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Predictors of elevated C-reactive protein among pre-treatment, newly diagnosed breast cancer patients: A cross-sectional study

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ABSTRACT

Background & Aims: Accumulating evidence showed that inflammation contributes markedly to cancer progression, with C-reactive protein (CRP) being one of the lengthily studied inflammation marker. For breast cancer (BCa), pre-treatment elevated CRP upon diagnosis was linked with increased mortality. This study aimed to identify factors predictive of elevated CRP in pre-treatment BCa population that can serve as potential therapeutic targets to reduce inflammation.

Methods: This is a cross-sectional study using multiple logistic regression to identify predictors of elevated CRP among pre-treatment, newly diagnosed BCa patients. Studied variables were socio-demographic and medical characteristics, anthropometric measurements [body weight, Body Mass Index, body fat percentage, fat mass/fat free mass ratio, muscle mass, visceral fat], biochemical parameters [albumin, hemoglobin, white blood cell (WBC), neutrophil, lymphocyte], energy-adjusted Dietary Inflammatory Index, handgrip strength (HGS), scored Patient Generated-Subjective Global Assessment, physical activity level and perceived stress scale (PSS).

Results: A total of 105 participants took part in this study. Significant predictors of elevated CRP were body fat percentage (OR 1.222; 95 % CI 1.099–1.358; $p < 0.001$), PSS (OR 1.120; 95 % CI 1.026–1.223; $p = 0.011$), low vs normal HGS (OR 41.928; 95 % CI 2.155–815.728; $p = 0.014$), albumin (OR 0.779; 95 % CI 0.632–0.960; $p = 0.019$), and WBC (OR 1.418; 95% CI 1.024–1.963; $p = 0.036$).

Conclusion: Overall, predictors of elevated CRP in pre-treatment, newly diagnosed BCa population were body fat percentage, PSS, HGS category, albumin and WBC.

1. Introduction

Breast cancer (BCa) is the most commonly diagnosed malignancy with an estimated incidence of 2.26 million globally, and the primary cause of cancer mortality in women with the figure of 685, 000 in year 2020 alone [1]. Similarly, BCa is the most common malignancy among women and regardless of gender in Malaysia [2]. Over the years, there has been increasing evidence to show that inflammation contributes markedly to cancer growth and progression [3]. Today, the recognition of inflammation as a cancer hallmark has provided opportunity to target these inflammatory responses to improve cancer outcomes [3].

C-reactive protein (CRP) is one of the most lengthily studied inflammation marker in cancer [4]. CRP level above 10 mg/L is commonly recognized as a sign of acute inflammation whereas lower readings are exhibited in low-grade chronic inflammation [5]. For BCa, CRP has been suggested as a long-term prognostic marker due to its consistent association [6,7]. Pre-treatment elevated CRP upon diagnosis was linked with increased BCa mortality [8]. In post-diagnosis stage,

Abbreviations: CRP, C-reactive protein; BMI, Body mass index; FM/FFM, Fat mass/fat free mass; WBC, White blood cell; E-DII, Energy-adjusted dietary inflammatory index; HGS, Handgrip strength; PG-SGA, Patient generated - subjective global assessment; MET-min/week, Metabolic equivalent minutes per week; PSS, Perceived stress scale; IKN, Institut Kanser Negara; NMRR, National Medical Research Registry; MREC, Medical Research and Ethics Committee.

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elevated CRP was associated with poorer survival in several cancer including BCa, signifying the implication of inflammation towards cancer progression [4].

Although anti-inflammatory pharmaceutical approach is available to cancer survivors, there are significant side effects such as anemia, intestinal bleeding and perforation [9]. In recent years, more alternative efforts such as exercise and healthy body composition are being explored to lessen chronic inflammation; and these options had been showing positive outcomes in decreasing inflammation-associated cytokines and CRP [10–12]. More literature has emerged on the role of dietary components towards chronic inflammation including the development of dietary inflammatory index (DII) to study the diet inflammatory capacity as a whole [13,14].

Therefore, this study aimed to identify factors predictive of elevated CRP levels in a newly diagnosed BCa population who has yet to commence on oncological treatment in Malaysia. We hypothesized that besides socio-demographic characteristics, potentially modifiable anthropometric, dietary, behavioural, and psychosocial factors would be associated with elevated CRP. By identifying the predictors of elevated CRP levels, it could provide insights as the basis for future interventional studies intended to improve potential therapeutic targets to reduce inflammation in BCa.

2. Materials and methods

2.1. Study design and participants enrolment

Universal sampling was used in this cross-sectional study carried out at Institut Kanser Negara (IKN), the national referral center for oncology patients all over Malaysia. Participants were approached to participate during outpatient visit. The inclusion criteria include (1) Malaysian female aged 18 years old and above, (2) newly diagnosed BCa confirmed with biopsy, (3) yet to start on oncological treatment be it chemotherapy, radiotherapy, hormonal or immunotherapy, and (4) at least 4-weeks post operation if undergone breast surgery. Conversely, the exclusion criteria include (1) complicated with fluid retention illness, (2) comorbid of autoimmune or inflammatory conditions such as lupus, (3) multiple primary malignancies, (4) comorbid of psychiatric disorder including major depressive disorder, (5) on long term anti-inflammatory medication such as steroid, and (6) had acute or recent infection in less than 4 weeks ago. Out of the 128 eligible patients who agreed to participate, four were excluded due to incomplete questionnaire. Another 19 were excluded before statistical analysis stage due to CRP$\geq$10 mg/L to avoid potential confounder where acute infection cannot be ruled out. None of the participants reported implausible total daily energy intake of $<$600 kcal or $>$3500 kcal. Overall, 105 participants were included in the final statistical analysis (response rate = 82.0 %). This study was registered in the National Medical Research Registry Malaysia and ethical approval received from Medical Research and Ethics Committee of Ministry of Health, Malaysia. Verbal and written informed consent were sought from all participants prior assessment and the period of assessment was around 45 min to one hour.

2.2. Sample size calculation

The sample size calculation was performed using single correlation formula [15]. Prior data indicated that the correlation coefficient between body weight and CRP was 0.40 [16]. Hence, a minimum sample size of 47 samples were able to reject the null hypothesis with probability (power) 0.80. The Type I error probability associated with this test of a null hypothesis was 0.05. With an additional of 50 % dropout rate, the sample size required was 94 samples.

2.3. Study variables

2.3.1. Socio-demographic and medical characteristics

Face-to-face interview and record retrieval from computerized Hospital Information System using standardized data collection form were used to collect socio-demographic information including age, household income, race, education level, and marital status as well as medical characteristics including menopausal status, smoking history, cancer staging, duration of cancer onset, hormone receptor status, history of breast surgery and comorbidities.

2.3.2. Anthropometric measurements

All anthropometric data were gathered by a qualified dietitian using standardised protocols before the interview session. Body weight and body composition components (body fat percentage, fat mass, fat free mass, muscle mass and visceral fat) were measured using scheduled calibrated Total Body Composition Analyzer (TANITA) model SC-330MA (Tanita Corporation, Japan) with accuracy of body fat percentage up to 0.1 %, body weight, fat mass, fat free mass, muscle mass, and visceral fat up to 0.1 kg respectively. Stadiometer (Seca 222, Medical Scales & Measuring Systems Seca, United Kingdom) was used to measure height to the nearest of 0.1 cm. Body mass index (BMI) was calculated with the formula, BMI = weight (kg)/height(m^2), and classified according to World Health organisation (2000) categorization [17].

2.3.3. C-Reactive protein and other biochemical parameters

Biochemical parameters which include CRP, serum albumin, hemoglobin, white blood cells (WBC), neutrophil and lymphocyte count were obtained through blood sampling. Prior to blood sampling, participants were asked to fast for at least eight hours. Venous blood samples (10 mL) were collected using single puncture on peripheral vein by registered nurse in IKN and sent for laboratory analysis done by medical laboratory technologist in IKN Pathology Department. Blood collection and analysis were done within same day following standardized procedures. Serum albumin and CRP levels were measured using an automated biochemical analyzer (Olympus AU400 Chemistry Analyzer, Japan).

2.3.4. Energy-adjusted dietary inflammatory index (E-DII) score

Dietary assessment was done by a qualified dietitian via face-to-face interview using a 165-items Food Frequency Questionnaire (FFQ) adapted from Malaysian Adults Nutrition Survey, National Health and Morbidity Survey (NHMS), 2014 [18]. Participants were requested to answer on the type of typically consumed food items, number of serving sizes consumed based on standard serving size, and the consumption frequency for every food item in the past one year prior to interview by choosing only one out of the four options provided in the FFQ which were number of times daily, number of times weekly, number of times monthly, and never. Standard serving size based on the Atlas of Food Exchanges and Portion Sizes [19] was given to each items using food models and typical household measures such as teaspoons, tablespoons, cups and matchbox sizes. Nutrient intakes were analyzed with Nutritionist Pro™ Diet Analysis Software version 3.1.0 (Axxya Systems, 2023), using the database of Nutrient Composition of Malaysian Foods in the software. For items not listed on the Malaysian food database, data from Singapore Food Composition database and the U.S. Department of Agriculture database (USDA) were included. The FFQ-derived nutrient analysis was then used to compute the Dietary Inflammatory Index (DII) scores for each participant. The detailed explanation of DII development had been described elsewhere [13]. In current study, 24 out of the 45 food parameters were included with other parameters excluded because they were not used in Malaysian diet such as ethanol or data were not available such as some spices. Analyzed nutrients were translated into z-scores using a global mean divided by global standard deviation. These scores were converted to proportions and centered on zero by doubling each and subtracting "1", followed by multiplication

with their own inflammatory effect scores to obtain DII scores for each food parameter. The summation of these scores resulted in the overall DII score. The global mean, global standard deviation, and inflammatory effect scores of each food parameter were described elsewhere [13]. Energy-adjusted DII (E-DII) scores were calculated using the density approach by calculating DII per 1000 kcal consumption using the energy-adjusted global comparison database [20,21]. This E-DII scores potentially range from approximately -9 (minimally pro-inflammatory) to +8 (maximally pro-inflammatory) [21].

2.3.5. Handgrip strength (HGS)

HGS were measured three times on dominant hand using calibrated Jamar hand dynamometer (Fred Sammons Inc, USA). The average score of three consecutive readings was used as the final HGS results and compared to the reference value in Asian Working Group for Sarcopenia, 2019 where low HGS is defined as <18 kg for female [22].

2.3.6. Scored patient generated-subjective global assessment (PG-SGA)

Participants' nutritional status was determined using PG-SGA by trained dietitian. The first part of this tool was filled via face-to-face interview and consisted of four components including weight history (any weight loss in one month or six months), food intake, symptoms such as vomiting, and activities. The second part of PG-SGA was filled out by dietitian (interviewer) to assess metabolic and physical demands. The components of this part consisted of diagnosis, age, metabolic stress, and physical exam including loss of subcutaneous fat, muscle wasting and edema or ascites. Based on the global guideline of PG-SGA [23], the sum of scores for each component were used to generate the total PG-SGA score.

2.3.7. Physical activity level

Physical activity level was assessed with International Physical Activity Questionnaire (IPAQ)-short form by recording participants' vigorous physical activity, moderate physical activity, walking, and sitting in the past 7 day. By using the instrument's scoring protocol [24], total physical activity per week was quantified in the form of metabolic equivalent minutes per week (MET-min/week).

2.3.8. Perceived stress scale (PSS)

Stress level was assessed using 10-item Perceived Stress Scale (PSS-10) by asking on the frequency of participants' feelings and thoughts during last month. PSS-10 included six negatively worded items (e.g., How often have you felt nervous and "stressed"?) and four positively worded items (e.g., How often have you been able to control irritations in life?), each rated on a 5-point Likert-type scale. PSS scores were obtained by reversing responses (e.g., 0 = 4, 1 = 3, 2 = 2, 3 = 1 & 4 = 0) to the four positively worded items (items 4, 5, 7, & 8) and then summed across all items [25].

2.4. Statistical analysis

Data obtained was analysed using statistical software IBM SPSS, version 27.0 (SPSS Inc, USA). For normality testing of continuous variables, Kolmogorov-Smirnov test was performed. Independent *t*-test was used to determine the relationship between an independent variable with inflammation (CRP) while Mann-Whitney U test were used for skewed data. Chi square test was used to identify differences between categorical variables, and Fisher's exact test will be used if ≥20 % of the cells had expected count of less than 5 in 2 × 2 tables. Single logistic regression using Enter method was performed for each independent variable to examine the relationship with CRP. All independent variables with a p-value <0.25 were entered into multiple logistic regression using Forward LR method. The variables which provided a better overall model fit of inflammation were chosen. The level of statistical significance was set at $p < 0.05$.

Table 1
Socio-demographic and medical characteristics between normal and elevated CRP participants ($N = 105$).

Characteristics	Normal CRP ($n = 65$) n (%)/ Median (IQR)	Elevated CRP ($n = 40$) n (%)/ Median (IQR)	Statistical value X^2 / Z	p-value
Age (years)	49.0 (42.5–61.0)	51.0 (42.0–60.8)	-0.162 [a]	0.871
Household Income (RM)	4000 (2500–7100)	4000 (1800–7000)	-0.425 [a]	0.671
Ethnic				
Malay	45 (62.5)	27 (37.5)		
Chinese	16 (76.2)	5 (23.8)		
Indian	4 (40.0)	6 (60.0)		
Others	0 (0)	2 (100)		
Ethnic group			0.034 [b]	0.853
Malay	45 (62.5)	27 (37.5)		
Non-Malay	20 (60.6)	13 (39.4)		
Education group			1.072 [b]	0.300
Secondary and below	39 (58.2)	28 (41.8)		
Tertiary	26 (68.4)	12 (31.6)		
Marital status group			0.362 [b]	0.547
Married	52 (63.4)	30 (36.6)		
Single/ Widow/ Divorced	13 (56.5)	10 (43.5)		
Employment			0.717 [b]	0.397
Unemployed	38 (65.5)	20 (34.5)		
Employed	27 (57.4)	20 (42.6)		
Menopause Status			0.013 [b]	0.908
Pre	35 (61.4)	22 (38.6)		
Post	30 (62.5)	18 (37.5)		
Smoking history group			0.621 [b]	0.431
Never	50 (64.1)	28 (35.9)		
Active/Second-hand smoker	15 (55.6)	12 (44.4)		
Presence of Comorbidities				
No known comorbidity	41 (68.3)	19 (31.7)	2.453 [b]	0.117
Type 2 Diabetes Mellitus	8 (66.7)	4 (33.3)	- [c]	1.000
Hypertension	19 (51.4)	18 (48.6)	2.698 [b]	0.100
Dyslipidemia	11 (50.0)	11 (50.0)	1.673 [b]	0.196
Family history				
Family history of BCa	18 (64.3)	10 (35.7)	0.092 [b]	0.762
Family history of other cancer	20 (60.6)	13 (39.4)	0.034 [b]	0.853
Cancer Site				
Right	36 (66.7)	18 (33.3)		
Left	29 (59.2)	20 (40.8)		
Bilateral	0 (0)	2 (100)		
Duration of Diagnosis			0.931 [b]	0.335
≤2 months	48 (64.9)	26 (35.1)		
≤9 months	17 (54.8)	14 (45.2)		
Staging group			0.006 [b]	0.938
1–2	30 (62.5)	18 (37.5)		
3–4	31 (63.3)	18 (36.7)		
Yet to rule out	4 (50.0)	4 (50.0)		
Hormone receptor status				
ER positive	41 (67.2)	20 (32.8)	1.639 [b]	0.200
PR positive	34 (65.4)	18 (34.6)	0.471 [b]	0.492
HER2 positive	24 (58.5)	17 (41.5)	0.375 [b]	0.540
Triple Negative	9 (52.9)	8 (47.1)	0.732 [b]	0.392
Breast Surgery history			0.096 [b]	0.756
Nil	28 (63.6)	16 (36.3)		
Mastectomy/ Lumpectomy	37 (60.7)	24 (39.3)		

Normal CRP = <3 mg/L; Elevated CRP = 3.0–9.9 mg/L.
[a] Mann Whitney *U* test.;
[b] Chi square test for proportions;.

[c] Fisher's exact test.

3. Results

3.1. Participants' characteristics

Participants were categorized into two groups based on CRP reading in Table 1. There were no statistically significant differences for all socio-demographic and medical characteristics between normal and elevated CRP participant groups. Majority were Malay (68.6 %), married (78.1 %) never smoke (74.3 %), in premenopausal stage (54.3 %), and had no other known comorbidities (57.1 %). All participants were within first year of BCa diagnosis.

3.2. Anthropometric, biochemical, nutritional status, E-DII, HGS, physical activity and PSS score of participants

As portrayed in Table 2, participants in the elevated CRP group were more likely to have higher body weight ($p < 0.001$), BMI ($p < 0.001$), body fat percentage ($p < 0.001$), muscle mass ($p < 0.001$), FM/FFM ratio ($p < 0.001$) and visceral fat ($p < 0.001$). Moreover, those in elevated CRP group had lower albumin ($p = 0.030$) and HGS ($p = 0.016$) but higher hemoglobin ($p = 0.035$), WBC ($p = 0.004$), neutrophil ($p = 0.036$), and PSS score ($p = 0.014$).

3.3. Predictors of CRP

From multiple logistic regression analysis shown in Table 3, the predictors of elevated CRP levels were body fat percentage ($p < 0.001$), PSS ($p = 0.011$), HGS category ($p = 0.014$), albumin ($p = 0.019$) and WBC ($p = 0.036$). Based on classification table, the predictive accuracy of this model was good at 78.1 %. Current model can significantly discriminate 12.6 % of elevated CRP among newly diagnosed BCa patients' prior oncological treatment. The predicted equation, Ln (elevated CRP) = -5.225 + 0.200 (body fat percentage) + 0.114 (PSS) + 3.736 (HGS-low) - 0.250 (albumin) + 0.349 (WBC).

4. Discussion

CRP levels were used to monitor the presence and degree of inflammation in cancer patients [26]. In two recent review papers that specifically described the diagnostic interpretation of CRP in cancer, baseline CRP levels were defined at 1–3 mg/L while blood CRP levels above 10 mg/L were indicative of advanced cancer or confounding pathologies including infections [26,27]. Therefore, elevated CRP was defined at 3–9.9 mg/L in this study as it was found that invasive BCa patients with CRP >3 mg/L at diagnosis had a 1.7-fold of increased BCa mortality than those with lower CRP levels [28]. Body fat percentage, PSS, HGS category, albumin and WBC were found to be significant predictors of elevated CRP levels in newly diagnosed BCa population. Although diet and physical activity were not direct predictor in this study, these two modifiable lifestyle factors have been proven in literature to affect body fat percentage, HGS and albumin level.

Other anthropometric measurements such as body weight and BMI were only associated with CRP levels in univariate but not multivariate model likely due to multicollinearity with body fat percentage as all these parameters constitute body composition as a whole. Our study is consistent with previous findings linking obesity with elevated CRP. Among BCa patients who had completed treatment or undergoing hormonal treatment, CRP was positively associated with BMI, waist and hip

Table 2
Anthropometric, biochemical, nutritional status, E-DII, HGS, physical activity and PSS score between normal and elevated CRP participants ($N = 105$).

Characteristics	Normal CRP ($n = 65$) n (%)/ Median (IQR)/ Mean ± sd	Elevated CRP ($n = 40$) n (%)/ Median (IQR)/ Mean ± sd	Statistical value t/ Z/ X^2	p-value
Anthropometric Parameters				
BMI (kg/m2)	24.3 ± 4.23	28.3 ± 4.72	-4.503 [a]	<0.001***
BMI groups			10.206 [b]	<0.001***
<25.0 kg/m^2	37 (78.7)	10 (21.3)		
≥25.0 kg/m^2	28 (48.3)	30 (51.7)		
Body weight (kg)	59.1 ± 10.92	69.2 ± 11.70	-4.452 [a]	<0.001***
Fat Percentage	34.3 ± 6.43	40.0 ± 5.54	-4.637 [a]	<0.001***
Muscle Mass	36.1 ± 3.63	38.6 ± 3.61	-3.452 [a]	<0.001***
FM/FFM	0.54 ± 0.150	0.68 ± 0.171	-4.550 [a]	<0.001***
Visceral Fat	7.0 (5.0–8.5)	8.5 (7.5–10.0)	-4.006 [c]	<0.001***
Biochemical Parameters				
Albumin (g/L)	42 (41–44)	41 (39–43)	-2.165 [c]	0.030*
Hemoglobin (g/dL)	12.3 (11.7–13.2)	12.8 (12.2–13.5)	-2.103 [c]	0.035*
WBC (x10^9/L)	6.4 (5.3–7.5)	7.9 (6.0–8.5)	-2.875 [c]	0.004**
Neutrophil (x10^9/L)	3.49 (2.80–4.38)	4.06 (3.13–5.43)	-2.092 [c]	0.036*
Lymphocyte (10^9/L)	2.14 ± 0.743	2.37 ± 0.599	-1.678 [a]	0.096
Nutritional status				
PG-SGA score	2 (1–6)	3 (1–5)	-0.105 [c]	0.916
E-DII score	0.54 (-1.00 – 1.58)	0.82 (-0.03 – 1.41)	-0.719 [c]	0.472
HGS category			- [d]	0.016*
Low (<18 kg)	53 (57.6)	39 (42.4)		
Normal (≥18 kg)	12 (92.3)	1 (7.7)		
Physical Activity (MET-min/week)	840.0 (609.8–1605.0)	926.3 (299.3–1854.0)	-0.515 [c]	0.607
PSS score	14.5 ± 6.21	17.5 ± 5.35	-2.507 [a]	0.014*

Normal CRP = <3 mg/L; Elevated CRP = 3.0–9.9 mg/L.
[a] Independent *t*-test;.
[b] Chi square test for proportions;.
[c] Mann Whitney *U* test.;
[d] Fisher's exact test.
* $p < 0.05$;.
** $p < 0.01$;.
*** $p < 0.001$.

Table 3
Predictors of CRP.

Variable	Simple Logistic Regression						Multiple Logistic Regression					
	Unadjusted Coefficient	Crude OR	SE	95 % CI for Odds Ratio		p-Value	Adjusted Coefficient	Adjusted OR	SE	95 % CI for Odds Ratio		p–Value
				Lower Bound	Upper Bound					Lower Bound	Upper Bound	
Intercept	–						-5.225		4.716			
Fat Percentage	0.163	1.176	0.042	1.084	1.277	<0.001***	0.200	1.222	0.054	1.099	1.358	<0.001***
PSS	0.087	1.091	0.037	1.016	1.172	0.017*	0.114	1.120	0.045	1.026	1.223	0.011*
HGS												
Normal	Reference						Reference					
Low	2.178	8.830	1.062	1.102	70.786	0.040*	3.736	41.928	1.514	2.155	815.728	0.014*
Albumin	-0.146	0.864	0.073	0.749	0.998	0.046*	-0.250	0.779	0.107	0.632	0.960	0.019*
WBC	0.356	1.428	0.127	1.114	1.830	0.005**	0.349	1.418	0.166	1.024	1.963	0.036*

Multicollinearity and interaction were checked.
Forward LR was applied, Hosmer and Lemeshow test ($p = 0.839$), classification table (overall percentage: 78.1%), Cox and Snell R Square (0.378), Nagelkerke R Square (0.514), ROC = 0.126.
* $p < 0.05$;.
** $p < 0.01$;.
*** $p < 0.001$.

circumference [29]. In a cohort study among BCa survivors, it was found that obese survivors with body fat ≥35 % had a significantly raised CRP than non-obese survivors with body fat <35 % [30]. Excess adipose tissue produced various cytokines and acute-phase proteins including CRP that activate pro-inflammatory signaling pathways, fostering chronic low-grade inflammation that encouraged tumor progression [31]. Obese BCa patients undergoing treatment were also associated with more complication and less effective therapies as compared to their non-obese counterpart [32].

For women, BCa is a stressful diagnosis due to its lethality besides femininity-destroying characteristic [33]. Compared to healthy women or those with benign breast tumours, the degree of perceived psychological stress in BCa patients is much higher [34,35]. BCa survivors with higher perceived stress in the prior month also showed heightened left amygdala activity in response to social threat, and such intensified amygdala activity occurred at the same time with increased inflammation demonstrated by higher CRP levels [36]. Nonetheless, study results on association between inflammatory marker and stress among BCa patients had been limited and inconsistent [33]. Both physical and psychological stressors of diagnosis and treatment may activate inflammatory pathways leading to raised inflammation in BCa [37]. However, as our study only comprised of pre-treatment BCa patients, we propose that even psychological stressors of BCa diagnosis alone can lead to elevated inflammation marker.

HGS was an excellent predictor of functional decline in BCa [38] and significantly associated with BCa mortality (HR=1.593, 95 % CI=1.230–2.063, $P < 0.001$) [39]. Most of the literature has detected low grip strength owing to the effect of breast surgery or treatment. A local study in Malaysia found that 98.2 % of BCa patients undergoing oncological treatment had low HGS [40]. However, it is alarming to note that majority of the current participants (87.6 %) had low HGS <18 kg even before treatment commence. Cancer accelerates the muscle decline process due to chronic consumptive characteristics resulting in fatigue, cachexia, and sarcopenia [39]. In a study among mixture of cancer and non-cancer hospitalized, non-critically ill patients, CRP was inversely correlated with HGS (r= -0.211, $p = 0.003$) [41]. Skeletal muscle repair and regeneration is affected by acute and chronic inflammation in the entire body and therefore induce HGS weakening [42]. Nevertheless, among BCa survivors, CRP was only significantly associated with lower limb strength measured by sit-to-stand test ($r = 0.19$, $p = 0.002$) but not with HGS that assessed upper limb strength [29]. However, resistance training designed to improve muscular fitness has been shown to decrease CRP levels in older woman >60 years old [43]. As HGS measurement is a simple, low-cost but high general applicability method, individuals can make preliminary predictions on the current body immunity and inflammation level through routine grip-strength tests [42].

Albumin has also been detected as predictive of CRP and this concurred a previous finding among pre-treatment, advanced pancreatic cancer patients that showed that albumin was inversely associated with CRP (r= −0.387; $P < 0.001$) [44]. CRP and albumin were commonly produced in the liver, regulated by interleukin-6-promoted inflammation and has been demonstrated to be independent prognostic factor of BCa survival [45]. Elevated CRP levels and low serum albumin during diagnosis significantly and adversely affected BCa survival [8,46]. At present, there are not many studies on WBC in BCa [47]. However, as WBC is also clinical marker of inflammation [48], it is not surprising that it was found to be significant predictor of CRP in this study.

The strength of this study is the strict inclusion criteria of only pre-treatment BCa patients to eliminate the confounding effect of oncological treatment towards inflammation. Besides, most of the inflammation predictors identified are modifiable and can be improved with appropriate interventions. As far as we know, no previous research has used DII to investigate the effect of diet towards inflammation among BCa population in Malaysia. There are several limitations to this study. Firstly, no causal inferences can be made due to the nature of a cross-sectional study. Secondly, dietary data obtained through FFQ cannot

eliminate the possibility of recall bias. Thirdly, other factors not included such as sleep quality might also affect CRP levels. Moreover, the long-term effect of elevated CRP in this population has not been observed. Therefore, future study with longer study period or repeated CRP measurements can be conducted to confirm the discoveries in this study. Nonetheless, this study could serve as the basis of intervention studies to explore the therapeutic effect of improving specific factors to reduce inflammation in BCa population.

5. Conclusion

Overall, this study provided an insight into predictors of elevated CRP levels among newly diagnosed, pre-treatment BCa population which were mostly modifiable including body fat percentage, PSS, HGS category, albumin and WBC. Therefore, tailor-made strategies can be planned to reduce these modifiable risk factors in order to improve inflammation among BCa patients.

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Data statement

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

CRediT authorship contribution statement

Wai Han Ng: Conceptualization, Methodology, Formal analysis, Investigation, Project administration, Writing – original draft, Writing – review & editing. **Zalina Abu Zaid:** Conceptualization, Supervision, Funding acquisition, Writing – review & editing. **Barakatun Nisak Mohd Yusof:** Supervision, Writing – review & editing. **Syafinaz Amin Nordin:** Supervision, Writing – review & editing. **Poh Ying Lim:** Validation, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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