Impact and Association of Anaemia Severity and Its Treatment With Quality of Life of Breast Cancer Patients in Malaysia

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Abstract

Anaemia is a crucial issue among cancer patients and need to be treated properly. High incidence of anaemia in patients with cancer have been associated with several physiological manifestations, leading to decreased quality of life (QOL).

The current study aimed to assess the severity of anaemia, evaluate the current treatment guideline of anaemia, and to determine the association between the level of anaemia and its treatment on quality of life of breast cancer patients in Malaysia. This prospective study conducted among breast cancer patients in multicancer centers in Malaysia including three follow ups after receiving their chemotherapy. Clinical data were collected from their medical records and at each follow up, they asked to fill up a functional assessment chronic therapy (FACT-An) questionnaire. Descriptive and inferential statistical analysis were done using SPSS.

The mean age of participants was 52 ± 11 years old, and out of 120 participants, 32% received anti-anaemic treatments including 87% of them were prescribed with iron supplementation and only 13% received combination of blood transfusion and iron therapy. Surprisingly, none of the participants received erythropoietin stimulating agents (ESAs). Statistical tests also indicated a significant association between anti-anaemic treatments with haemoglobin level and QOL scores. However, this association was insufficient to significantly improve QOL or palliate anaemia severity among participants.

This study showed a great evidence that, the current practice of anaemia treatment (iron therapy) among breast cancer patients in Malaysia's healthcare setting, was not sufficient to palliate anaemia severity or to improve patients' QOL. There is still a lot of gaps to improve in the management of anaemia among breast cancer patients to show a significant improvement in haemoglobin level. Therefore, respective organisations and oncologists are required to raise awareness about the optimal treatment of anaemia among breast cancer patients, as a result, improve their general wellbeing.

Keywords Anaemia, Quality of Life, Breast Cancer

تأثير وترابط شدة فقر الدم وعلاجه مع جودة حياة مرضى سرطان الثدي في ماليزيا

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الخلاصة

يعد فقر الدم من القضايا الحساسة بين مرضى السرطان ويحتاج إلى العلاج المناسب. ارتبط ارتفاع معدل الإصابة بفقر الدم لدى مرضى السرطان بالعديد من المظاهر الفسيولوجية ، مما أدى إلى انخفاض جودة الحياة. تهدف الدراسة الحالية إلى تقييم شدة فقر الدم ، وتقييم الدلائل العلاجية الحالية لفقر الدم ، وتحديد العلاقة بين مستوى فقر الدم وعلاجه على جودة حياة مرضى سرطان الثدي في ماليزيا. أجريت هذه الدراسة التحليلية بين مرضى سرطان الثدي في مراكز متعددة لأمراض السرطان في ماليزيا و شملت ثلاث متابعات بعد تلقي العلاج الكيميائي. تم جمع البيانات السريرية من سجلات المرضى الطبية وفي كل متابعة ، تم الطلب منهم بملء استبيان التقييم الوظيفي للعلاج المزمن. تم إجراء التحليل الإحصائي الوصفي والاستنتاجي باستخدام برنامج التحليل الأحصائي. كان متوسط عمر المشاركين ٥٢ ± ١١ عامًا ، ومن بين ١٢٠ مشاركًا ، تلقى ٣٢ ٪ علاجات مضادة لفقر الدم بما في ذلك ٨٧ ٪ منهم تم وصفهم بمكملات الحديد وتلقى ١٣ ٪ فقط مزيجًا من نقل الدم والعلاج بالحديد. والمثير للدهشة أن أيا من المشاركين لم يتلق علاج إرثروبويتين. أشارت الاختبارات الإحصائية أيضًا إلى وجود ارتباط كبير بين العلاجات المضادة لفقر الدم ومستوى الهيموجلوبين ونوعية الحياة. ومع ذلك ، لم يكن هذا الارتباط كافياً لتحسين نوعية الحياة بشكل ملحوظ لتخفيف فقر الدم بين المشاركين ، وأظهرت هذه الدراسة دليلاً قوياً على أن الممارسة الحالية لعلاج فقر الدم (العلاج بالحديد) بين مرضى سرطان الثدي في بيئة الرعاية الصحية في

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ماليزيا ، لم تكن كافية لتقليل شدة فقر الدم أو لتحسين نوعية حياة المرضى. لا يزال هناك الكثير من الثغرات لتحسين التعامل مع فقر الدم بين مرضى سرطان الثدي ليتم من خلاله ملاحظة تحسن كبير في مستوى الهيموجلوبين. لذلك ، يتعين على المنظمات وأطباء الأورام الخبيثة المعنية بهذا الأمر برفع مستوى الوعي حول العلاج الأمثل لفقر الدم بين مرضى سرطان الثدي ، ونتيجة لذلك ، سوف تتحسن صحتهم العامة.
الكلمات المفتاحية فقر الدم ، جودة الحياة ، سرطان الثدي

Introduction

Breast cancer is the most prevalent form of cancer among females globally [1]. It is the second most common cancer among Malaysian women, accounting for approximately 31% of total cancer cases [2]. One of the major side effects is anaemia [3]. Anaemia is common in cancer, its incidence ranging from 63% [4] to 83% [5] amongst solid cancer patients. Incidence of anaemia in cancer patients was reported to be 41% before receiving chemotherapy but increased to 43.1% upon anti-neoplastic therapy [6]. Increased incidence of anaemia among cancer patients will negatively impact both patients QOL [7], worsening the progression of disease and affect anti-cancer treatments [8]. This can significantly reduce their survival rate, specifically among those treated with chemotherapy [9-13]. Health related quality of life (HRQOL) is defined as a multi-dimensional aspect that could be used as a prognostic indicator for treatment of breast cancer patients and for survival [14, 15]. It has been found that HRQOL of cancer patients is affected negatively and significantly from the moment of being diagnosed with cancer. i.e. negative impact will set in once the person hears the word "cancer" [16]. During the last decade, HRQOL has become an important factor in the management of breast cancer. Evaluation of QOL in breast cancer patients is becoming increasingly important in health care and in assessing treatment outcomes [17]. Improving of QOL primarily would help in the development of health care medicine and treatment of breast cancer patients [18]. A previous literature study suggested that information and data provided by cancer patients via QOL assessments, is very helpful for clinical decision-making and better patient treatment [19]. Therefore, evaluating anaemia treatment and its impact on cancer patients QOL found to be an essential matter. This study used the functional assessment cancer therapy of anaemia (FACT-An) scales to evaluate the effect of anaemia on QOL among Malaysian breast cancer patients. The purpose for using FACT-An is that it covered all aspects of QOL domains (physical well-being (PWB), social well-being (SWB), emotional well-being (EWB), and functional well-being (FWB) which was necessary to reflect the real quality of care among cancer patients comparing to other scales. In addition, FACT-An is a specific scale for anaemia condition compared to other scales that are in general. Both tools are valid, reliable, easy to understand, and fast to be filled and completed by participants (5-10 min).

Regarding QOL and breast cancer patient, a study has been conducted in China in 2016 to detect the effects of social support, financial situation and clinical factors on breast cancer patients, to evaluate QOL. A total number of 1,160 breast cancer patients have been included; the quality of life is evaluated using the Functional Assessment of Cancer Therapy-Breast Cancer that comprise of five domains. The results reveal that financial and stoical support has affected QOL significantly [11]. Another trial that has been conducted in Korea in 2013 included 534 breast cancer patients in the study. Results showed that QOL among patients with a history of receiving chemotherapy were affected negatively as compared to those without chemotherapy treatment [12]. In addition to that, a study conducted in Morocco had 1,463 breast cancer patients who enrolled in the study. Results indicated that financial support and fear of death were the two main factors that affect QOL negatively [13]. In Malaysia, there is a lack of information regarding QOL among breast cancer patients. Up to date only limited trials have been conducted in Malaysia to detect the factors affecting QOL among breast cancer patients. Results from a study have demonstrated that as the age increases, the QOL for breast cancer patients also improve [3].

Moreover, several studies revealed that the management of anaemia needs to be evaluated regularly in order to ensure that it is up to date and help to achieve better health outcome [20, 21]. This is due to the fact that evaluation and treatment of anaemia will significantly increase the response to antineoplastic *therapy*, improve QOL, increase survival and improve clinical outcomes [22]. A large number of studies demonstrated and recommended the use of erythropoiesis-stimulating agents (ESAs) in the treatment of anaemia among cancer patients [23]. Taking into consideration the potential risk of ESAs which in some cases cause thrombosis, ESAs suggested to be the best medication that significantly increase hemoglobin levels, reduce the need of blood transfusion requirements, and improve quality of life. [22, 23]. However, to the best of our knowledge, internationally, there are limited studies focused on detecting the effects of anemia on breast cancer patients' QOL. Besides, up to date, there is no study in Malaysia that focuses on detecting the negative effects of anemia on the breast cancer patients QOL. Hence, the current study aimed to detect and evaluate treatment given to breast cancer patient suffering from anaemia and to determine its impact on cancer patients QOL.

Method

Study design and setting

This is a prospective, observational, and longitudinal design among breast cancer patients in multi-cancer centres in Malaysia which are Hospital Kuala Lumpur (HKL), University Malaya Medical Centre (UMMC), and Institute Kanser Negara (IKN), Putrajaya, Malaysia. The present study conducted for 8 months starting from July 2019 to March 2020. Sample size was calculated using Raosoft online sample size calculator. The calculation was based on 50 % response distribution, 5 % margin of error and 95 % confidence interval. The online software foundation is based on widely utilized descriptive studies sample size estimation formula. Setting the response distribution to 50% is the most conservative assumption (Raosoft Inc). The assumption that the response rate is 50 % was based on the idea that both responses and response rates were completely unknown since only limited studies conducted in Malaysia which were similar to the current study and the response rate was more than 50% [24] .

Based on the incidence of anaemia (10-40%) (6) of breast cancer patients, with a confidence interval of 95% and a margin of error at 5%,.the sample size fell between 95-135 patients. These numbers were derived based on an estimated total population of 125 -207 breast cancer patients attending hospitals regularly .The total number of patients who met the inclusion criteria in this study were 120 female anaemic breast cancer patients.

Anaemic breast cancer patients identified based on blood analysis results i.e., haemoglobin level in their medical files. Inclusion criteria stipulated were patients aged 18 and above, Hb ≤ 12 g/dL, diagnosed with breast cancer regardless of stage, currently receiving chemotherapy and able to understand as well as sign the informed consent. While the exclusion criteria stipulated were patients with haematological, inherited disease, pancreatitis or dementia. Besides that, those receiving different management procedure such as radiotherapy, biological therapy or endocrine therapy were also excluded from the study.

Research instrument and data collection procedure

Upon identification, breast cancer patients were approached to participate in this study and data was collected using convenient sampling method. Anaemic cancer patients were identified based on blood analysis results in their medical files. The specific patient was approached to participate in the study. The patient was then briefed regarding the purpose of the study. Upon agreeing, a consent form was provided to be signed. Subsequently, patients were provided with the Functional Assessment of Cancer Therapy- Anaemia (FACT-An) questionnaire which has been

validated using pre-test and pilot study and results of Cronbach's Alpha was 0.891 indicated that questionnaires yields reliable. This questionnaire was available in two languages (English and Bahasa Melayu) from the original developer so that it was provided according to patient's language preference (i.e. Bahasa Melayu or English version) to measure QOL [25]. Permission to use the research instruments (both English and Bahasa Melayu version) was obtained from the developers and validated accordingly. The questionnaire took 10-15 minutes to complete, and patients were followed-up for the next two cycles of chemotherapy (total three cycles). Besides that, Hb levels were measured prior to each cycle by a well-trained staff and Hb readings were extracted from the patients' medical records. Severity of anaemia corresponds to 10.0–10.9 g/dl as mild, 7.0–9.9 g/dl as moderate, and less than 7.0 g/dl as severe [26]. In addition, demographic, clinical, and anaemia treatments data, were collected from patients' medical records.

Data analysis

Data was analysed via SPSS Version 25. Estimated mean scores and 95% confidence intervals were calculated for QOL score and Hb levels, evaluated based on all three follow ups. Difference in mean scores for all three follow ups was observed and findings were expressed as mean and standard deviation (SD). Computation of results was done in accordance with FACT-G group guidelines. A repeated measured ANOVA was used to detect the association between Hb level and QOL scores with time across the three follow-ups, and one-way repeated measured MANOVA was performed to identify the relationship between anti-anaemic medications and both dependent variables (QOL and Hb levels) along the three subsequent follow ups. To overcome problems related to data mining, post hoc analysis was conducted using Bonferroni adjustments to identify differences between each cycle. Significance level was set at p < 0.05 for all analyses.

Ethical approval

All the aspects and protocols of this study were reviewed and approved by Clinical Research Centre (CRC) of UiTM (REC/392/19), HKL (HCRC.IIR-2019-07-163), IKN (IKN/500-5/1/25 JId 4 (18), UMMC & Medical Research Ethical Centre (MREC) (NMRR -18-3902-45218). Researcher adhered to the principles of the Declaration of Helsinki and the Malaysian Good Clinical Practice Guidelines.

Results

From the 120 respondents, the majority were elderly (n=89; 74.2%) with mean age of 52.63 years (± SD 11.27), Malay (n = 77; 64.2%), married (n=108; 90%), and postmenopausal (n=87; 72.5%) (6). Only 39 (32.5%) patients received anti-anaemic management. Out of the 39 patients who received anaemia treatment, about 87% of the patients were treated with only iron supplements plus multivitamins while 13% received a combination of iron products with multivitamins and underwent blood transfusion and none of the patients received Erythropoiesis-stimulating agents (ESAs). Furthermore, more than two third of the anaemic patients (n = 81, 67.5%) were not treated for anaemia. Additional clinical and demographic data are shown in Table 1.

Table 1 Demographic data in breast cancer patients undergoing chemotherapy (N= 120)

Variable		N (%)
Mean age	52.63 (SD 11.27)	
Age (years)	≥ 60	89 (74.2%)
	< 60	31 (25.8%)
Race	Malay	77 (64.2%)
	Indian	14 (11.7%)
	Chinese	27 (22.5)
	Others	2 (1.7%)
Marital status	Married	108 (90%)
	Single	8 (6.7%)
	Divorced	4 (3.3%)
Stage of Breast Cancer	Stage I	5 (4.2%)
	Stage II	29 (24.2 %)
	Stage III	62 (51.7 %)
	Stage IV	24 (20 %)
Anti-anaemic medications	Treated	33 (27.5%)
	Un treated	81 (67.5%)
	Un detected	6 (5%)
Type of anti-anaemic treatment	Iron therapy & multi-vitamins	34 (87.2%)
	Blood transfusion	2 (5.1%)
	Mixed	3 (7.7%)
	ESAs	0 (0%)

Treated = All patients received anti-anaemic treatment , Un-treated = Patients who did receive any type of anti-anaemic medication ,Un detected = Patients who received anti-anaemic medication either at 1st or 2nd or 3rd interviews . ESAs = Erythropoietin Stimulating Agents . Mixed = iron therapy & multi-vitamins+ blood transfusion

Haemoglobin levels and QOL across three consecutive follow ups

The total average mean (i.e., sum of 3 follow-up means) and standard deviation for overall Hb levels was 10.34 g/dL ± 0.73 (mean ± SD). Specifically, the Hb mean for patients for the first follow-up was 10.64 ± 0.85, 10.26± 0.85 for the second follow-up, and 10.13 ± 0.83 g/dL for the third follow-up. Results revealed a decline in Hb levels across the three follow ups (i.e., increased anaemia severity across the three follow ups). Similarly, the total average mean and SD for overall QOL was 96.38 ±16. 15. The mean of QOL at first follow-up (108.96±20.94) was higher than the mean of QOL at second follow-up (95.11 ±17.58). The mean of QOL at third follow-up was the lowest (85.06 ± 25.88) signifying a decline in the QOL among anaemic cancer patients along the three follow ups as shown in Table 2.

Table 2.Mean of Hb level (severity of anaemia) and QOL in breast cancer patients (N= 120)

Hb g/dL		(Mean ±SD) g/dL
Total Average Hb		10.34 ± 0.73
Hb g / dL	Mild (10-12) g/dL	78 (65%)
	Moderate (8-10) g/dL	41 (34.2%)
	Severe (6-8) g/dL	1 (0.83.3%)
QOL Total (0-188)		96.38 ±16.15
QOL FACT-An	1st Follow up (0-188)	108.96 ± 20.94
	2nd Follow up (0-188)	95.11±17.58
	3rd Follow up (0-188)	85.06 ± 25.88

Hb – Hemoglobin

Association between the level of Hb , QOL , and anti-anaemic treatments

One-way repeated measured MANOVA was used to determine if there was any significant interaction between (anti-anaemia treatments) as independent variable and (Hb and QOL) as dependent variables at three follow ups. Results indicated a statistically significant difference in the mean of Hb levels and QOL scores based on anti-anaemic medications (Table 3). Univariate analysis between anti-anaemic treatment and both Hb levels and QOL scores across the three follow ups indicated a significant association between anti-anaemic treatment with Hb levels across three follow ups and QOL scores at the three follow-ups. However, this association was not enough to improve the Hb level and QOL of participants.

Table 3. Association between anti-anaemic medications and Hb level + QOL at 3 follow ups

Variables		F(df)	F	Sig	η^2
Anti-anemic treatment	**Hb 1st Follow up**	2.117	6.8	0.002	0.10
	Hb 2nd Follow up		12.4	<0.001	0.17
	Hb 3rd Follow up		3.9	0.023	0.06
	QOL 1st Follow up		3.4	0.036	0.05
	QOL 2nd Follow up		6.9	<0.001	0.10
	QOL 3rd Follow up		1.6	0.020	0.02

η^2= partial Eta square

Discussion

In Malaysia, to our best knowledge, the current study is the first of its kinds to evaluate the association between anaemia severity and its treatment with quality of life among breast cancer patients. It is proved that cancer-related anaemia (CRA) adversely affects quality of life [7,27] and is associated with reduced overall survival [28]. Correction of anaemia in cancer patients has the potential to improve treatment efficacy and as a result increase survival [29]. Pourali et al, mentioned that prevalence and severity of anaemia among breast cancer patients in their advanced stages have been well documented, but the same cannot be said amongst those in the earlier stages. Hence signifying the value of this study as it focuses on detection and evaluation of anti-anaemic treatment among breast patients across various stages [6]. Imran et al., 2019, who conducted a study amongst female breast cancer patients in Saudi Arabia to assess their QOL mentioned that there was a direct relationship between choice of treatments used for breast cancer patients, side effects, medical issues, and QOL [18].

The current obtained data indicate that, the mean for haemoglobin level declined across the three follow ups. Meaning the number of patients who were suffering from moderate anaemia was increasing. This indicates that treatments used for treating and/or palliating anaemia within this study may not be enough to improve Hb levels. In line with these findings, a study denotes that CRA treatment is only considered effective when haemoglobin level improves significantly, specifically among those with mild and moderate anaemia [22]. Moreover, another study highlights that the main objectives for CRA treatment is to palliate and/or treat anaemia besides improving QOL among cancer patients with anaemia [30]. However, results from the current study shows otherwise.

Concerning anaemia treatment, our data showed that only 32.5% of our respondents received general anti-anaemic treatment (i.e., non-specific anti-anaemic treatment). A large majority did not receive any kind of anti-anaemic medications. Among those who received treatment, almost all received iron supplements and vit b-complex or multivitamins,

while only two respondents were treated with blood transfusion. None were treated with Erythropoiesis-Stimulating Agents (ESAs). As per our data, the use of iron supplements did not improve haemoglobin level across the three follow ups. This finding is consistent with another study conducted in Ethiopia, where only 32% out of its total respondent were treated with supportive treatments - which include blood transfusion and iron supplements [31]. Based on the suggestion and recommendation by Hassan BA et al., [21], the future studies should evaluate and improve the guideline used for treating anaemia among cancer patients [21]. This suggestion stemmed from results of their prospective study, which was conducted in a cancer center in Penang, Malaysia. Their results found that treatment of anaemia among solid cancer patients was neither effective nor specific. Their efforts in evaluating treatment were one that is novel and crucial. In addition, a previous study concluded that clinicians and oncologists need to evaluate the negative effects of anaemia towards cancer patients QOL and treat it accordingly [32]. Moreover, another researchers mentioned that it is important to determine incidence of anaemia among cancer patients and its impact on cancer patients QOL as it helps identify correct method of treatment (i.e. The right treatment method will significantly enhance QOL among cancer patients) [22]. Besides, evaluating and detecting proper treatment methods and guidelines for treating mild and/or moderate anaemia among cancer patients should be the foremost objective [22]. This was precisely the focus of the current study. Bohlius et al. [20] , also mentioned in their review article that the treatment guideline used for CRA, especially among cancer-patients suffering from non-curative and advanced cancers like breast cancer, need to be evaluated and updated. Besides, there is a need for evaluating the use of erythropoiesis-stimulating agents (ESAs) among cancer patients to highlight benefits and risks of using ESAs [20]. The ASCO guideline recommends using ESAs for treatment of CRA in early or advanced stages of breast cancer [20].

Statistically, our results showed a significant negative association between anaemia severity with type and pattern of anaemia treatment. This indicates that neither the type nor the pattern of anaemia treatment used was appropriate enough to palliate or solve the main problem i.e., anaemia. Moreover, results across the three follow ups further confirmed that anaemia treatment type and pattern did not improve both anaemia severity and QOL. Therefore, emphasising a need for rectification. Busti et al. [22] explains that iron therapy is only useful in enhancing efficacy of ESAs and reducing the need of blood transfusion. Iron therapy is not to be used as main protocol for treatment of anaemia, as it is in this setting. Busti et al. also recommends that iron therapy should be replaced with ESAs for the treatment of anaemia in cancer patients (22).

Effectiveness of ESAs in treating anaemia in comparison with oral iron has been substantiated by Busti et al., 2018, which showed that the use of ESAs is far more superior than the use of oral and intravenous iron in treating anaemia among cancer patients [22,33]. A reliable indicator of effectiveness of anaemia treatment is the improvement haemoglobin (Hb) level. Specifically, 2g/dL within 4-8 weeks from treatment initiation. Otherwise, it is considered ineffective and must be modified accordingly. Hence strongly endorses findings from the current study.

Moreover, Hassen et al. highlights in his study the major and essential need to determine the proper treatment, so that it can significantly improve QOL among breast cancer patients receiving chemotherapy [34]. Besides, evaluating the impact of anaemia among breast cancer patients on their QOL will significantly help the clinicians to determine several positive outcomes [34]. Direct interviews assessing QOL were found to be highly advantageous in guiding healthcare professionals to attain a clear idea about the patient's QOL, to evaluate patient's medical situation and to tailor treatment accordingly so as to avoid medical problem that may negatively affect patient's QOL [35,36]. Barnadas et al., [37], denotes the necessity to understand impact of cancer disease-associated complications such as anaemia among others, as well as palliative care treatments towards breast cancer patients QOL. Moreover, Chen et al. [38] mentions that studies focused on detecting QOL among women suffering from breast cancer is the cornerstone for evaluating clinical situation, clinical decision making as well as health policy or reimbursement decisions. Though these may be currently obscure, it strongly advocates the importance and novelty of this study.

Overall, there are two key points based on our findings. The first is anaemia treatments did not significantly improve Hb levels and QOL scores. Even if there were some significant association between anaemia treatments with anaemia severity and/or QOL, there were no improvements of the dependent variables (Hb and QOL) across the three follow ups.

Secondly, anaemia treatment (i.e., the entire treatment plan) must be replaced with a proper treatment guideline designed specifically to treat anaemia among cancer patients in Malaysia. The reason being though significant associations were found among anti-anaemic treatment used with anaemia severity and QOL, the effect of the treatment remains weak. Meaning it neither improved anaemia severity nor patients QOL, as indicated by low value of partial Eta squared in accordance to guideline by Cohen, Miles and Shevlin [39].

Limitations

Although this study answers the research questions set, several limitations need to be acknowledged. This study was conducted in a few cancer-centres and only breast cancer patients who received chemotherapy and gave a consent, were interviewed. Therefore, further studies are required to be conducted among different type of cancers at various number of oncology centers.

Conclusion

Findings from this study conclude that anaemia treatments used among anaemic breast cancer patients were ineffective enough to palliate anaemia severity or improve QOL quality of life. Therefore, there is an urgent need to improve anaemia treatment guideline for effective management of anaemia as well as to improve QOL among breast cancer patients. There is a need to use strategies that will unfetter the QOL of cancer patients so that they will have a better sense of control over their illness and treatment.

Conflicts of interest

The authors have declared no conflicts of interest for this article.

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