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Coping, Emotional Processing, and Cancer-Related Symptoms in Breast Cancer Survivors: Cross-Sectional Secondary Analysis of the REPAT Study

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ABSTRACT

Objective: As survival rates from breast cancer increase, the post-treatment period poses several challenges, including a high burden of cancer-related symptoms that interfere with quality of life. This study aims to provide a better understanding of the relationship between coping (approach and avoidance), emotional processing (emotional awareness and acceptance of emotions), and cancer-related symptoms.

Methods: This is a cross-sectional, secondary analysis of baseline data from a randomized controlled trial entitled “The Role of Emotional Processing in Art Therapy” (REPAT) study. Participants included 179 breast cancer survivors 6.1 months on average after completing primary treatment. Participants completed questionnaires measuring approach and avoidance coping, acceptance of emotions, cancer-related symptoms (depression, fatigue, and pain), and the Level of Emotional Awareness a performance scale. Hierarchical linear regressions were performed while adjusting for background variables.

Results: Participants experienced significant depressive symptoms (51.7%), fatigue (78.8%), pain interference (78%), and pain intensity (66%). There were strong correlations between depression, cancer-related fatigue, and pain. After adjusting for confounders, acceptance of emotions was negatively associated with depression, and avoidance coping was positively associated with depression, cancer-related fatigue, and pain interference. Emotional awareness and approach coping were not associated with cancer-related symptoms, but both were significantly associated with acceptance of emotions.

Conclusions: Breast cancer survivors' post-treatment period presents the challenge of dealing with elevated cancer-related symptoms. Regardless, breast cancer survivors with high acceptance of emotions and low avoidance coping experienced fewer cancer-related symptoms.

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1 | Background

Cancer-related symptoms may co-occur in Breast Cancer Survivors (BCS) [1], affecting many areas of life. A meta-analysis [2] reported a global depression prevalence of 32.3% among BCS. A meta-analysis [3], reported approximately one in four BCS reported severe Cancer-Related Fatigue (CRF) (26.9%), which in some cases was reported to last 5–10 years post-diagnosis and negatively affect QoL. The pooled prevalence of significant pain among BCS post-surgery was 29.8% ($n = 3746$), 27.3% among BCS post-radio therapy ($n = 15,019$), and 21.8% ($n = 135,437$) among BCS receiving various treatment combinations [4].

Depression, CRF, and pain are intercorrelated, often sharing clinical symptoms, and biological pathways (e.g., inflammation), creating a vicious amplifying cycle. However, their manifestation is not always simultaneous [1]. These symptoms are associated with several sociodemographic variables for example, lower income [2] and educational levels [5], chemotherapy, and not having a partner [3], being younger, comorbid diseases, and long, rigorous treatment courses, including treatment combinations [3, 5]. A systematic review demonstrated that coping and emotion regulation directly affect psychological and physiological symptoms (e.g., depression, CRF, and anxiety) [6]. Despite this relationship, pain symptoms were not included in the review [6], and fatigue was reported in only two studies associated with coping [7, 8].

Lazarus and Folkman's [9] transactional theory of stress and coping, theorizes that the intensity and effectiveness of a stress response are influenced by cognitive appraisal and environmental resources. According to the theory, the individual's perception of the stressful event, rather than the event itself, along with the assessment of available personal resources, impacts their coping strategies and subsequent responses to the stressor. Additionally, coping strategies may impact an individual's emotional state, including negative affect, and symptoms such as depression and anxiety.

Approach and Avoidance Coping refers to “constantly changing cognitive and behavioral efforts to manage specific external and/or internal demands that are appraised as being taxing or exceeding the resources of the person” [9, p. 141] and which are classified to align with motivations of approaching and avoiding emotions [10]. *Approach coping* involves cognitive or behavioral efforts to engage actively with the demands associated with the stressor [11]. *Avoidance coping* is the tendency to distance oneself emotionally, cognitively, and behaviorally from demands associated with the stressor [11]. In a meta-analysis ($n = 11,948$), avoidance coping strategies were found to be associated with high negative affect, low positive affect, and low physical health [12]. Also, the meta-analysis found approach coping, including acceptance of cancer and positive reappraisal, was associated with high positive affect and high psychological and physical health. A systematic review reported that in 95% of studies (43 studies, among them 39 with early-stage breast cancer), coping (approach and avoidance) was a statistically significant predictor of depression, anxiety, and health-related QoL [13]. Emotional processing as an active attempt to acknowledge and understand emotions and gain awareness of

the emotions arising from the stressors, may support coping strategies and be a resource for coping through approaching emotions [14].

Emotional processing is an active attempt to acknowledge, explore meanings, validate, reflect, and verbally (or not) label, reappraise, and be aware of arising emotions and somatic sensations, and understanding one's and others' emotional experiences [15, 16]. In this process, a person nurtures feelings and accepts that emotions provide valuable information. Emotional processing might change a person's understanding of themselves and the situation, as well as decrease their guilt, shame, or fear. By engaging with differentiated and processed emotional experiences and adopting an accepting approach, one might better express and cope with emotions [17]. Poor emotional processing and avoiding or repressing emotions for prolonged periods may result in the use of avoidant coping strategies [11].

Emotional processing referring to acceptance of emotions and emotional awareness is positively associated with emotional and physical health outcomes [18–20]. Acceptance of emotions may be associated with decreased emotional distress and increased survival time among BCS [18, 19]. However, emotional awareness has not yet been associated with psychological or physical outcomes in BCS.

Despite the above-mentioned studies [18, 19] and meta-analysis [12] emphasizing the positive impact of approach coping and emotional processing on cancer-related symptoms, one study [21] using several coping strategies (relational coping, active coping, positive reinterpretation, religious coping, substance use, denial, and blame), found approach coping (active coping) was negatively associated with mental health (5–15 years from breast cancer diagnosis). Therefore, in the present study approach coping includes both a broad definition (positive reinterpretation, problem-solving, seeking social support, and acceptance of cancer) in addition to coping through emotional processing and expression [22], which is expected to perform differently as a predictor of BCS symptoms.

There are only a few studies of the relationship between acceptance of emotions, and cancer-related symptoms among BCS post-treatment [19], and results regarding the associations between coping and CRF and pain are limited. Additionally, the relationship between emotional awareness and BCS symptoms has not been examined. Therefore, this study aimed to examine the distinct relationship between approach and avoidance coping (coping), emotional awareness and acceptance of emotions (emotional processing), and BCS symptoms of depression, CRF, and pain (cancer-related symptoms).

2 | Methods

2.1 | Participants and Procedure

This descriptive, cross-sectional study was conducted as a secondary analysis of the baseline data of the randomized

controlled trial entitled “The Role of Emotional Processing in Art Therapy for Breast Cancer Patients” (REPAT) [23]. Participants were recruited between May 2019 and March 2022, from the Integrative Oncology Medicine unit of the Davidoff Center for Cancer Treatment at Rabin Medical Center, Israel. The medical staff of Davidoff Center recruited participants through phone calls and personal applications during follow-up appointments and collected informed consent and medical information. In addition, participants were recruited through social media and community organizations by the REPAT team that collected medical information and self-report questionnaires. An equivalent of US\$200 in New Israeli Shekels was provided to each participant as compensation. The study was approved by the Helsinki Committee of the Beilinson Hospital (0778-17-RMC) and the Ethics Committee of the Faculty of Welfare and Health Sciences at the University of Haifa (234/18).

The eligibility criteria included: (1) adult female (> 18 years) BCS with primary, first-recurrence breast cancer (including recurrence of breast cancer) or second primary diagnosis of breast cancer; (2) any additional or replacement standard medical treatment for cancer (i.e., surgery, chemotherapy, radiotherapy, neo-adjuvant chemotherapy, endocrine therapy); (3) not less than 3 months after finishing chemotherapy or radiotherapy, not less than 1 month after surgery (lumpectomy, mastectomy, or reconstructive surgery), and no more than 19 months after the end of treatment; (4) able to complete assessments in Hebrew. Ineligibility criteria included: (1) diagnosis or lifetime history of bipolar disorder, schizophrenia, or schizoaffective disorder; (2) fibromyalgia or chronic fatigue syndrome; (3) current suicidal ideation; (4) dementia or other cognitive disorder that would preclude informed consent.

Two hundred eighty-seven BCS met the inclusion criteria and signed informed consent. Of them, 18 dropped out for various reasons (e.g., loss of follow-up, no interest, work, lack of time, and medical conditions). Data from another 28 participants was excluded due to missing data. In total, 241 participants were included in the final baseline analysis of the REPAT study. However, due to cultural and value differences, beyond the scope of this paper, a subsample of 179 Jewish participants was included in this analysis. Further details regarding these differences can be found in Hebi, Czamanski-Cohen et al. [24]. A priori power analysis using G*Power for multiple regression analysis, with 12 variables (study and background), showed that a sample of 127 participants is adequate sample size for analysis at a power of 0.80, and $\alpha = 0.05$ (medium effect size) [25].

Measures of emotional awareness and acceptance of emotions, along with approach and avoidance coping, were translated for the present study from English into Hebrew by two bilingual experts using the back translation method and tested in a pretest phase (not published yet). Pain intensity and interference were translated from English into Hebrew and validated by the Patient-Reported Outcomes Measurement Information System–PROMIS [26]. A Hebrew translation and validation of the depression scale [27], and the CRF scale [28] were used.

2.2 | Measures

2.2.1 | Demographic and Medical Information

Sociodemographic variables (categorical variables e.g., age, religiosity), and medical information (e.g., cancer diagnosis, cancer stage) were collected.

2.2.2 | Coping and Emotional Processing

The Situational Approach and Avoidance coping scales [11, 14, 29] were adjusted to the experience of women coping with breast cancer [11]. The 24-item situational approach scale consists of 16 items from the COPE scale using four subscales (problem-solving, positive reinterpretation, acceptance of cancer, and seeking social support) [29] and eight items from the Coping through Emotional Approach [14] scale using two subscales (emotional expression and emotional processing). Situational avoidance coping is a 12-item scale [11] using three subscales from the COPE scale (behavioral disengagement, mental disengagement, denial [29]).

As Carver, Scheier, and Weintraub [29] suggested, we performed an exploratory factor analysis of principal component analysis using all these scales to determine which factors capture most features and a Kaiser-Meyer-Olkin and Bartlett's test of sphericity to check their sufficiency for factor analysis. Additionally, we conducted a scree plot presenting an eigenvalue of two factors. Accordingly, we examined a rotation method of varimax with Kaiser normalization (item loadings on the indexes) using two factors. Three items from the situational approach coping had low loadings and were dropped from further analysis. Items from the situational avoidance coping scale had good loadings and matched the original scale [11]. Further details of the factor analysis can be found in Supporting Information S1: Tables S1 and S2. Cronbach's alpha for the present study (after factor analysis) was respectively 0.91 and 0.72 for approach and avoidance coping.

Emotional awareness was assessed using the Levels of Emotional Awareness Scale (LEAS) performance measure in its short (10-item) version [15]. In response to evocative interpersonal scenarios, participants were asked to write about their and the others' expected feelings, using the word “feel” in their answers. Responses were scored on a 0-to-50 scale. Higher scores reflect greater differentiation and complexity of emotional awareness in self and others. Cronbach's alpha for the present study was 0.70.

The 13-item Acceptance of Emotions Scale was designed to measure the extent to which participants accept and nurture their feelings [18]. Responses on a 10-point Likert scale assess how much each statement describes the participant's feelings, from 0 (*not at all like me*) to 100 (*exactly like me*). Cronbach's alpha for the present study was 0.94.

2.2.3 | Cancer-Related Symptoms

Depressive symptoms were measured using the Center for Epidemiologic Studies-Depression (CES-D) scale (10 items), using a frequency scale of 0 (*never*) to 3 (*most of the time*) [27]. The suggested cutoff for clinical depression is 10 points [30]. Cronbach's alpha for the present study was 0.79.

CRF was measured using the Fatigue Symptom Inventory scale (13 items and one qualitative question), designed for measuring CRF intensity (four items), interference (seven items), and duration (two items) with QoL [31]. Intensity and interference were rated from 0 (*not at all fatigued/no interference*) to 10 (*extremely fatigued/extreme interference*). Duration was measured on a scale from 0 (*no days*) to 7 (*all days*) over the past week and by the percentage of time fatigue was present each day. The suggested cutoff for being clinically fatigued is three points (derived by calculating the mean across the four intensity items) [32]. Cronbach's alpha for the present study was 0.95.

Pain was measured using the PROMIS six-item Pain Interference Scale (PIQ-6a) which measured how much pain interfered with various aspects of life in the past 7 days, and the three-item Pain Intensity Scale (3a) which measured the pain's intensity [33]. The pain interference and intensity Likert scale ranged from 0 (*not at all interfered/intense*) to 4 (*very much interfered/extremely intense*). According to the PROMIS coding instructions, item-level calibration *t* scores were calculated for each measurement using the Research Electronic Data Capture (REDCap) auto-score, based on raw scores. The cutoff for clinic pain interference and intensity is a *t* score above 50 [34]. The present study's Cronbach's alpha for pain interference and intensity were respectively 0.95 and 0.96.

2.3 | Data Analysis

We used IBM SPSS (version 27) to examine the study's database. We imputed an item mean within the scale for each participant with 20% or fewer missing responses in the scale [35]. For all variables, descriptive statistics were first calculated. Pearson correlations were used to assess correlations between the study variables. *T* tests and analysis of variance (ANOVA) were used to compare differences between study variables and background variables (demographic/medical). We conducted hierarchical linear regressions controlling for background variables to assess the adjusted variance of each cancer-related symptom explained by coping strategies and emotional processing variables.

3 | Results

Table 1 contains the sociodemographic and medical characteristics of study participants. Most women were married, and their income was average or above average for their communities. Most had early-stage (0, 1, or 2) breast cancer and they had completed primary treatment (surgery, chemotherapy, and radiation therapy) 6.11 ± 4 months before study entry.

The average scores of cancer-related symptoms were above the clinical cutoff points, for depression (52%), CRF (78.8%), pain interference (78%), and pain intensity (66%). In univariate analyses, higher acceptance of emotions and lower avoidance coping were both significantly associated with lower depression ($r = -0.37$ and 0.26 , respectively) and with lower CRF ($r = -0.17$ and 0.30 , respectively). Further, lower avoidance coping was significantly associated with lower pain interference ($r = 0.20$). Neither emotional awareness nor approach coping was associated with cancer-related symptoms but interestingly, both were positively associated with higher acceptance of emotions ($r = 0.18$ and 0.49 , respectively). Cancer-related symptoms were positively and strongly correlated with each other. See Table 2 for Pearson zero-order correlations, means, and standard deviations of study variables.

Multiple regression analyses were used to assess the associations of coping and emotional-processing variables with cancer-related symptoms. Study variables were examined for significant differences related to demographic and cancer characteristics. ANOVA and *t*-tests revealed only income and religiosity levels were significantly correlated with cancer-related symptoms. Therefore, they were included as controlled variables in Step 1 of the regression analyses.

Step 1 showed income level was negatively associated with depression and CRF, but not with pain intensity or interference, meaning that when income level was lower, depression and CRF were higher. In Step 2, the independent variables of emotional awareness, acceptance of emotions, approach, and avoidant coping were entered. Acceptance of emotions was negatively related to depression but not to CRF or pain (interference and intensity), meaning that the greater the acceptance of emotions, the lower the depression. Coping through avoidance was positively related to depression, CRF, and pain interference but not pain intensity. This means that the more coping through avoidance was used, the higher the depression, CRF, and pain interference. Income level, acceptance of emotions, and coping through avoidance explained 24.7% of the variance in depression. Income level and coping through avoidance explained 21.2% of the variance in CRF. Additionally, coping through avoidance explained 3.4% of the variance in pain interference, but the model was not significant. See Table 3 for the hierarchical multiple linear regression analyses.

4 | Discussion

The average levels of depression, pain, and CRF were above clinical cutoff points among the BCS in this sample of Jewish women in Israel who had finished primary treatment for breast cancer 6 months (on average) before study enrollment. Depression levels were within the upper range of findings from one meta-analysis [2], and CRF rates were high compared to one meta-analysis [3], but the meta-analysis reported high heterogeneity. Compared to results among BCS in Israel, CRF levels were similar [36]. The present study's pain levels were high compared to another meta-analysis [4] but like those of BCS in Israel [37]. Psychological, social, and physical challenges, such as elevated anxiety levels [5], pain catastrophizing

TABLE 1 | Demographic and characteristics of Jewish breast cancer survivor participants.

	<i>n</i> (%)	<i>M</i> (<i>SD</i>)
Age (years)		
26–35	6 (3.4)	
36–45	35 (19.6)	
45–70	121 (67.6)	
Older than 70	17 (9.5)	
Education		
High school and below	33 (18.4)	
Certificate (14 years) and above	145 (81)	
Employed	103 (57.5)	
Income		
Below average	24 (13.4)	
Average	89 (49.7)	
Above average	64 (35.8)	
Married or in long-term relationship	127 (70.9)	
Have children	159 (88.8)	
Level of religiosity		
Secular	99 (55.3)	
Traditional	49 (27.4)	
Religious	31 (17.3)	
Cancer stage		
Stage 0	5 (2.8)	
Stage 1	58 (32.4)	
Stage 2	72 (40.2)	
Stage 3	30 (16.8)	
Stage 4	8 (4.5)	
Treatment (combinations are possible)		
Chemo	111 (62)	
Radio	147 (82.1)	
Surgery	165 (92.2)	
Hormonal	133 (74.3)	
Biological	37 (20.7)	
Months from the end of treatment to the baseline		6.11 (3.97)
Months from diagnosis to the baseline		13.75 (5.7)
Body mass index		26.72 (5.27)

Abbreviations: *M* (*SD*), mean and standard deviation; *n* (%), number of participants and percent.

[38], and coping with the long post-treatment course, may elevate the cancer-related symptoms and be exhausting. How Jewish women in Israel come to have higher symptoms than other populations of breast cancer patients has yet to be elucidated. Experiencing the stress of the COVID pandemic during data collection from over 50% of participants in this study may account for some of this difference.

In accordance with a systematic review [1], there are strong interrelationships between cancer-related symptoms, which can lead to a snowball effect, which means that symptoms' bidirectional effects could amplify the persistence of a given

symptom. Considering these interrelationships, the present study and its main findings are important as high acceptance of emotions and low avoidance coping may potentially dampen the above-mentioned snowball effect.

The associations between high avoidance and high depression, fatigue, and pain interference in this study align with a meta-analysis and systematic review [12, 13] that reported associations between suppressing or avoiding emotions and high negative affect and lower physical health. In the meta-analysis [12] a few studies examined the associations between avoidance coping and pain, with no associations found. Our study is

TABLE 2 | Pearson zero-order correlation between study variables and means.

Variable	1	2	3	4	5	6	7	<i>M</i> (<i>SD</i>)
1. Depression								10.54 (5.86)
2. CRF total (13 items) ^a	0.50**							57.69 (28.8)
3. Pain intensity	0.25**	0.40**						55.86 (12.68)
4. Pain interference	0.30**	0.49**	0.79**					57.46 (9.83)
5. Avoidance coping ^b	0.26**	0.30**	0.03	0.20**				1.84 (0.47)
6. Approach coping ^c	−0.04	0.04	0.01	0.04	0.10			3.20 (0.57)
7. Acceptance of emotions	−0.37**	−0.17*	−0.11	−0.12	−0.05	0.49**		63.56 (23.31)
8. Emotional awareness	0.06	0.12	−0.08	−0.08	0.07	0.09	0.18*	28.50 (6.41)

Abbreviations: CRF, cancer-related fatigue; *M* (*SD*), mean and standard deviation.^aCRF intensity (four items) *M* = 5.00; *SD* = 2.29.^b*N* = 165.^c*N* = 146.**p* < 0.05, ***p* < 0.01 (2-tailed).**TABLE 3** | Multiple linear regression analyses of the associations (standardized coefficients beta) between the study's variables and cancer-related symptoms.

Model		Depression β	CRF β	Pain interference β	Pain intensity β
1	Income level	−0.25**	−0.29**	−0.08	−0.12
	Religiosity	0.01	0.15	0.06	0.01
	<i>F</i>	4.55*	9.35**	0.80	1.07
	<i>R</i> ²	0.63	0.11	−0.00	0.00
2	Income level	−0.23**	−0.27**	−0.09	−0.14
	Religiosity	−0.01	0.10	0.03	0.01
	Avoidance coping	0.29**	0.30**	0.18*	−0.01
	Approach coping	0.13	0.03	0.09	0.06
	Acceptance of emotions	−0.44**	−0.12	−0.16	−0.11
	Emotional awareness	0.04	0.11	−0.13	−0.11
	<i>F</i>	8.47**	7.09**	1.81	0.76
	<i>R</i> ²	0.28	0.21	0.03	−0.01

Abbreviations: β , beta coefficient; CRF, cancer-related fatigue.**p* < 0.05, ***p* < 0.01.

the first to find an association between avoidance coping and pain interference. The fear of pain and avoiding situations that may provoke pain [38] may explain this association.

Fear of pain (including pain anticipation) and pain catastrophizing may provoke the behavioral response of avoiding the threatening situation, leading to greater fear of pain and disability [38]. Physical disability (inactivity) affects the musculoskeletal, cardiovascular, and inflammatory-immune systems associated with increased pain [5], contributing to a vicious cycle that may exacerbate the pain.

Avoiding emotions can be an exhausting affair, especially during a continual health crisis, which requires considerable energy to suppress, avoid, and deny emotions [21]. As a result, coping through avoidance of emotions may be related to higher CRF, as found in this study. However, avoidance coping may be a useful short-term strategy (e.g., during acute treatment) to enhance a person's perception of control and reduce emotional arousal

[18]. An urge to control and manage emotional situations results from feelings of general anxiety strongly associated with CRF [1]. However, as this study's findings indicate, excessive avoidance coping is associated with increased cancer-related symptoms during the posttreatment period.

The association between increased acceptance of emotions and decreased symptoms of depression in this study accords with one previous report [19]. Research has demonstrated a link between higher approach coping and lower depression around the time of breast cancer diagnosis and a significant decrease in approach coping over time [10]. Despite this, our study found no significant associations between approach coping or emotional awareness and cancer-related symptoms. This may be the result of our assessments being done much later in the disease course (13.75 ± 5.7 months after diagnosis as compared to 2–14 months post diagnosis [10]) when approach coping is waning. According to Lazarus and Folkman [9], coping efforts decrease once a stressor has been resolved. Post-treatment may mark such a

period when less approach coping is needed. According to a recent systematic review, time from diagnosis plays an important role in predicting coping strategies [39]. The review suggests representing coping with a longitudinal model, and thinking of cancer adaptation as a process, is a better way to understand how patients adjust to cancer and use different coping strategies over time. Further investigation of the association of emotional processing and coping at varying times after diagnosis is needed to set the stage more effectively for designing interventions that can help ameliorate persistent cancer-related symptoms.

4.1 | Limitations

The cross-sectional design of this study limited us from concluding directionality and causality. Further, the use of self-report measures targeting emotional processing and coping prevented us from fully portraying the participants' experiences, expectations, and behaviors. Part of the data was collected during the COVID-19 pandemic. This may limit our findings' applicability to breast cancer patients who do not have pandemic restrictions. Among breast cancer patients in the United Kingdom, concern about COVID-19 and disruptions in oncology services were associated with elevated levels of depression [40]. However, an Israeli study during COVID-19 among cancer patients found their mean psychological distress level to be low, and the patients were determined to continue treatment [41]. In addition, the results of the present study are limited to Israeli Jewish women BCS and may not demonstrate the same results in other populations.

4.2 | Conclusions and Implications for Cancer Survivors

This study's findings of high clinical symptom levels and intercorrelations between depression, CRF, and pain emphasize the need to understand emotional processing and coping and how they may help to reduce cancer-related symptoms. These results confirm the findings of a meta-analysis [12] that associated avoidance coping with higher depression. Our study adds novel findings regarding higher avoidance coping associated with CRF and pain interference. In addition, these results support findings [19] of low depression associated with acceptance of emotions. Our findings may have practical implications. They add knowledge supporting the importance of identifying and considering early psychosocial intervention for BCS with low acceptance of emotions, excessive use of avoidance, and especially those from low income because these can compromise their rehabilitation and contribute to lower QoL [6]. This study provides information to help oncology patients understand how accepting their emotions may regulate depression and improve mental and physical health and QoL.

Author Contributions

K.H., J.C.-C. M.C., and K.L.W. were responsible for the study design. K.H., J.C.-C. and O.C. were responsible for patient recruitment and

data collection, and K.H. was responsible for data analysis, with the guidance of J.C.-C. and M.C. The first draft of the manuscript was written by K.H. and J.C.-C., M.C. and K.L.W. commented on the following versions of the manuscript. All authors read and approved the final manuscript.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.