

Impact of COVID-19 on Breast Cancer Management in a Multiethnic Middle-Income Asian Country Setting

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ABSTRACT

Objective: Coronavirus disease-2019 (COVID-19) has caused hospitals to suspend routine procedures. As the world recovers, there is concern that the outcome of many diseases has been impaired. This study aimed to assess the impact of the pandemic on breast cancer demography, clinicopathological characteristics and patient management at a teaching hospital in Kuala Lumpur, Malaysia.

Materials and Methods: Pre-COVID data were collected between January 1, 2019, to March 18, 2020, when a national lockdown was implemented, which caused the suspension of services at the breast clinic of University Malaya Medical Centre (UMMC). COVID data was obtained from March 2020 until June 2021.

Results: This study compared 374 breast cancer patients in the COVID-19 period with 382 patients in the pre-COVID period. There was no significant difference in the median (range) time to surgery between pre-COVID [45 (26.50–153.50) days] and COVID [44 (24.75–156.25) days] periods. The clinicopathological features of breast cancer showed reduction in *in situ* carcinoma and increase in Stage 4 diagnoses during the COVID period. There was a reduction in screening-detected carcinoma (9% vs. 12.3%), mastectomy followed by immediate reconstruction (5.6% vs. 14.5%) and adjuvant chemotherapy (25.8% vs. 32.9%) in the COVID period.

Conclusion: In this center COVID-19 caused operational changes in breast cancer management, including a reduction in reconstructive procedures and adjuvant treatment. Healthcare disruption and fear of COVID may have caused delayed diagnosis, resulting in a higher frequency of Stage 4 disease and lower proportion of *in situ* carcinoma during the pandemic. However, there was no delay in the time to surgery, reduction in surgical volume, or change in surgery types.

Keywords: Breast neoplasm; pandemic; therapeutic; patient

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Key Points

- COVID-19 had caused operational changes on breast cancer management especially in low and middle-income countries.
- We have found higher proportion of advanced breast cancer during COVID pandemic.
- However, there was no delay in duration of diagnosis to time of surgery, surgical volume and surgery types.

Introduction

The rapid spread of Coronavirus disease-2019 (COVID-19) worldwide led to an unprecedented strain on healthcare services (1, 2). Malaysia recorded its first case among tourists on Jan 24, 2020, and thereafter, the disease began spreading rapidly among the local population (3). Subsequently, the government was forced to implement a lockdown, known as the Movement Control Order (MCO), on March 18, which restricted the movement and social life of citizens, caused non-essential businesses to close and suspended the operations of various services to mitigate the spread of COVID-19 (4). In the medical setting, healthcare operations were reviewed, and treatment was provided only to patients in urgent need of life-saving procedures (5). All nonurgent services, such as breast cancer screening and routine outpatient

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clinics, were suspended to minimize the risk of community-based transmission and prioritize manpower for COVID care. In light of this, the mortality risk and disease severity at presentation of breast cancer patients may have been affected, since the prolonged time to diagnosis and to treatment initiation may have negatively impacted outcome (6).

The objective of this study was to evaluate whether restrictions imposed because of COVID-19 affected the surgical operations and outcome of breast cancer management at the University Malaya Medical Centre, which is a primary teaching hospital serving a suburban population in the Malaysian capital of Kuala Lumpur. The study reviewed the institution's primary treatments, surgical services and adjuvant therapy administration. In addition, the impact on initial presentation and clinicopathological characteristics of breast cancer were also investigated.

Materials and Methods

Study Populations and Patient Selection

This retrospective study was conducted between Jan 1, 2019, to March 18, 2020 (defined as the pre-COVID period), and from March 19, 2020, to December 31, 2021 (defined as COVID period) in University Malaya Medical Centre (UMMC). Electronic data records of all patients who were diagnosed in their first consultation at the institution during the study period were reviewed. In view of its retrospective nature, patients' consent was not deemed necessary for this study.

Patients who had confirmed breast carcinoma of any histological type were included. Exclusion criteria comprised those with recurrence or relapse, those who presented with benign lumps, and those who had undergone breast surgery prior to the defined periods. Timeline to surgery was defined by the number of days from the date of diagnosis to date of surgery. Types of surgery undertaken were modified radical mastectomy, simple mastectomy, breast-conserving surgery and mastectomy with reconstruction. For all the reconstructive cases included in this study, immediate reconstruction was carried out in conjunction with mastectomy in a single session.

Breast cancer staging was performed according to the 7th Edition of the tumour-lymph node-metastasis system (TNM classification) by the American Joint Committee on Cancer and the Union for International Cancer Control (7). However, phyllodes tumours were not graded using the TNM classification. Radiotherapy, antihormonal therapy, targeted therapy, and chemotherapy were classified as adjuvant and/ or neoadjuvant therapy.

Estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER-2) positivity were determined through immunohistochemical staining. Sectioned patient biopsies on slides with >1% of tumour cells demonstrating ER nuclear staining were considered ER positive. For PR status, biopsy slides with >1% of tumour cells demonstrating PR nuclear staining were considered PR positive. If the HER/neu score was 2+, the HER-2 status was equivocal and required further testing with silver *in situ* hybridisation (SISH). HER-2 positive samples were defined as a HER/neu score of 3+ and positive SISH test, whereas HER-2 negative was defined as a score of 0 or 1+ and negative SISH test.

Statistical Analysis

Demographic data, clinical characteristics and treatment administration in pre-COVID and COVID period patients were compared using a chi-square test for categorical data. For continuous variable analysis, normality was assessed using Kolmogorov-Smirnov test. The nonparametric continuous variables were analyzed using Mann-Whitney U tests. All analyses were performed using IBM SPSS, version 24 (IBM Corp, Armonk, NY, USA).

Results

The study compared 374 breast cancer patients during the COVID-19 pandemic period with 382 patients during the pre-COVID period, each period spanning nine months. In the pre-COVID period, eight (2.1%) patients had bilateral breast cancer, while in the COVID period, 13 (3.5%) patients had bilateral breast cancer, resulting in a total of 398 and 387 breast cancer cases in the pre-COVID and COVID periods respectively. All patients were female, with a median age of 60 years in both groups, with a range of 51.75–70 years in the pre-COVID group and 51–69 years in the COVID group. The majority of patients comprised those of Chinese ethnicity, which made up almost half of the study population in both periods as shown in Table 1. Malays made up almost one-third of patients, followed

Table 1. Patient demographic features

	Time period n (%)		<i>p</i> - value	chi-square value	
	Pre-COVID n (%)	COVID n (%)			
Age, years	n = 382	n = 374	0.934	0.832	
<40	19 (5.0)	23 (6.1)			
40–49	57 (14.9)	57 (15.2)			
50–59	108 (28.3)	102 (27.3)			
60–69	101 (26.4)	103 (27.5)			
>70	97 (25.4)	89 (23.8)			
Ethnicity			0.661	1.594	
Chinese	190 (49.7)	182 (48.7)			
Malay	117 (30.6)	117 (31.3)			
Indian	68 (17.8)	63 (16.8)			
Others	7 (1.8)	12 (3.2)			
Nationality			0.203	5.945	
Malaysian	376 (98.4)	363 (97.1)			
Singaporean	1 (0.3)	0 (0)			
Indonesian	4 (1.0)	4 (1.1)			
Filipino	1 (0.3)	4 (1.1)			
Others	0 (0)	3 (0.8)			
Marital status			0.993	0.001	
Yes	338 (88.5)	331 (88.5)			
No	44 (11.5)	43 (11.5)			
COVID: coronavi	COVID: coronavirus				

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by Indians (around 18%) and other ethnicities (<4%). Being a government hospital, almost all patients were of Malaysian nationality (>97%), but there was a small proportion of Filipinos, Indonesians and Singaporeans (together <2%). There were no significant differences in age of diagnosis, ethnicity, nationality and marital status between pre-COVID and COVID period.

Screening-detected cases accounted for 9% of diagnoses in the COVID period, compared to 12.3% in the pre-COVID period, whereas symptomatic cases were slightly more frequent in the COVID period (91% vs. 87.7%) as shown in Table 2. The clinicopathological features of breast cancer cases, such as tumor type, grade, stage, hormone receptor (ER/PR) and HER-2 status, were similar in both groups, except for a reduction in in situ carcinoma and an increase in Stage 4 diagnoses during the COVID period in accordance with Table 2. Invasive ductal carcinoma was the most common tumor detected in both periods (>75%), followed by ductal carcinoma in situ (11-13%) and other tumor types (around 5%). Invasive lobular carcinoma (2-5%) and malignant phyllodes (<1%) were in the minority of tumor types detected in both periods. In line with the type of tumor detected, the tumor grade of patients also seemed to be quite advanced, with most having Grade 2, followed by Grade 3 disease. Grade 1 tumors made up approximately 13% of patients in both periods. The tumour type and grading results were similarly reflected in the cancer and clinical T staging, where non-invasive stage 0 and Tis patients comprised fewer than 13% in the pre-COVID period and fewer than 10% in COVID period. Most patients presented in Stage 2 or T2 of the disease. In terminal cases, there seemed to be more patients either in Stage 3 or T4. There was also a higher number of ER and PR positive patients, although the differences were not significant. However, the opposite was true for HER-2 positivity.

The median time from tumor diagnosis to surgery was 45 days (range 24.75-156.25 days) during the pandemic and 44 days (range 26.5-153.5 days) in the pre-COVID period. Interestingly, the time was not significantly different between the periods (p = 0.958).

In terms of management, most patients received upfront surgery as the primary treatment, followed by neoadjuvant systemic therapy and palliative treatment, with no significant difference between the pre-COVID and COVID as listed in Table 2. The type of surgery performed was significantly different (p = 0.002), in which there is a significant reduction in the mastectomy rate followed by immediate reconstruction (5.6% vs. 14.5%) in the COVID period. However, the numbers receiving breast-conserving surgery and simple or modified radical mastectomy performed were identical in both groups. The number of patients receiving adjuvant and palliative chemotherapy was also significantly different (p = 0.026). Patients who were given such treatment were more likely during the pre-COVID than the COVID period (131 vs. 103). The total number of patients who were not prescribed such treatment was higher in COVID compared with pre-COVID period (297 vs. 267). This was inevitable as chemotherapy was considered a routine clinical service and this would definitely be limited during the pandemic. There were also no significant changes in the rates of radiotherapy, hormonal therapy, targeted therapy, and axillary surgery. Furthermore, the positivity rate and pathological grouping of lymph nodes did not show significant changes between the two group. A total of 10 patients were diagnosed with COVID-19 and two succumbed to the disease. The median time from tumor diagnosis to surgery was 45 days (range 24.75-156.25 days) during the pandemic and 44 days (range 26.5-153.5days) in the pre-COVID Table 2. Patient clinical pathological characteristics and management

	Time period n (%)		p-value	chi- square value
	Pre- COVID n (%)	COVID n (%)		
Mode of detection	n = 398	n = 400	0.129	2.299
Screening detected	49 (12.3)	36 (9.0)		
Symptomatic	349 (87.7)	364 (91.0)		
Tumour type			0.151	6.733
Ductal carcinoma <i>in situ</i>	54 (13.6)	44 (11.0)		
Invasive ductal carcinoma	310 (77.9)	303 (75.8)		
Invasive lobular carcinoma	9 (2.3)	19 (4.8)		
Phyllodes (malignant)	4 (1.0)	3 (0.8)		
Others	21 (5.3)	31 (7.8)		
Tumour grade			0.281	2.540
Grade 1	53 (13.5)	47 (12.1)		
Grade 2	197 (50.1)	216 (55.8)		
Grade 3	143 (36.4)	124 (32.0)		
Breast cancer staging			0.120	7.308
Stage 0	49 (12.3)	39 (9.8)		
Stage 1	75 (18.8)	70 (17.5)		
Stage 2	125 (31.4)	147 (36.8)		
Stage 3	101 (25.4)	81 (20.3)		
Stage 4	48 (12.1)	63 (15.8)		
Clinical T			0.321	4.686
Tis	42 (10.6)	34 (8.5)		
T1	72 (18.1)	93 (23.3)		
T2	157 (39.4)	141 (35.3)		
Т3	37 (9.3)	35 (8.8)		
T4	90 (22.6)	97 (24.3)		
Clinical N			0.596	0.282
N0	253 (63.6)	247 (61.8)		
N1-N3	145 (36.4)	153 (38.3)		
Clinical M			0.132	2.268
MO	350 (87.9)	337 (84.3)		
M1	48 (12.1)	63 (15.8)		
ER status	207 (74 4)	204 (75 2)	0.838	0.042
Positive	297 (74.6)	301 (75.3)		

Table 2. Continue		/ •		
Negative	101 (25.4)	99 (24.8)		
PR status			0.335	0.930
Positive	250 (64.8)	264 (68.0)		
Negative	136 (35.2)	124 (32.0)		
Her-2 status		()	0.540	0.375
Positive	85 (21.2)	77 (23.8)		
Negative	243 (61.1)	246 (76.3)		
Primary treatment			0.404	2.924
Upfront surgery	218 (54.8)	206 (51.5)		
Neoadjuvant systemic therapy	86 (21.6)	90 (22.5)		
Palliative	70 (17.6)	86 (21.5)		
Types of breast cancersurgery			0.002*	12.816
Breast conserving surgery	75 (24.8)	78 (27.3)		
Simple mastectomy/ modifiedradical mastectomy	184 (60.7)	192 (67.1)		
Mastectomy + reconstruction	44 (14.5)	16 (5.6)		
Neoadjuvant chemotherapy			0.961	0.002
Yes	86 (21.6)	87 (21.8)		
No	312 (78.4)	313 (78.3)		
Chemotherapy				
(adjuvant & palliative)			0.026*	4.941
Yes	131 (32.9)	103 (25.8)		
No	267 (67.1)	297 (74.3)		
Radiotherapy			0.346	4.473
Adjuvant radiotherapy	147 (36.9)	145 (36.3)		
IORT	8 (2.0)	9 (2.3)		
Palliative radiotherapy	10 (2.5)	3 (0.8)		
IORT + ERBT	7 (1.8)	10 (2.5)		
No	226 (56.9)	233 (58.3)		
Hormonal therapy			0.701	0.147
Yes	251 (63.1)	247 (61.8)		
No	147 (36.9)	153 (38.3)		
Targeted therapy			0.531	0.393
Yes	45 (11.3)	51 (12.8)		
No	353 (88.7)	349 (87.3)		
Axillary surgery			0.214	3.087
SLNB	145 (52.3)	138 (52.1)		

Table 2. Continued					
Axillary dissection	130 (46.9)	120 (45.3)			
SLNB to axillary dissection	2 (0.7)	7 (2.6)			
LN positivity			0.266	1.239	
Yes (N1-N3)	105 (37.8)	89 (33.2)			
No (N0)	173 (62.2)	179 (66.8)			
Pathological LN			0.371	3.139	
N0	173 (62.2)	179 (66.8)			
N1	62 (22.3)	54 (20.1)			
N2	27 (9.7)	27 (10.1)			
N3	16 (5.8)	8 (3.0)			
SLNB positivity			0.719	0.129	
SLN positive	25 (16.9)	27 (18.5)			
SLN negative	123 (83.1)	119 (81.5)			

COVID: coronavirus; IORT: intraoperative radiation therapy; SLNB: sentinel lymph node biopsy; ERBT: external beam radiation therapy

period. Interestingly, the time was not significantly different between the periods (p = 0.958) as listed in Table 3.

Discussion and Conclusion

The impact of operational changes in multidisciplinary breast cancer management within a large, integrated healthcare system were observed during the pandemic (8). There was an overall decrease in the number of breast cancer patients undergoing surgery as the number of procedures and admission in hospitals were reduced (9). There was also a decline in patients seeking consultation in the oncology clinic (10). However, our study showed a similar number of patients admitted to our institution in both study periods. In the present study, the "COVID period" was defined as the period of the Movement Control Order that was implemented from 18 March to 3 May 2020, and was followed by the Conditional Movement Control Order (CMCO), Recovery Movement Control Order, and Movement Control Order by states in the subsequent months with relaxed regulations. This relaxation of regulations may be a possible reason for the similar number of patients in both the pre-COVID and COVID periods. It can also be attributed to the rapid adaptation of policies to address the pandemic, which focused on identifying and managing suspicious breast lesions and cases. The median age of breast cancer patients was 60 years in both the pre-COVID and COVID groups, and the range of ages in the two periods was also similar.

The present study investigated system-wide operational changes and their likely sequelae on breast cancer management in an integrated care system. One publication had promoted the use of neoadjuvant systemic therapies to delay definitive surgery until personal protective equipment and resources to resume surgery during the pandemic became available (11). Upfront surgery was widely implemented in another institution because their facilities had the capacity to do so (12). The upfront surgery received by patients in this study included breast-conserving surgery, simple mastectomy and modified radical mastectomy. Breast conservative surgery, also known as lumpectomy or partial mastectomy, is a type of breast cancer surgery that involves removing only the cancerous tumor and a small amount of surrounding

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Median (range)	Pre-COVID	COVID	p-value	Mann-Whitney U value
Age, years	60.00 (51.75–70.00)	60.00 (51.00–69.00)	0.555	69662.000
Time to surgery	45.00 (26.50–153.50)	44.00 (24.75–156.25)	0.958	42936.000
COVID: coronavirus				

Table 3. Patients' age a	nd surgical wa	it time
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tissue while preserving as much of the breast as possible (13, 14). Mastectomy is a surgical procedure in which the entire breast tissue is removed. In simple mastectomy, also known as total mastectomy, the entire breast including nipple and areola are removed but not all the axillary lymph nodes while a modified radical mastectomy removes the entire breast along with the axillary lymph nodes (14). The University Malaya Medical Centre employs Clinical Practice Guideline and National Comprehensive Cancer Network (NCCN) guidelines to determine if neoadjuvant chemotherapy would be the best course of action for patients. As per the NNCN guidelines, neoadjuvant systemic therapy, including neoadjuvant chemotherapy, is recommended for women with inoperable breast cancer to attempt to convert the lesion to a resectable form (15). Additionally, a meta-analysis revealed that neoadjuvant chemotherapy resulted in a higher response rate among triple-negative and HER2-positive breast cancer patients (16). It also decreases the tumor size, making breast-conserving surgery a possible option over traditional chemotherapy (16). Our results showed similar rate of upfront surgery and neoadjuvant systemic therapy and palliative therapy during the pandemic. We hypothesize that this was due to continuation of breast care service, despite being in the midst of the pandemic (17-20).

A multicentre review of 432 patients had found delays in providing breast cancer treatment during the onset of the pandemic compared with normal treatment times (17). With governments recommending the postponement of surgeries and patients' reluctance to come to hospital due to the fear of COVID-19 infection, the average time to surgery might be expected to take longer in the pandemic cohort (11). However, the scenario in University Malaya Medical Centre (UMMC) showed no significant difference because such operations were encouraged as long as they could be performed safely. The absence of a significant difference in time to treatment between the two periods probably reflected the beneficial effects of a well-coordinated hospital in terms of medical resource re-allocation and definition of clinical priorities. Reconstruction was the treatment of choice after mastectomy. However, due to prioritization of facilities and manpower for COVID-19, many healthcare institutions had suggested keeping breast cancer surgery simple by deferring the reconstructive procedures (12). This policy was adopted in University Malaya Medical Centre (UMMC) leading to a significant drop in reconstructive procedures. This is because healthcare providers have had to divert their attention, as well as resources such as manpower, wards, and beds, to managing COVID-19 cases. As a result, longer surgeries were discouraged, and only patients who required shorter surgeries, such as skin coverings or implants, were prioritized for reconstructive procedures. In addition, reconstructive procedures involving expanders were often split into two stages to allow healthcare personnel to focus on COVID-19 management. Certain reconstructive procedures were redirected to hospitals that did not handle patients infected with COVID-19.

Delays in breast cancer diagnosis during the COVID-19 pandemic might be expected to affect oncological outcomes. There was a study

that also compared breast cancer patients operated on in the COVID period with a similar cohort identified prior to the pandemic (17). This study found significantly more cases of lymph node metastasis and advanced histological grades in the COVID period patients (17). Another study detected an increase in metastatic disease in April 2020 compared with the previous year, before the pandemic began (11). There was an estimated increase of 8 to 10% in deaths due to breast cancer during the pandemic (19). However, in our study, there were no significant differences in tumor size, grade or clinical and pathological lymph node involvement between the two periods.

Research in Northern California found a higher percentage of patients presenting with symptomatic disease during the pandemic. Another study also observed a larger number of symptomatic detections and a decrease in screening detection (11). We observed a similar scenario in which symptomatic detection was slightly different between the pre-COVID and COVID periods. Fear of COVID-19 may have discouraged women from seeking routine breast cancer screening, which resulted in delayed diagnoses and more breast cancer cases being diagnosed symptomatically.

The main concern of late cancer detection was the high risk of getting a more severe diagnosis, as observed in our study. In addition, the suspension of screening services might lead to a loss of opportunity in treating pre-malignant lesions. Indeed, in a British modelling study it was shown that a 12-month delay in breast cancer diagnoses caused by the pandemic would increase the death rate by 7.9% to 9.6% after five years (22). Similarly, a Canadian model suggested that a six-month suspension of screening would result in 670 extra advanced cases and 250 additional deaths (23). Several studies predicted that there would be more patients presenting with advanced disease as a result of stage migration and possibly worse outcomes (24, 25). A recent study from a university referral hospital in northern Italy investigated this issue. They performed a retrospective single-institution review of women diagnosed with breast cancer between May and July 2020, when there was an interruption in breast cancer screening, and then fast-tracked those who had been delayed through their screening and comparing them with patients diagnosed in a similar period prior to COVID-19. They did not detect a significant difference in tumor biology, which concurred with the results of the present study. However, they did see a significant increase in locally advance stage at diagnosis (26). In University Malaya Medical Centre (UMMC), there is a slight increase in Stage 4 breast cancer cases and reduction in *in situ* breast carcinoma cases during the COVID period (22). This is most likely due to patients' reluctance to seek medical attention because of the fear of contracting COVID-19 or overwhelming the healthcare system, resulting in fewer opportunities for early detection. Furthermore, the changes in hospital policies and resources during the pandemic may have resulted in different diagnostic and treatment strategies that favored presentation with late-stage invasive carcinoma over in situ carcinoma.

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Though our study did not focus on determining the incidence of COVID-19 among patients, only a small number (0.4%, n = 2) died due to COVID contraction in hospital, indicating that patients did not face a higher risk of COVID-19 infection when seeking treatment in hospitals. Moreover, we found out that the COVID-19 status itself did not have a significant impact on definitive treatment or surgery (6).

The main limitation of the present study was the small number of patients from a single center. Therefore, the results do not represent a general scenario, but it may be useful in helping healthcare institutions to come up with better treatment strategies as they try to adapt to the pandemic. A multicentric study with a large sample size would be needed to study the overall impact of COVID-19 on breast cancer patients and disease progression, which will also vary from country to country. More importantly, the COVID-19 pandemic, which began in March 2020, has persisted, and a longer follow-up period would be needed to assess the long-term impact on breast cancer stage migration and death rate.

COVID-19 brought operational changes in breast cancer management that have resulted in a reduction in screening-detected breast cancer cases, an increase in *de novo* Stage 4 cases, a reduction in reconstructive procedures, and a decrease in adjuvant chemotherapy. These findings are concerning because delays in screening and diagnosis can lead to more advanced cancer at diagnosis, which can negatively impact treatment outcomes and survival. The reduction in reconstructive procedures and adjuvant treatment may also affect the quality of life and long-term outcomes for breast cancer patients. Therefore, it is important to address these operational changes and their impact on breast cancer management as the pandemic persists. Patients should be encouraged to attend their outpatient appointments and screening programs once they resume.

Ethics Committee Approval: The study was approved by the Medical Research Ethics Committee University of Malaya Medical Centre MECID. NO: 20211012-10689 and conformed to the Declaration of Helsinki 1975.

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: T.J.M., N.S.A.L., L.L.L.; Design: N.J.H., S.M.H., T.J.M.; Data Collection or Processing: N.J.H., S.M.H., T.J.M., T.M.S., M.D., N.S.A.L., A.A.M., L.L.L; Analysis or Interpretation: N.J.H., S.M.H., T.M.S., M.D., N.S.A.L., A.A.M., L.L.L.; Literature Search: N.J.H., S.M.H., N.S.A.L., A.A.M., L.L.L; Writing: N.J.H., S.M.H., T.J.M., T.M.S., N.S.A.L., A.A.M., L.L.L.; Writing: N.J.H., S.M.H., T.J.M., T.M.S., N.S.A.L., A.A.M., L.L.L.

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