ORIGINAL ARTICLE

Molecular Classification of Breast Cancer using Immunohistochemistry and Fluorescence in Situ Hybridization as Surrogate Markers in Maiduguri, Northeastern Nigeria

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ABSTRACT

Background: Breast cancer is the most common malignant neoplasm and the leading cause of cancer related deaths among women worldwide. Traditional breast cancer classification based on histopathologic features has limited prognostic and predictive value compared to the molecular classification which although was developed based on hierarchical clustering analysis of gene expression profiling, has been shown to be similar to immunohistochemically defined schemes which can predict clinical outcomes. These immunohistochemically defined schemes are being used as surrogate markers for molecular classification of breast cancer especially in low resource settings like ours. **Objectives:** Paucity of publications on the molecular classification of breast cancer from Northeastern Nigeria prompted this study. **Methods:** The study was a hospital based, descriptive and cross sectional one. One hundred and thirteen (n=113) archived tissue blocks from confirmed cases of breast cancer that fulfilled the inclusion criteria for the study were retrieved along with their request cards. Immunohistochemistry was performed on the tissue blocks using monoclonal mouse antibodies to human ER, PR and HER-2 (Novocastra post primary, Leica Biosystems REF7111, 7102 and 7101 respectively). The slides were evaluated using the semi-quantitative quick score and ASCO/CAP 2013 guidelines. Equivocal HER-2 cases had FISH done on them at Unistel medical laboratories, South Africa using the IQFISH protocol. The slides were evaluated using the ASCO/CAP 2013 guidelines. **Results:** Out of the 1415 cancers diagnosed at the Department of Histopathology, UMTH over the study period, breast cancer accounted for 276 (19.5%) cases. Of the 113 breast cancer cases analysed by immunohistochemistry for the study, 24 (21.2%), 11 (9.7%) and 13 (11.5%) cases were positive for ER, PR and HER-2 respectively. Three (2.8%) cases were equivocal for HER-2 by immunohistochemistry and had FISH done. Using immunohistochemistry as surrogate markers for molecular classification, Luminal A subtype constituted 23 (20.4%) cases, Luminal B had 2 (1.8%) cases, HER-2/neu over expressing had 10 (8.8%) cases and triple negative/Basal-like subclass had 78 (69%) cases. **Conclusion:** The present study buttresses the fact that breast cancer in Nigeria is predominantly triple negative (69%) and have a high unfavourable molecular subclass (Basal-like). It also shows that FISH if available, can influence management decisions in cases that are HER-2 equivocal by immunohistochemistry.

Key words: Breast cancer, immunohistochemistry, in Situ Hybridization, Surrogate Markers, Maiduguri

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Introduction

Breast cancer is a clinically heterogeneous disease.[1] It is the most common cancer among women worldwide.[1] More than one million cases occur annually worldwide.[2] GLOBOCAN 2020 data indicated that breast cancer is the most frequently diagnosed cancer worldwide accounting for 11.7% of all diagnosed cancer.[2] It is also the most frequently diagnosed cancer in Africa (16.8%)[3] and Europe (13.1%)[4]. An estimated 2.9 million women live with breast cancer in the United States of America.[5] The incidence in the USA is higher among non-Hispanic whites but mortality is higher among African Americans. In Africa, breast cancer accounts for

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27.6% of all cancers in females.[5] The incidence varies with regions across the continent. In Nigeria, breast cancer has been reported to be the most common cancer in females in many centres. Ezenkwa *et al* in a recent study in Northeastern Nigeria showed that breast cancer is the leading cancer accounting for 22.9% of all cancers in the region.[6] In Maiduguri, it accounted for 13.9% of all diagnosed cancers and 34.5% of all breast biopsies reported at the department of Histopathology, University of Maiduguri Teaching Hospital (UMTH) from 2001 to 2005.[7]

Breast cancer has traditionally been classified on the basis of its histopathological features which have been shown to have low prognostic and predictive value. A more recent molecular classification that is based on hierarchical clustering analysis of gene expression profiling has been proposed. This microarray based molecular classification has better prognostic value and is of predictive value therapeutically.[8] The molecular classification has been shown to bear striking similarity to those of immunohistochemically defined schemes using antibodies to known breast markers.[7]

These markers are used as surrogates for the molecular classification. Several markers including estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor-2 (HER-2), Ki67, EGFR have been used for this classification.[9] The index study utilized immunohistochemistry (ER, PR and HER-2) and FISH (fluorescent in situ hybridization) as surrogates.

METHODS

The study was conducted at UMTH, Maiduguri which is the apex referral centre in the Northeastern region of Nigeria.

The study was a hospital based and descriptive. One hundred and thirteen (113) archived tissue blocks from histologically confirmed breast cancer cases over a five-year period (2010-2014) were retrieved along with their request cards.

Immunohistochemistry was performed on the tissue blocks using monoclonal mouse antibodies to human ER, PR and HER-2 (Novocastra Post Primary Leica Biosystems REF711, 7102 and 7101 respectively).

Sections from the tissue blocks were initially stained with haematoxylin and eosin (H&E) to determine their adequacy for immunohistochemistry. Four micrometer thick sections were taken from each tissue block and mounted on adhesive coated glass slides preparatory to immunohistochemical staining. Sections were deparaffinised in xylene for 10 minutes, rehydrated in grades of alcohol followed by blocking of endogenous peroxidise activity using 0.5% hydrogen peroxide. Heat induced epitope retrieval was achieved using microwave incubation in citrated buffer (0.1M: PH6.0). Antigen localisation was achieved by incubating sections with primary antibody followed by application of primary antibody enhancer. The indirect avidin-biotin complex procedure using 3,3-aminobenzidine tetrahydrochlorate (DAB) as substrate chromogen was applied for detection of bound antibodies.

The slides were evaluated using the semi-quantitative quick score and ASCO/CAP 2013 guidelines. Luminal A molecular subclass is defined by ER and PR positivity and HER2 negativity.[1,10,11] Luminal B molecular subclass is defined by ER and PR positivity and HER2 positivity.[1,11,] HER2/neu subgroup is defined by ER and PR, negativity, HER2 positivity.[12,13] Basal-like subgroup is defined by ER, PR and HER2 negativity.[1,11-14]

Equivocal HER-2 cases had FISH done using the standard IQFISH protocol at Unistel Medical Laboratory, Stellenbosch University, South Africa and reported using the 2013 American Society of Clinical Oncologists /College of American Pathologists (ASCO/CAP) guideline.

Statistical analysis was carried out using statistical package for the social sciences (SPSS) version 20.0 Chicago IL, USA computer software.

RESULTS

Out of the 113 breast tissue biopsies that had immunohistochemistry done on them, 12 (10.6%) were positive for ER only. One (0.9%) was positive for PR only and 10 (8.8%) showed positivity for HER-2 as a single marker out of which 2 biopsies were initially equivocal by immunohistochemistry and over amplified on doing FISH. Co-expression of ER and PR together was seen in 10 (8.8%) tissue biopsies while 1 (0.9%) biopsy each was positive for ER and HER-2/neu and PR and HER-2/neu co-expression respectively. Triple positive immunohistochemistry staining was not recorded.

Table I: Frequency Distribution of ER, PR and HER-2 among Breast Cancer

Marker	ER Freq(%)	PR Freq (%)	HER-2 Freq(%)
Negative	89 (78.8)	102 (90.3)	100 (88.5)
Positive	24 (21.2)	11 (9.7)	13 (11.5)
Total	113 (100)	113 (100)	113 (100)

Out of the 113 tissue biopsies analysed by immunohistochemistry and FISH, Luminal A subtype constituted 23 (20.4%) while Luminal B made up 2 (1.8%). HER-2/neu over expressing had 10 (8.8%) and the basal subclass had 78 (69%).

Among the 23 luminal A biopsies, 10 (43.5%) biopsies were positive for ER and PR together. Another 12 (52.1%) were positive for ER alone and 1 (4.4%) was positive for PR alone.

The luminal B subclass showed one biopsies each with positivity for ER/HER-2/neu (50%) and PR/HER-2/neu (50%).

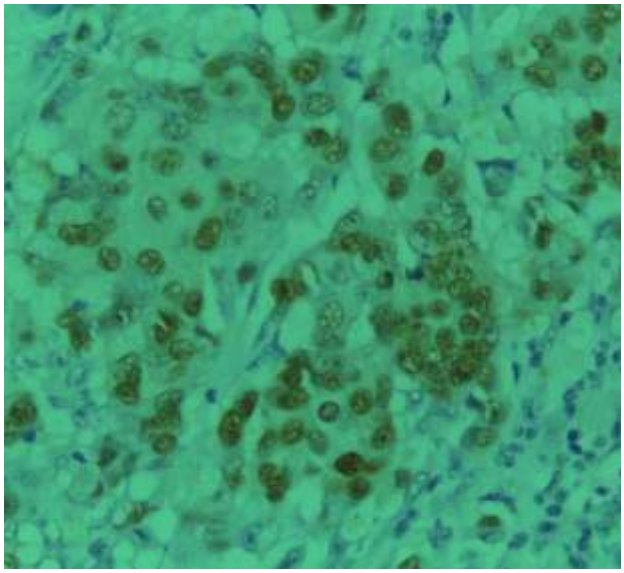

Figure 1: Photomicrograph of ER positive breast cancer

The section shows nuclear staining that is strikingly visible even at low magnification. Seventy percent of the tumour cells had 3+ positivity (Quick Score 6/7) (X200)

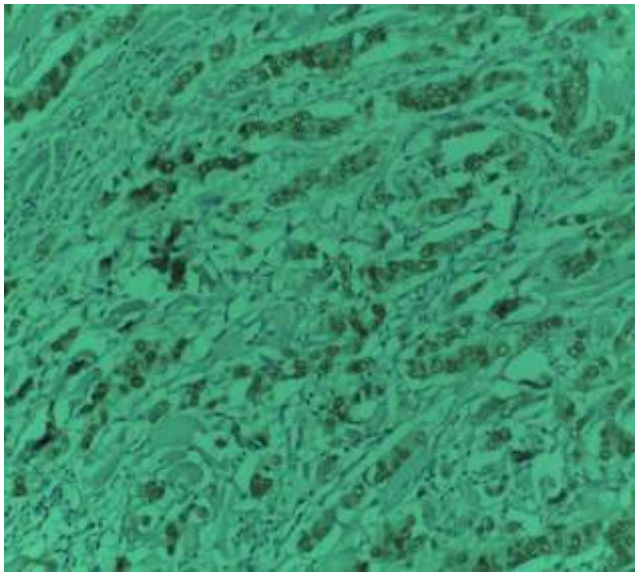

Figure 2: Photomicrograph of PR positive breast cancer

The section shows nuclear staining that is strikingly visible even at low magnification. Sixty percent of the tumour cells had 3+ positivity (Quick Score 6/7 (X200)

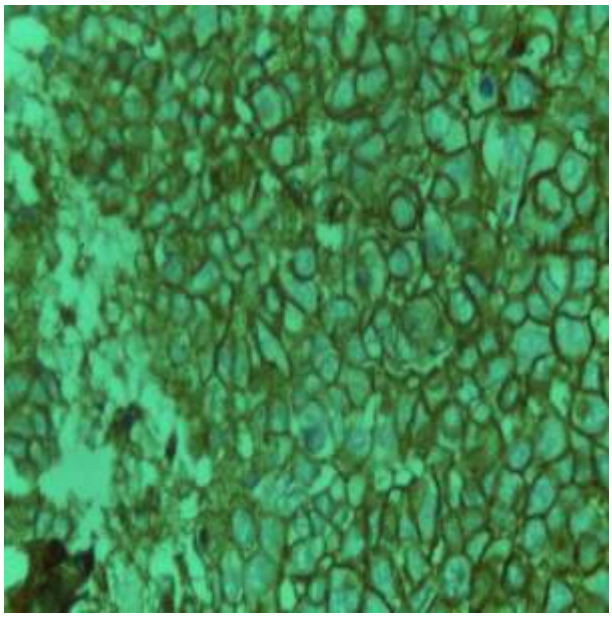

Figure 3: photomicrograph of HER-2 positive breast cancer
The section shows complete, strong membrane staining in 90% of tumour cells. (X200)

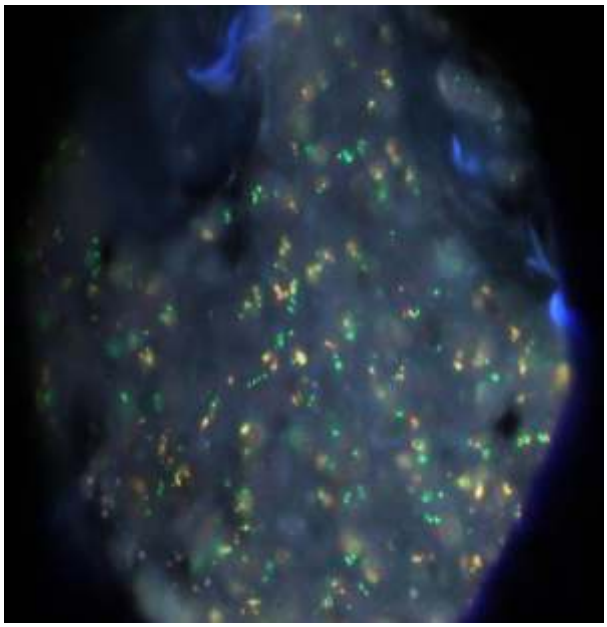

Figure 4: fluorescent in situ hybridization photomicrograph.

The photomicrograph shows amplification of HER-2. The orange signal represents *HER2* and the green signals chromosome 17(*CEP17)*. The HER-2/cep 17 ratio was 3.49 and the average HER-2 copy number equals 12.05

Table II: Frequency Distribution of ER, PR and HER-2 among individual Breast Cancer Cases from 2010-2014

Immunohistochemical markers	Frequency distribution	Percentage (%)
ER, PR, HER-2 negative	0	0
ER, PR, HER-2 negative	78	69
ER, PR positive	10	8.8
ER, HER-2 positive	1	0.9
PR, HER-2 positive	1	0.9
ER positive	12	10.6
PR positive	1	0.9
HER-2 positive	10	8.8
Total	113	100.0

Table III: Molecular Classification of Breast Cancer using Immunohistochemical Markers

Molecular Classification	Frequency	Percentage
Luminal A	23	20.4
Luminal B	2	1.8
HER-2	10	8.8
Basal	78	69.0
Total	113	100.0

Discussion

There were a total of 1415 histologically diagnosed cancers in the diagnosis register of Histopathology Department UMTH during the study period (2010-2014). Out of this number, breast cancer constituted 276 cases accounting for 19.5% of all cancers diagnosed during the study period. This figure is higher than the 13.9% reported by Nggada *et al*[7] in the same centre 2001-2005.This may be attributable to more awareness on breast cancer and its screening methods as well as increased access to health care facilities by the rural dwellers in the regions that were displaced by the Boko Haram insurgency to Maiduguri, the state capital. The higher figure of this study compared to the previous one could also be due to the global increase in the incidence of breast cancer.[2]

The Index study observed the frequency of hormone receptors (ER and PR) and HER-2/neu (as shown in table I and II) to be 24 (21.2%) for ER, 11(9.7%) for PR and 13 (11.5%) for HER-2 while 78 (69%) were negative for all three markers.

The total frequencies agree with most studies from other parts of Nigeria[10-17] that show a low hormone receptor and HER-2 positivity and high triple negativity. Minoza *et al*[13] in the same facility in 2016, reported ER of 36.8%, PR of 34.2%, HER-2 of 21.1% and triple negative of 52.6%. Makanjuola *et al*[12] in Lagos reported 7% for ER, 2.1% for PR and 3.8% for HER-2. Agboola *et al* in two separate studies in Southwestern Nigeria,[14,15]reported hormone receptor and HER-2 positivity of 15% and 16.3% for ER, 20.3% and 23.6% for PR and 18.2% and 17.6% for HER-2 respectively. Two studies in Ile-Ife also reported ER of 38% and 34.6%, PR of 21% and 25%, with HER-2 of 5.2% and 38.2% respectively.[11,16] A study in Ilorin showed a frequency of 27%, 16% and 30% for ER, PR and HER-2 respectively.[18] In Jos, Gucas *et al*[10] reported 25% for ER, 27.8% for PR and 25% for HER-2.

In Sokoto Northwestern Nigeria, the findings were 47.8%, 41.3% and 43.5% for ER, PR and HER-2 respectively.[17]

Stark *et al*[19] in Ghana compared hormone receptor and HER status between White Americans, African Americans and Africans (Ghanaian) breast cancer patients and recorded ER of 22.8%, PR of 30.8% and HER-2 of 5.3%among Ghanaians.

Their findings show a low hormone receptor and HER-2 positivity like the index study.

In two comparative studies between Nigerian and British breast cancer women, Agboola *et al*[14,15] reported ER of 72% and 51%, PR of 58.3% and 38.7% and HER-2 of 12.5% and 14.7% respectively among the British cohort. Masumi *et al*[20] in Japan reported 71.1% for ER, 60.1% for PR and 30.3 % for HER-2. These findings are at variance with the index study and most other studies from Africa. A study in India recorded 36% each for ER and HER-2 and 33% for PR.[21]

The results for hormone receptors ER and PR in the index study are like other studies in Nigeria and Africa where breast cancer cases are more likely to be hormone receptor negative[10] Some studies have shown that there is significant difference in oestrogen signalling and levels between Blacks and Caucasians with blacks having a decreased level of the protective $ER\alpha$ isoform.[10,22] Oestrogen and progesterone act through binding to their receptors ER and PR. They are known to play important roles in regulating growth and differentiation of breast cancer thus making them important prognostic markers.[22]

well established as it determines response to hormonal therapy with anti-oestrogens such as Tamoxifen while that of PR is less well established. Some studies show that loss of PR expression was associated with worse prognosis in ER+ breast cancer.[23]

HER-2/neu protein overexpression is seen in 10%-35% of human breast cancers.[24] In addition to being an important prognostic marker, it is important in selecting treatment strategies, predicting response to treatment and improving survival.[10] HER-2/neu overexpression is important for treatment with Herceptin. There is an inverse relationship between HER-2 positivity and response to hormonal therapy with tamoxifen. The patients with HER-2 positive tumours however show response to anthracycline based adjuvant therapy and taxanes.[24,25]

Immunohistochemistry is currently the most frequently used method of assessing HER-2 status in breast cancer. Other methods include FISH, CISH, PCR among others.[26] Immunohistochemistry has the advantage of having lower technical requirements and cost hence it can be done routinely in most pathology laboratories.[26] FISH is however considered a better technique for assessing HER-2 because it is more reliable and reproducible.[27]

Immunohistochemistry detects the HER2/neu protein overexpression while FISH measures HER2/neu gene amplification which is more accurate because protein overexpression is the result of gene amplification. Introduction of fluorescence in situ hybridization (FISH) allows assessment of the level of gene amplification with information about distribution of gene copies in histologic sections.[27,28]

A series of reports have verified the accuracy and apparent superiority of FISH over immunohistochemistry in a prediction of response to transtuzumab in metastatic breast carcinoma patients. The main difficulty for adopting FISH in a clinical setting is the need of additional equipment for analysis such as fluorescence microscopy and multiband fluorescence filters.[26]

Advancement in the FISH procedure is the introduction of instant quality FISH (IQFISH) buffer which reduces the time required for hybridization from 16 hours to one hour. This reduces the time of the procedure from 16-20hours to3.5-4 hours.[26]

HER-2 protein overexpression by immunohistochemistry in the index study was observed in 10(8.8%) of cases with 3 (2.4%) cases being equivocal (2+). The equivocal cases were subjected to FISH (IQ FISH) and the outcome was 2(67%) cases out of three showing HER2 gene amplification while the third was considered not fit for the procedure. Following review of the sample by immunohistochemistry, it was downgraded and considered negative. Studies have shown that FISH positivity in 2+immunohistochemistry samples varies between 7% and 89%. The figure stands at 67% in the index study which is within the quoted range. Seglican *et al*[27] compared HER-2/neu by immunohistochemistry and FISH and concluded that consistency between the 2 procedures were higher for negative (0-1+) and positive (3+) than for equivocal (2+) cases. They showed that consistency between IHC and FISH was 17% and 67% for previous IHC 2+ and 3+, respectively, whereas it was 23% and %75 for re-reviewed IHC 2+ and 3+, respectively.

Triple negative breast cancer (TNBC) in the index study accounted for 78 (69%) of cases. This high figure is in keeping with most studies in Nigeria that show high TNBC. Studies in Maiduguri, Ile-Ife and two studies in Lagos show triple negative breast cancer comprising 52.6%, 53.4%, 87% and 55.5% respectively.[11-15] Adebomowo *et al*[29] in Ibadan got a low triple negative breast cancer of 17% similar to what has been reported among Caucasians but in contrast to the index study. Stark *et al*[19] reported 34% TNBC among Ghanaians. Agboola *et al*[15] reported TNBC of 21% among patients in the United Kingdom.

Triple negative breast cancer (TNBC) refers to breast cancer which is negative for ER, PR and HER-2 receptors. This form of breast cancer has been shown to mostly occur among individuals of African ancestry, low socio-economic group and at a younger age.[19] It accounts for about 15%-20% of breast cancer in most series.[1] TNBC is associated with higher recurrence rates, faster growth, poorer prognosis, higher P53 mutation, inactivation of BRCA 1 gene and over expression of EGFR. It shows response to chemotherapy and anti EGFR therapy.[19,30]

Several studies have shown the usefulness of immunohistochemistry for hormone receptors and HER-2 among others, as surrogate markers for molecular classification of breast cancer. Studies have shown that although immunohistochemical surrogates accurately identifies the molecular subtypes, there is no complete overlap between the two.[9,31,32] These molecular subtypes have both prognostic value as well as also being predictive of response to chemotherapy.[8]

Using immunohistochemical markers as surrogates, the index study recorded 23 (20.2%) cases of Luminal A, 2 (1.8%) cases of Luminal B, 10 (8.8%) cases of HER-2/neu and 78 (69%) cases of Basal-like subtypes as shown in table III. The findings show a lower luminal and HER-2/neu subtypes and a high basal-like subtype. Similar findings have been recorded in studies from other parts of Nigeria.[13-17] Minoza *et al*,[13] in a prospective study looking at hormone receptor status in patients attending one of the general surgery units of department of Surgery UMTH over a three-year period recorded Luminal A of 23.6%, Luminal B of 13.2% and HER-2/neu of 7.9%. Triple negative cases constituted 52.6%. Two studies in Lagos recorded Luminal A of 23.7% and 14.5%, Luminal B of 4.4% and 2.2%, HER-2/neu of 22.8% and 12.3% while Basal subtype was 49.1% and 32.6% respectively.[14,15] The findings in Ile-Ife by Omoniyi-Esan *et al*[16] were 14.7% for Luminal A, 15.4% for Luminal B, 22.1% for HER-2 and 33.1 for Basal subtype. A study in Sokoto in 2016 recorded Luminal A of 24%, Luminal B of 22% HER-2/neu of 26% and Basal-like of 28%.[17] Studies from other African

countries have recorded similar findings.[33-36] Huo *et al*.[36] reported Luminal A of 33%, Luminal B of 3%, HER-2 of 14% and Basal of 23%. In Uganda, Galukande *et al*.[33] recorded 38% for Luminal A, 5% for Luminal B and 22% for HER-2. Ohehe-Yeboah *et al*.[36] in 2012 recorded basal-like subtype of 42.7%. Tesfamariam *et al*.[34] in Eritrea, the horn of Africa, recorded Luminal A of 55%, Luminal B of 5%, HER-2 of 5% and Basal type of 25%.

Other studies from Nigeria[29,37] show high luminal type tumours which are at variance with the findings in the index study. Adebomowo *et al*.[37] in Ibadan recorded Luminal A of 77.6%, Luminal B of 2.6%, HER-2 of 4% and basal type of 15.8%. They concluded that the findings are similar to that of Caucasian breast cancers as opposed to the majority of studies conducted in the country.

Conclusion

The study shows an increase in breast cancer accounting for 19.5% of all cancer diagnosed making it the most common cancer similar to results obtained in other parts of the country and indeed the world. Also, hormone receptor positivity was low in agreement with most other studies in Nigeria. Tumours with triple negative hormonal status constitute the highest percentage in this study. Molecular classification shows low luminal type tumours and high basal type tumours buttressing similar findings from other parts of Nigeria.

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Conflict Of Interest

The authors declare no conflicts of interest with respect to this research.

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