed no significant difference in DFS between the “intensive” and “minimal” group (hazard ratio [HR] 1.50; 95% CI 0.92–2.46, *p* = 0.1; Fig. 1).

In total, 139 (20.4%) patients died. The median follow-up for OS was 67.9 months (interquartile range 51.4–80.0 months). Univariable cox regression analysis, with centre included as strata to adjust for centre heterogeneity, showed a significant OS benefit for the “intensive” group compared to the “minimal” group (HR 1.87; 95% CI 1.29–2.72, *p* = 0.001; Fig. 2), and showed a significant association between OS and age, ASA classification, the type of surgical procedure, side of the cancer, tumour stage and angioinvasive growth. In the conditional backward multivariable cox regression model including gender, ASA classification, surgical procedure, side of the cancer, tumour stage, tumour grade, angioinvasive growth and adjuvant therapy, and again including centre as strata to adjust for centre heterogeneity, led to a similar OS benefit for patients in the “intensive” group compared to the “minimal” group (HR 1.70; 95% CI 1.11–2.60, *p* = 0.01; Table 4).

For 74 of the 85 patients (87.1%) with recurrence of disease, the reason for the disease recurrence (complaints or during a follow-up visit) could be determined. Significantly more patients in the “complaints” group had metastases at more than one anatomical site at the time of recurrence compared to the “follow-up” group (73.7 vs. 47.1%, *p* = 0.04). The number of patients treated with curative intent did not significantly differ between the “follow-up” group and the “complaints” group (25.0 vs. 11.8%, *p* = 0.2). However, patients in the “follow-up”

Table 2. Baseline characteristics

	All (<i>n</i> = 681)	Intensive (<i>n</i> = 544)	Minimal (<i>n</i> = 137)	<i>p</i> value
Age, years, mean (SD)	69.3 (10.7)	68.9 (10.5)	70.9 (11.5)	0.06
Gender, <i>n</i> (%)				0.6
Female	313 (46.0)	253 (46.5)	60 (43.8)	
Male	368 (54.0)	291 (53.5)	77 (56.2)	
ASA ^a , <i>n</i> (%)				0.4
I	94 (17.2)	70 (16.0)	24 (21.8)	
II	376 (68.7)	307 (70.3)	69 (62.7)	
III	75 (13.7)	58 (13.3)	17 (15.5)	
IV	2 (0.4)	2 (0.5)	0 (0)	
Surgical procedure ^b , <i>n</i> (%)				0.01
Open	313 (46.3)	237 (43.9)	76 (55.9)	
Laparoscopic	363 (53.7)	303 (56.1)	60 (44.1)	
Radicality ^c , <i>n</i> (%)				0.8
Yes	675 (99.8)	539 (99.4)	136 (99.3)	
No	4 (0.2)	3 (0.6)	1 (0.7)	
Side of cancer, <i>n</i> (%)				0.7
Right	318 (46.7)	252 (46.3)	66 (48.2)	
Left	363 (53.3)	292 (53.7)	71 (51.8)	
TNM stage, <i>n</i> (%)				0.046
1	196 (28.8)	161 (29.6)	35 (25.5)	
2	339 (49.8)	277 (50.9)	62 (45.3)	
3	146 (21.4)	106 (19.5)	40 (29.2)	
Tumour grade ^d , <i>n</i> (%)				0.04
Good	84 (12.6)	63 (11.8)	21 (15.9)	
Moderate	505 (75.6)	416 (77.6)	89 (67.4)	
Poor	65 (9.7)	49 (9.1)	16 (12.1)	
Other	14 (2.1)	8 (1.5)	6 (4.5)	
Angioinvasive growth, <i>n</i> (%)				0.6
No	623 (91.5)	499 (91.7)	124 (90.5)	
Yes	58 (8.5)	45 (8.3)	13 (9.5)	
Adjuvant therapy ^e , <i>n</i> (%)				0.04
No	516 (76.0)	421 (77.7)	95 (69.3)	
Yes	163 (24.0)	121 (22.3)	42 (30.7)	
Recurrence, <i>n</i> (%)				0.2
No	596 (87.5)	481 (88.4)	115 (83.9)	
Yes	85 (12.5)	63 (11.6)	22 (16.1)	

^a *n* = 134; ^b *n* = 5; ^c *n* = 2; ^d *n* = 13; ^e *n* = 2.

group did have a significantly better SAR compared to patients in the “complaints” group (HR 3.60; 95% CI 1.92–6.74, *p* = 0.00006; Fig. 3).

Discussion and Conclusions

The frequency of follow-up of patients after curative surgery of CRC and the tests to be used during follow-up still is a topic of debate. Current literature suggests an intensive follow-up with CEA measurements and/or CT

imaging. Due to the labour intensity of the follow-up, NPCs are increasingly employed for the follow-up of these patients. However, no literature has been published assessing the added value of an NPC in the follow-up.

In our cohort, significantly more patients seen in an outpatient clinic with an NPC were categorized in the “intensive” group compared to patients followed up in an outpatient clinic without an NPC (84.3 vs. 73.9%, *p* = 0.001). Patients in the “intensive” group had a similar DFS but a significantly better OS compared to patients in the “minimal” group, even when adjusting for other prog-

Table 3. Characteristics for NPC present or not present

	NPC not present (<i>n</i> = 287)	NPC present (<i>n</i> = 394)	<i>p</i> value
Age, years, mean (SD)	69.1 (10.7)	69.4 (10.8)	0.9
Gender, <i>n</i> (%)			0.5
Female	136 (47.4)	177 (44.9)	
Male	151 (52.6)	217 (55.1)	
ASA ^a , <i>n</i> (%)			0.002
I	61 (23.5)	33 (11.5)	
II	160 (61.5)	216 (75.3)	
III	38 (14.6)	37 (12.9)	
IV	1 (0.4)	1 (0.3)	
Surgical procedure ^b , <i>n</i> (%)			0.4
Open	126 (44.4)	187 (47.7)	
Laparoscopic	158 (55.6)	205 (52.3)	
Radicality ^c , <i>n</i> (%)			0.09
Yes	0 (0)	4 (1.0)	
No	287 (100)	388 (99.0)	
Side of cancer, <i>n</i> (%)			0.09
Right	123 (42.9)	195 (49.5)	
Left	164 (57.1)	199 (50.5)	
TNM stage, <i>n</i> (%)			0.6
1	80 (27.9)	116 (29.4)	
2	149 (51.9)	190 (48.2)	
3	58 (20.2)	88 (22.3)	
Tumour grade ^d , <i>n</i> (%)			0.00002
Good	48 (17.0)	36 (9.3)	
Moderate	186 (66.0)	319 (82.6)	
Poor	39 (13.8)	26 (6.7)	
Other	9 (3.2)	5 (1.3)	
Angioinvasive growth, <i>n</i> (%)			0.7
No	261 (90.9)	362 (91.9)	
Yes	26 (9.1)	32 (8.1)	
Adjuvant therapy ^e , <i>n</i> (%)			0.6
No	221 (77.0)	295 (75.3)	
Yes	66 (23.0)	97 (24.7)	
Recurrence, <i>n</i> (%)			0.1
No	245 (85.4)	351 (89.1)	
Yes	42 (14.6)	43 (10.9)	

^a *n* = 134; ^b *n* = 5; ^c *n* = 2; ^d *n* = 13; ^e *n* = 2.

nostic factors (HR 1.71; 95% CI 1.12–2.62). Finally, patients in the “follow-up” group less often had metastases at more than one anatomical site at the time of recurrence (47.1 vs. 73.7%, *p* = 0.04), and a better SAR compared to the “complaints” group (HR 3.60; 95% CI 1.92–6.74).

Our study supports the added value of NPCs in the follow-up of patients after curative surgery for CRC to improve adherence to the surveillance program. Nonetheless, its effect on DFS and OS remains to be determined.

Fig. 1. Kaplan-Meier curve of the disease-free survival for the “intensive” and “minimal” group. **Fig. 2.** Kaplan-Meier curve of the overall survival for the “intensive” and “minimal” group.

This study has several limitations. First, no detailed information on the actual attendance of the NPCs during the follow-up visits was available. Although all follow-up visits were documented in the patient charts, these may have been conducted by either the NPC or the treating specialist. Yet, the follow-up visits alone probably do not accurately reflect the role of the NPC. In practice, they also make sure that a patient seen by a specialist receives an invitation for the next visit, including the appropriate

Fig. 3. Kaplan-Meier curve of the survival after recurrence for the “complaints” and “follow-up” group.

Table 4. Univariable and multivariable cox regression model for OS with centre included as strata to adjust for centre heterogeneity

	Univariable	<i>p</i> value	Multivariable	<i>p</i> value
Follow-up group				
Intensive	1		1	
Minimal	1.87 (1.29–2.72)	0.001	1.70 (1.11–2.60)	0.01
Age, years	1.08 (1.06–1.10)	8×10^{-15}	1.08 (1.06–1.11)	7×10^{-10}
Gender, <i>n</i> (%)				
Female	1			
Male	1.16 (0.83–1.63)	0.4		
ASA ^a , <i>n</i> (%)				
I	1	0.0000006	1	0.008
II	2.71 (1.35–5.44)		1.38 (0.65–2.91)	
III	6.70 (3.16–14.18)		2.44 (1.08–5.52)	
IV	13.76 (1.59–118.93)		14.02 (1.46–134.98)	
Surgical procedure ^b , <i>n</i> (%)				
Open	1			
Laparoscopic	0.65 (0.46–0.93)	0.02		
Radicality ^c , <i>n</i> (%)				
Yes	1			
No	20.59 (0.0004–1.1 × 10E6)	0.6		
Side of cancer, <i>n</i> (%)				
Right	1			
Left	0.69 (0.49–0.96)	0.03		
TNM stage, <i>n</i> (%)				
1	1	0.005	1	0.0003
2	1.32 (0.86–2.03)		1.45 (0.89–2.36)	
3	2.11 (1.32–3.37)		3.26 (1.80–5.89)	
Tumour grade ^d , <i>n</i> (%)				
Good	1	0.2		
Moderate	0.91 (0.51–1.63)			
Poor	1.49 (0.74–2.98)			
Other	1.42 (0.46–4.36)			
Angioinvasive growth, <i>n</i> (%)				
No	1		1	
Yes	2.09 (1.30–3.35)	0.002	1.98 (1.15–3.39)	0.01
Adjuvant therapy ^e , <i>n</i> (%)				
No	1			
Yes	0.69 (0.45–1.06)	0.09		

^a *n* = 134; ^b *n* = 5; ^c *n* = 2; ^d *n* = 13; ^e *n* = 2.

tests. Therefore, we chose to include the presence of an NPC in a participating centre in our analyses. If deemed useful, the effect of the “behind-the-scenes” actions should be assessed prospectively, since they cannot be reliably recalled from the patient charts. Second, the first year after resection was used to divide the patients into the 2 groups. Therefore, all patients who died within the first year were excluded and thus no conclusions can be drawn for that selected group of patients. Patients who died in the first year had a higher mean age, a higher ASA III score, more open surgery, less often adjuvant chemotherapy and more frequent disease recurrence compared to the included patients (data not shown). However, given the short time period after resection in which these events occurred, the impact of the follow-up is likely to be minimal. Third, the study cohort was derived from an observational study cohort. Therefore, patients at risk for recurrence may be intentionally followed more intensively than patients at low risk for recurrence, that is, bias by indication. However, the groups did not significantly differ in terms of age, gender, location of the tumour, TNM stage or total recurrences. Last, the differences in frequency of the follow-up visits might have resulted in lead time bias. However, the average difference in the interval between visits is small (3 months), and lead time bias would have overestimated the DFS in the “minimal” group, which would not explain the differences found in OS. Furthermore, lead time bias may also account for part of the observed survival difference between the “follow-up” and the “complaints” group. However, the difference in median survival time (35.5 vs. 10.4 months) is not likely to be explained by a potential lead time bias with an average interval between visits of 3 months. Furthermore, similar survival estimates are observed when stratifying patients to “one metastatic site” and “more than one metastatic site” (data not shown), suggesting that the observed effect may largely be explained by the disease burden at the time of recurrence.

NPCs are progressively involved in medical work [14]. They are appointed for both in hospital as well as outpatient clinic tasks, ranging from invasive diagnostic procedures to consultation. For instance, literature has reported that invasive procedures like the placement of intracranial pressure monitors, ultrasound-assisted percutaneous liver biopsy and dermatologic surgical procedures are both feasible and safe in the hands of trained NPCs [15–17]. In the field of CRC, training programs for flexible sigmoidoscopy in the context of screening have been set up and are currently being evaluated [18–20]. Interestingly, a survey conducted in 2000 among 1,900 health care professionals showed that more than half of

the physicians involved in CRC were reluctant to let NPCs perform these procedures [21]. Therefore, future efforts should not only be focused on training programs for the NPCs but also on understanding and resolving the reasons for these reluctances. Although experience in the clinical practice suggests the existence of an added value of involving NPCs in the follow-up after curative colorectal surgery, literature supporting these suggestions is scarce. In the field of cardiology, Albert et al. [22] published an article describing an increased adherence to the guideline-recommended heart failure therapies when employing NPCs. This study supports the concept that NPCs may have an important role in the follow-up of patients with CRC as adherence is improved and the surgeon’s workload is reduced.

Although follow-up after curative surgery for CRC is considered effective, both the tests used during follow-up and the frequency of the follow-up are still under debate. Meta-analyses have shown that CEA measurement and CT imaging are the only diagnostic tests with significant potential to detect curatively treatable metastatic recurrence in patients with CRC [7, 8]. However, although the sensitivity of ultrasound is inferior to the sensitivity of CT imaging at a patient level (73 vs. 84%), ultrasound in clinical practice is used as an alternative for CT imaging for the detection of liver metastasis [4, 23]. The recently published FACS trial, a prospective randomized controlled trial compared no follow-up with 3 intervention arms with CEA follow-up, CT follow-up, or CEA + CT follow-up. They showed that significantly more patients with recurrence of disease in all 3 intervention arms were treated with curative intent, although the number of recurrences and the time of detection of the recurrence did not significantly differ from the control group. However, no survival benefit was found for any of the intervention arms compared to the control group [3]. Following these findings, only follow-up visits during which any combination of CEA testing, an abdominal ultrasound and an abdominal CT-scan were performed, were taken into account in our study. Follow-up visits with an abdominal ultrasound were also included in our study, since it is generally accepted as imaging modality to assess the presence of colorectal liver metastases. Patients in the “intensive” group had a similar DFS but a significantly better OS compared to patients in the “minimal” group even when adjusting for other prognostic factors (HR 1.71; 95% CI 1.12–2.62). Interestingly, significantly more patients in the “complaints” group had metastases at more than one anatomical site at the time of recurrence compared to the “follow-up” group (47.1 vs. 73.7%, $p = 0.04$). Patients in the “follow-up” group were not signifi-

cantly more often treated with curative intent compared to the patients in the “complaints” group. However, patients in the “follow-up” group had a significantly better SAR compared to the patients in the “complaints” group (HR 3.60; 95% CI 1.92–6.74), which may be explained by the difference in disease burden at the time of recurrence.

In conclusion, our data indicates that hospitals having an NPC have a better adherence to the surveillance program for patients resected for CRC. Overall, patients in surveillance programs do have less multifocal disease recurrence and a better 3-year SAR, which substantiates the beneficial effect of this approach.

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Ethical Statement

All subjects gave informed consent and the study protocol was approved by the Medical Ethical Committee of the Erasmus MC (MEC-2007-088).

Disclosure Statement

The authors declare no conflicts of interest.

Author Contribution

R.R.J.C.B., Z.S.L., and S.B. have acquired, analysed and interpreted the data, drafted the article and approved the final version; B.E.H. has analysed the data, critically revised the article and approved of the final version; J.N.M.I. has designed the study, critically revised the article and approved of the final version.

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