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Original Research

Serum Chemokines and Quality of Life among Patients with Endometriomas and Teratomas

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Abstract

Background: Endometriosis is a chronic inflammatory condition characterized by the presence of endometrial tissue outside the uterus, which can cause pelvic pain, infertility, and other symptoms. The disease may manifest as superficial peritoneal or deep-infiltrating endometriosis or as ovarian endometriomas. Although the mechanisms associated with the regulation and production of inflammatory mediators in endometriosis have been widely investigated, the precise mechanism responsible for inflammation-induced pain remains unclear, and the findings related to the cytokine expression profile and the location of cytokines in cells are contradictory. The intensity of pain experienced by endometriosis patients is not proportional to the degree and severity of their disease. Pain has a significant impact on women suffering from endometriosis. **Methods**: The following inclusion criteria to the study were: presence of endometriomas vs teratomas, negative pregnancy test result, no prior obstetric and infertility treatment, and good health condition with no diseases or coagulation disorders. Blood samples were collected from all patients. The serum levels of chemokines were determined by ELISA. The Nottingham Health Profile (NHP) questionnaire was made. **Results**: The median serum levels of chemokines: Monocyte Chemoattractant Protein 1 (MCP-1) and Monocyte Chemoattractant Protein 3 (MCP-3) were statistically higher in the endometriomas group compared to the other two groups. In the NHP questionnaire the comparison of the subjective health dimensions in individual groups showed that the patients in the endometriomas group experienced a significantly higher intensity of "PAIN" compared to other groups. Correlation analysis between NHP dimensions and serum chemokine levels: spearman's rank correlation analysis indicated a statistically significant relationship between the "VITAL ENERGY" dimension and the level of MCP-2 ($r = –0.295$; $p = 0.022$), MCP-3 ($r = 0.254$; $p = 0.050$), and RANTES ($r = –0.353$; $p = 0.006$); between the "EMOTIONS" dimension and the level of MCP-3 ($r = 0.262$; $p = 0.043$); and between the "INCONVENIENCE IN DAILY LIFE" dimension and the level of Eotaxin-1 ($r = –0.283$; $p = 0.028$) and CCL13 ($r = –0.287$; $p = 0.026$). **Conclusions**: The chemokines serum levels (i.e., MCP-1 and MCP-3) and intensity of "PAIN" were statistically higher in the endometriomas compared to the teratomas group of women. Therefore, understanding their role in endometriosis-related pain could help in the development of novel, multidisciplinary treatments.

Keywords: endometriomas; teratomas; quality of life; health problems; Nottingham Heath Profile; SARS-CoV-2 pandemic

1. Introduction

Endometriosis is a chronic inflammatory condition characterized by the presence of endometrial tissue outside the uterus, which can cause pelvic pain, infertility, and other symptoms [1]. The disease may manifest as superficial peritoneal or deep-infiltrating endometriosis or as ovarian endometriomas [2]. Endometriosis provokes a neurovascular response mediated by hormones. The growth of ectopic endometrial tissue stimulates an estrogen-dependent chronic inflammatory reaction, causing severe pain, which can be attributed to an increased prostaglandin production accompanied by compression and/or infiltration of approximal nerves [3]. Increased expression of nerve growth factors, high nerve fiber density, angiogenesis, and changes in the pattern of uterus innervation may also play a role in the manifestation of endometriosis [3]. Chemokines (chemotactic cytokines), a small subgroup of cytokines, lead to the chemotaxis of monocytes, neutrophils, eosinophils, lymphocytes, and fibroblasts. One of the main functions of chemokines is to induce leukocytes to migrate to the site of inflammation [4]. Cytokines belonging to the CXC chemokine family, as well as their receptors, have been shown to be possibly involved in the proliferation and invasion of endometrial cells [4]. Although the mechanisms associated with the regulation and production of inflammatory mediators in endometriosis have been widely investigated, the precise mechanism responsible for inflammation-induced pain remains unclear, and the findings related to the cytokine expression profile and the location of cytokines in cells are contradictory [3,4].

Based on the location, depth, and size of lesions, endometriosis can be categorized into four stages. However,

this classification is ineffective in predicting the clinical outcomes, such as disease-related symptoms and associated discomfort [5]. The intensity of pain experienced by endometriosis patients is not proportional to the degree and severity of their disease. Pain has a significant impact on women suffering from endometriosis. Patients with chronic pain have a lower quality of life and a worse mental health condition, and are more likely to be depressed than patients living with a chronic disease without pain [6,7]. Psychological intervention is recommended for patients suffering from chronic pain [8]. Eighty percent of endometriosis patients suffer from chronic pelvic pain [9]. Unfortunately, there is currently no one tool available for assessing the level of pain experienced by endometriosis patients [8]. Two of the most frequently used pain scales, not just in the case of endometriosis, are the visual analog scale and the numerical pain rating scale [10]. In addition, the Nottingham Health Profile (NHP) questionnaire, which is a less commonly used tool, allows assessing health problems and their impact on the daily functioning of patients [11–15]. The results of this questionnaire were found to be consistent and strongly correlated with the findings of other tools, indicating that the measures are repeatable and reliable [11–15].

The current study aimed to assess the serum levels of MCP-1/Monocyte Chemoattractant Protein 1, MCP-2/Monocyte Chemoattractant Protein 2, MCP-3/Monocyte Chemoattractant Protein 3, Eotaxin-1/Eosinophil Chemotactic Protein, CCL13/Chemokine CC motif with ligand 13, RANTES/Regulated on Activation, Normal T cell Expressed and Secreted, CXCL9/Chemokine CXC motif with ligand 9, CXCL10/Chemokine CXC motif with ligand 10, CXCL11/Chemokine CXC motif with ligand 11 and determine their relationship with the quality of life or health problems among patients with endometriomas in comparison to patients with teratomas.

2. Materials and Methods

2.1 Materials

The study sample included patients with endometriomas and teratomas who were treated laparoscopically at the Gynecological and Obstetrics Clinical Hospital of the Medical University of Poznan, during 2019–2020, before the SARS-CoV-2 pandemic.

In the first stage of the study, the patients were subjected to a vaginal ultrasound examination. The initial diagnosis endometriomas (an ovarian tumor filled with hyperechoic fluid) or teratomas (hyper or hypoechoic tumor of the ovary) was made based on the ultrasound images. The final diagnosis was made based on histopathological examination of the tumors removed during surgery. The following inclusion criteria were applied for qualifying patients for surgery: presence of endometriomas vs teratomas, negative pregnancy test result, no prior obstetric and infertility treatment, and good health condition with no diseases or coagulation disorders. All the patients underwent laparoscopy during the first phase of the cycle (i.e., after the end of bleeding).

The control group included healthy patients who were undergoing preventive examination in the Gynecological Outpatient Clinic. Inclusion criteria for the study were: no ultrasound ovarian changes, negative pregnancy test result, no prior obstetric and infertility treatment, and good health condition with no diseases or coagulation disorders. After qualifying for the study, the patients came to the hospital the next morning (only to collect blood in a designated place and complete two questionnaires).

After surgery and histopathological examination, the patients were divided into three groups. Group E (endometriomas) included women who had been histologically diagnosed with endometriomas without macroscopic peritoneal endometriosis (n = 24). Group T (teratomas) included women with histologically diagnosed teratomas (n = 14). Group C (control) included healthy women who were undergoing routine, preventive gynecological examination (n = 22).

2.2 Methods

Blood samples were collected from all patients on the day of admission to the hospital, in the morning under fasting condition (i.e., 1 day before surgery). The levels of CA125 and HE4 were determined immediately after sample collection. The remaining blood samples collected for chemokine analysis were centrifuged and frozen at –20 °C.

The serum levels of chemokines were determined by ELISA (enzyme-linked immunosorbent assay). All the experiments were performed in duplicate to calculate measurement error. The concentrations of the analyzed parameters were determined in pg/mL by plotting a standard graph.

A total of 60 female patients aged 21–50 years participated in the study. Two questionnaires were used in the study: the questionnaire developed by the authors and the NHP questionnaire. The first one contained 10 questions concerning age, education, marital status, place of residence, financial situation, number of miscarriages and childbirths, and health condition [16,17]. There are different scientific tools to asses quality of life among patients, everyone emphasizes some aspects. The NHP questionnaire is a validated research tool in the Polish language. It is a simple questionnaire that allows measuring the perceived physical, social, and emotional health status of an individual. The NHP questionnaire is designed to assess the influence of social and personal factors on illness [15]. Worth noticing is also the fact, that NHP was more sensitive to physical aspect of the disease, whereas SF-36 was more coherent in evaluating social functioning [16]. In contrary to widely used QoL questionnaires there are also developing tools of narrow use, like the Endometriosis Health Profile (EHP-5) or World Endometriosis Research Foundation tool (WERF) [16].

Table 1. General characteristics of the examined groups.

		Mean	Standard deviation	95% confidence interval for significance		p
				Lower limit	Upper limit	
Age	endometriomas	33.500	7.138	30.485	36.514	0.000*
	teratomas	34.857	8.027	30.222	39.492	
	control	23.863	5.276	21.524	26.202	
Weight	endometriomas	64.608	11.187	59.770	69.446	0.272
	teratomas	67.928	12.086	60.950	74.906	
	control	62.045	8.555	58.252	65.838	
Growth	endometriomas	168.217	6.431	165.436	170.998	0.602
	teratomas	167.785	5.264	164.745	170.825	
	control	166.545	4.137	164.711	168.379	
Size of right ovary tumor [mm]	endometriomas	42.70	19.172	28.99	56.41	0.386
	teratomas	55.33	26.258	27.78	82.89	
	control					
Size of left ovary tumor [mm]	endometriomas	42.200	20.014	31.116	53.283	0.974
	teratomas	41.750	15.153	29.081	54.419	
	control					
HE 4	endometriomas	46.467	7.805	43.172	49.763	0.000*
	teratomas	43.170	7.397	38.899	47.441	
	control	32.000	8.298	28.320	35.679	
CA-125	endometriomas	46.826	32.812	32.971	60.682	0.000*
	teratomas	25.583	16.595	16.001	35.165	
	control	19.227	3.584	17.6379	20.816	

Based on estimated marginal means.

* Means difference is significant at 0.05.

It consists of two parts. The first fundamental part focuses on six dimensions, namely: "VITAL ENERGY," "PAIN", "EMOTIONS", "SLEEP DISORDERS", "SOCIAL ISOLATION", "PHYSICAL FITNESS", and "TOTAL". This part assesses the patients' current problems that have an impact on their health status, which includes their physical, psychological, and social functioning. The second part focuses on "INCOMPATIBILITIES IN EVERYDAY LIFE" and contains questions regarding the impact of the disease on the quality of life. All patients filled in the questionnaires on their own (1 day before the surgery and after their routine annual medical visit to the clinic).

2.3 Statistical Analysis

The results of the quantitative data analysis were presented as mean and standard deviation, and the median (Me) values were also calculated. Significant differences in the rank values obtained for parameters with a nonnormal distribution or parameters showing heterogeneous variance were evaluated by nonparametric Kruskal–Wallis test. The results of the statistical analysis of qualitative data obtained from the questionnaire, which concern the characteristics of the studied patients, were presented as the number of individuals in a particular category (n). The differences in qualitative characteristics between the groups were analyzed using the χ^2 independence test. The correlation between particular variables and the strength of this association was determined by calculating Spearman's rank correlation coefficients. The limit of significance was set at $p = 0.05$ in all the statistical tests.

3. Results

Group E included female patients with histopathologically confirmed endometriomas (n = 24), and their mean age was 33.50 $\pm$ 7.14 years. Group T included female patients with teratoma cysts (n = 14) who had undergone surgical treatment for benign ovarian lesions, and their mean age was 34.86 $\pm$ 8.03 years. Group C (control) comprised healthy women (n = 22) who were undergoing routine, annual gynecological examination, and their mean age was 23.86 $\pm$ 5.28 years (Table 1).

3.1 General Characteristics of the Studied Groups

All the studied women had good general health condition without coexisting diseases. The general characteristics, the size of ovarian tumors, and the levels of CA125 and HE4 markers determined in each of the analyzed groups are presented in Table 1.

3.2 Serum Chemokine Levels

The median serum levels of MCP-1 and MCP-3 were statistically higher in the endometriomas group compared to the other two groups (Table 2).

Table 2. Serum chemokine levels.

		Mean	Standard deviation	95% confidence interval for significance		*p*
				Lower limit	Upper limit	
MCP-1	endometriomas	241.031	414.457	66.020	416.041	0.056*
	teratomas	59.882	53.245	29.139	90.625	
	control	294.721	454.796	93.076	496.367	
MCP-2	endometriomas	9.283	4.556	7.359	11.207	0.786
	teratomas	9.753	3.968	7.461	12.044	
	control	12.680	10.257	8.132	17.228	
MCP-3	endometriomas	169.757	640.639	–100.760	440.275	0.056*
	teratomas	32.072	7.768	27.587	36.557	
	control	41.460	14.624	34.976	47.945	
Eotaxin-1	endometriomas	310.782	234.389	211.808	409.756	0.431
	teratomas	264.220	192.624	153.002	375.438	
	control	516.344	599.286	250.635	782.053	
CCL13	endometriomas	71.598	28.394	59.608	83.588	0.555
	teratomas	69.721	37.901	47.837	91.604	
	control	60.552	22.252	50.686	70.418	
CXCL9	endometriomas	74.963	112.327	27.532	122.395	0.754
	teratomas	46.809	67.632	7.759	85.858	
	control	240.056	749.962	-92.458	572.571	
CXCL10	endometriomas	69.677	70.826	39.770	99.585	0.704
	teratomas	66.499	35.097	46.234	86.764	
	control	92.843	122.404	38.572	147.114	
CXCL11	endometriomas	45.426	53.543	22.816	68.035	0.778
	teratomas	33.797	18.052	23.374	44.220	
	control	86.199	122.639	31.824	140.574	
RANTES	endometriomas	778.928	316.640	645.222	912.633	0.602
	teratomas	839.228	282.120	676.337	1,002.119	
	control	748.696	258.426	634.116	863.275	

Based on estimated marginal means.

* Means difference is significant at 0.05.

3.3 NHP Questionnaire

The comparison of the subjective health dimensions in individual groups showed that the patients in the endometriomas group experienced a significantly higher intensity of "PAIN" compared to other groups (Table 3). No statistically significant differences were observed between the groups in terms of the seven dimensions of life.

3.4 Correlation Analysis between NHP Dimensions and Serum Chemokine Levels

Spearman's rank correlation analysis indicated a statistically significant relationship between the "VITAL ENERGY" dimension and the level of MCP-2 (r = –0.295; p = 0.022), MCP-3 (r = 0.254; p = 0.050), and RANTES (r = –0.353; p = 0.006); between the "EMOTIONS" dimension and the level of MCP-3 (r = 0.262; p = 0.043); and between the "INCONVENIENCE IN DAILY LIFE" dimension and the level of Eotaxin-1 (r = –0.283; p = 0.028) and CCL13 (r = –0.287; p = 0.026). No statistically significant association between the NHP dimensions and the serum levels of chemokines was shown by the analysis for the control and teratomas group of women (Table 4).

4. Discussion

The predominant complaint reported by endometriosis patients is pain, which often persists even after the disease is treated. Endometriosis-related pain can be caused by several factors, including nociception, inflammation, and alterations in pain processing functions in the nervous systems. As observed in other chronic diseases, pain due to endometriosis often leads to psychological restlessness and fatigue, which can further worsen pain and reduce the quality of life of patients [18,19]. Compared to patients with asymptomatic endometriosis, endometriosis patients with pelvic pain have a poorer quality of life and mental health [8]. The issue of pain in endometriosis patients has already been studied [16,17]. Previous works, as well as the present study, showed that patients with endometriomas ex-

Table 3. Nottingham Heath Profile questionnaire.

		Mean	Standard deviation	95% confidence interval for significance		*p*
				Lower limit	Upper limit	
VITAL ENERGY	endometriomas	0.791	0.931	0.398	1.185	0.125
	teratomas	0.214	0.425	–0.031	0.460	
	control	0.590	0.734	0.265	0.916	
PAIN	endometriomas	1.375	2.183	0.453	2.296	0.035*
	teratomas	0.214	0.425	–0.031	0.460	
	control	0.454	1.738	–0.316	1.225	
EMOTIONS	endometriomas	1.333	1.129	0.856	1.810	0.307
	teratomas	1.142	1.511	0.269	2.015	
	control	1.090	1.770	0.306	1.875	
SLEEP DISORDERS	endometriomas	0.625	1.209	0.114	1.135	0.432
	teratomas	0.642	1.336	–0.128	1.414	
	control	1.136	1.641	0.408	1.864	
SOCIAL ISOLATION	endometriomas	0.208	0.588	–0.040	0.456	0.848
	teratomas	0.142	0.534	–0.165	0.451	
	control	0.227	0.685	–0.076	0.531	
PHYSICAL FITNESS	endometriomas	0.625	1.279	0.084	1.165	0.218
	teratomas	0.214	0.578	–0.120	0.548	
	control	0.227	0.685	–0.076	0.531	
TOTAL	endometriomas	4.958	5.204	2.760	7.155	0.179
	teratomas	2.571	3.588	0.499	4.643	
	control	3.727	5.649	1.222	6.232	
INCOMPATIBILITIES IN EVERYDAY LIFE	endometriomas	1.642	2.211	2.760	3.267	0.235
	teratomas	1.234	2.896	1.482	3.125	
	control	0.726	1.632	0.231	1.982	

Based on estimated marginal means.

* Means difference is significant at 0.05.

perienced a significantly higher intensity of "PAIN" compared to other groups. However, Bień *et al*. [20] highlighted that women with endometriosis rated the overall quality of life higher than the general state of health, which can be attributed to the patients' acceptance of their disease [20]. The degree of disease progression does not correlate with the subjective symptoms; therefore, the quality of life can be measured and compared using validated questionnaires [21]. Unfortunately, women with deep-infiltrating endometriosis have issues in various domains of quality of life, regardless of the questionnaire used for the assessment [22]. It seems that the NHP questionnaire could be routinely used for endometriosis patients and could be considered as a screening test by family doctors. Patients suffering from severe pain due to endometriosis can be assessed using the NHP questionnaire, and regardless of the COVID-19 pandemic, should be treated immediately.

In continuation of the previous research [23–25], the present study investigated the levels of selected chemokines and their relationship with the quality of life of patients with endometriomas. Endometriosis is a well-known chronic inflammatory condition in which endometrial tissue grows outside the uterus, mainly into the peritoneum [26]. The main source of endometriosis-related pain appears to be lesions and adhesions. However, removal of the lesions does not help with pain in all patients [9,27]. It has been observed that the peritoneal fluid undergoes several biological changes in endometriosis patients. The dynamic interactions between cytokines may contribute to developing an appropriate microenvironment for the implantation of endometrial cells as well as disease progression [26]. Chen *et al*. [28] observed that in patients with endometriosis progression peritoneal fluid chemokines (MCP-1, MCP-3, CXCL1, CXCL2) are produced at a significantly higher level [28]. CXCL12 can affect the proliferation, migration, and invasion of endometriotic cells [29]. The ligand–receptor complexes such as CXCR4–CXCL12 and CXCL12–CXCR7 are also activated in endometriosis [30]. Pizzo *et al*. [26] reported that the serum levels of MCP-1 and IL-8 decreased with increasing severity of endometriosis, while the concentration of peritoneal fluid significantly increased in severe stages [26]. Similarly, Hornung *et al*. [31] highlighted that the level of eotaxin-1 in the peritoneal fluid was higher in patients with moderate-to-severe endometriosis [31], suggesting that this protein interacts with other cytokines and immune cells, contributing to inflam-

Table 4. The correlation analysis between NHP and serum chemokine levels.

			MCP-1	MCP-2	MCP-3	Eotaxin-1	CCL13	CXCL9	CXCL10	CXCL11	RANTES
rho Spearmana	VITAL ENERGY	r	–0.102	–0.295*	0.254*	–0.222	–0.098	–0.011	–0.010	–0.001	–0.353**
		p	0.439	0.022	0.050	0.088	0.455	0.935	0.942	0.991	0.006
	PAIN	r	–0.125	–0.107	0.220	–0.144	–0.127	–0.163	–0.042	–0.028	–0.141
		p	0.342	0.414	0.091	0.271	0.332	0.214	0.751	0.829	0.283
	EMOTIONS	r	–0.002	–0.250	0.262*	–0.107	–0.116	0.101	0.234	0.085	–0.064
		p	0.989	0.054	0.043	0.414	0.378	0.441	0.072	0.518	0.627
	SLEEP DISORDERS	r	0.140	0.040	0.107	0.125	–0.217	–0.078	–0.056	–0.171	–0.077
		p	0.286	0.762	0.417	0.340	0.096	0.552	0.671	0.193	0.560
	SOCIAL ISOLATION	r	0.090	–0.100	0.196	–0.068	–0.059	0.099	0.116	0.168	–0.195
		p	0.492	0.449	0.134	0.607	0.656	0.451	0.377	0.199	0.136
	PHYSICAL FITNESS	r	–0.182	–0.181	–0.006	–0.188	–0.247	–0.091	–0.067	–0.082	–0.192
		p	0.165	0.167	0.965	0.151	0.057	0.491	0.611	0.533	0.142
	TOTAL	r	–0.017	–0.181	0.253	–0.122	–0.214	0.009	0.084	–0.008	–0.225
		p	0.898	0.168	0.051	0.353	0.100	0.947	0.522	0.953	0.084
	INCOMPATIBILITIES IN EVERYDAY LIFE	r	–0.185	0.045	0.007	–0.283*	–0.287*	–0.120	–0.065	–0.170	0.068
		p	0.157	0.733	0.956	0.028	0.026	0.360	0.624	0.193	0.603

Based on estimated marginal means.

* Means difference is significant at 0.05.

** Means difference is significant at 0.005.

mation [31]. Măluțan *et al*. [32] found increased levels of MCP-1 and IL-8 and lower levels of Eotaxin-1 in the serum of endometriosis patients, which may indicate that the immune activity is imbalanced in this disease [32]. These findings are in line with the results of the present study which demonstrated that the median values of MCP-1 and MCP-3 cytokines were statistically significantly higher in the endometriomas group.

Indeed, it seems that the effects induced by pelvic endometriosis, including the breakdown of peritoneal homeostasis and the production of pro-inflammatory and pro-angiogenic cytokines, are responsible for the altered innervation and modulation of pain pathways [33,34] and perhaps the higher intensity of pain. In this study, the correlation analysis did not show any statistically significant relationship between "PAIN" and the level of serum chemokines in the studied endometriomas patients. However, a statistically significant relationship was found between the "VITAL ENERGY" dimension and the serum levels of MCP-2, MCP-3, and RANTES; between the "EMOTIONS" dimension and the serum level of MCP-3; and between the "INCONVENIENCE IN DAILY LIFE" dimension and the serum levels of eotaxin-1 and CCL13. According to Roch *et al*. [35], cytokines and chemokines are not reliable markers for predicting the presence of endometriosis in women who show the symptoms of this disease [35].

Patients suffering from endometriosis, regardless of pathogenesis [36], experience pain every day [8–10,18–20] and often require immediate consultation, planned surgeries, or even emergency surgical interventions. SARS-CoV-2 pandemic has significant negative consequences for endometriosis patients worldwide, including postponed surgeries [37–39], reduced quality of life [40], worsened access to care [41], difficulties in repeating painkiller or hormone prescriptions, and missed appointments [42]. Clinicians should remember that patients suffering from endometriosis or its symptoms, especially pain, need long-term treatment and consultation with doctors. In case of contraindications to a face-to-face appointment, patients can use telemedicine techniques to have regular contact with clinicians [43,44]. In particular, patients who have had multiple surgeries or who experience sudden, substantial bleeding should be aware of the symptoms that prompt a visit to the gynecological emergency unit.

5. Conclusions

The chemokines serum levels (i.e., MCP-1 and MCP-3) and intensity of "PAIN" were statistically higher in the endometriomas compared to the teratomas group of women. Therefore, understanding their role in endometriosis-related pain could help in the development of novel, multidisciplinary treatments.

Author Contributions

MWo, KCW, AJ participated in design of the study and overseeing research. KCW, KW, PR performed the research, with help from IP, KB, MWi. KCW, KW, MWo wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

The methods used for patient enrollment, study material collection, and sample storage were approved by the Bioethics Committee at the Poznan University of Medical Sciences (Resolution No. 1127/18).

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Conflict of Interest

The authors declare no conflict of interest. The funders had no role in the design of the study. In the collection, analyses, or interpretation of data, in the writing of the manuscript, or in the decision to publish the results. KCW, KW and M-jW are serving as one of the Guest editors of this journal. We declare that KCW, KW and M-jW had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to GC.

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