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miR-125b expression in breast cancer: Insights into subtypes and demographic factors at Hospital Canselor Tuanku Muhriz (HCTM)

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ABSTRACT

Breast cancer (BC), the most prevalent and fatal female neoplasm worldwide, including in Malaysia, is a heterogeneous disease classified into subtypes based on hormone receptor status, including luminal A, luminal B, HER2-enriched and triple-negative. The heterogeneity of BC poses challenges for accurate diagnosis and treatment, necessitating novel biomarkers to aid cancer screening, diagnosis and therapy. MicroRNAs (miRNAs), which regulate gene expression, are often dysregulated in cancer. Specifically, miR-125b has been linked to mitochondrial dysfunction and chemoresistance, supporting its potential as a biomarker for BC, particularly as a predictive biomarker. This study aims to investigate the associations between miR-125b expression patterns in different BC subtypes and demographic profiles at Hospital Canselor Tuanku Muhriz, Universiti Kebangsaan Malaysia (HCTM). miR-125b expression was analysed in 18 formalin-fixed paraffin-embedded (FFPE) BC tissue samples and two control tissues by quantitative polymerase chain reaction (qPCR). Among 241 BC cases reported at HCTM in 2023, patients were predominantly Malay, aged 50 and above, with luminal A being the most common subtype, followed by triple-negative, luminal B and HER2-enriched. miR-125b expression was consistently downregulated in BC tissues compared to controls, although this difference was not statistically significant ($p = 0.263$). Trends of downregulation were observed across all subtypes and demographic groups, with no significant differences by age ($p = 1.000$), ethnicity ($p = 0.546$) or BC subtypes ($p = 0.701$). The consistent downregulation of miR-125b aligns with previous studies and highlights its biomarker potential for BC diagnosis and prognosis. Further research with a larger cohort is needed to validate these findings and explore the potential of miR-125b as a diagnostic, prognostic or predictive biomarker in BC.

Keywords: *Breast cancer; microRNA; miR-125b; demographic and Malaysia*

INTRODUCTION

Breast cancer (BC) is a heterogeneous disease, that leads to its classification into various subtypes with distinct molecular profiles and clinical outcomes (Tsang & Tse, 2020). These molecular subtypes, including luminal A, luminal B, HER2-enriched and triple-negative BC, are generally based on hormone receptor status such as the oestrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) (Orrantia-Borunda et al., 2022). BC is the most prevalent and fatal neoplasm among females worldwide,

including in Malaysia (Ferlay et al., 2024). Its heterogeneous nature poses significant challenges for accurate diagnosis, prognosis and treatment. Thus, developing new approaches to improve and supplement existing techniques for cancer screening, diagnosis and therapeutic approaches is crucial (Tsang & Tse, 2020).

MicroRNAs (miRNAs) are small non-coding RNAs that regulate gene expression by binding to the 3′-untranslated regions (3′UTRs) target gene, leading to mRNA degradation and translational repression (Yang & Liu, 2020). Dysregulation of miRNA expression has been well-documented in various cancers, particularly BC (Yang & Liu, 2020). The ability of miRNAs to target multiple genes makes them intriguing in the study of their association with mitochondria. Mitochondrial dysfunction is closely linked to oncogenesis, influencing malignant transformation, tumour progression, treatment response and anticancer immunosurveillance. These highlights the critical role of mitochondrial functions in cancer cell survival and therapeutic resistance (Porporato et al., 2017).

Previous research has established miR-125b as a tumour suppressor in BC, with studies showing its downregulation during BC tumorigenesis, suggesting its significant role in the disease's development (Feliciano et al., 2013; Zhang et al., 2011). According to miRNA profiling studies, miR-125b is one of the most downregulated miRNAs in BC (Iorio et al., 2005; Zhang et al., 2011). miR-125b was also proposed as a potential prognostic biomarker, with its downregulation being associated with lower survival rates in BC patients (Zhang et al., 2011). Furthermore, the downregulation of miR-125b is linked to doxorubicin resistance and its enforced expression has been shown to resensitize cancer cells to doxorubicin (Hu et al., 2018), thereby highlighting its potential as a prognostic biomarker and a therapeutic target for BC treatment.

This study investigates the potential role of miR-125b in BC, focusing on its known dysregulation and impact on the disease. Despite the established roles of miRNAs in cancer, the associations between miRNA expression patterns in BC subtypes across different demographic profiles in Malaysia remain underexplored. Previous studies have shown that Chinese women in Malaysia are more likely to present with Luminal A BC and favourable tumour characteristics such as ER and PR positivity, while Malays and natives of Sarawak have higher rates of triple-negative subtypes and Malay and Indian women frequently exhibit aggressive, high-grade and hormone-negative tumours (Bhoo-Pathy et al., 2012; Devi et al., 2012). Given Malaysia's diverse demographic profiles, particularly in terms of ethnicity, exploring these association could provide invaluable insights and lead to the identification of more specific diagnostic and prognostic biomarkers.

MATERIALS & METHODS

Ethical clearance and data collection

Ethical approval for the use of clinical tissues and data collection in this study was obtained from the Universiti Kebangsaan Malaysia, (UKM), Research Ethics Secretariat, under protocol number JEP-2023-453. Demographic data, including age, ethnicity and clinical characteristics, were collected from patients diagnosed with BC in 2023.

Retrieval of archived formalin-fixed paraffin-embedded (FFPE) samples

Archived FFPE samples were retrieved from the Department of Pathology at HCTM. All the archived FFPE samples (n = 18) were selected after evaluating for tumour percentage and representative tumour areas from the haematoxylin and eosin (H&E) slides of 30 potential samples, according to the pathologist in charge. The 30 potential samples were drawn from 2023 BC patients who underwent tumour resection and had completed hormone receptor status information. The inclusion criteria for the archived FFPE samples included a confirmed histological diagnosis of BC between January 2023 and December 2023, sufficient tissue for analysis and tumour areas with a tumour percentage of more than 10%. The selected archived samples represented luminal A, HER2-positive and triple-negative subtypes. Control tissue samples from resected fibroadenoma of the breast (n = 2) were also retrieved.

Total RNA extraction

Total RNA extraction from the selected FFPE tissue samples was performed using the miRNeasy FFPE Kit (Qiagen) following the manufacturer's protocol. The protocol for purification of total RNA, including miRNA from FFPE tissue sections, was followed. Deparaffinization was performed using xylene and the RNA was eluted in 30 µl of RNase-free water. Total RNA was extracted from double 10µm FFPE sections from the 17 BC samples and two fibroadenoma of the breast for control and triple 10µm FFPE sections for one BC sample.

Quantification of RNA

The RNA concentration and purity were determined by measuring absorbance of 260/280 nm using the Nanophotometer Pearl (Implen, Germany).

cDNA synthesis

Reverse transcription was performed using the Tetro cDNA synthesis kit (Bioline) according to the manufacturer's recommended protocol. The final volume of 20 µl containing primers (gene-specific primers in equal molarity), a dNTP mixture, 5× RT buffer, Tetro reverse transcriptase, Ribosafe RNase inhibitor, approximately 0.5 ng of mRNA and DEPC-treated water. The reaction mixture was incubated at 45 °C for 30 minutes, terminated at 85 °C for 5 minutes, and chilled on ice prior to quantitative polymerase chain reaction (qPCR).

Quantitative polymerase chain reaction (qPCR)

qPCR was performed in triplicate using the THUNDERBIRD™ Next SYBR® qPCR Mix (Toyobo) on the MyGo Pro ESR qPCR (Novacyt) system. The PCR reaction mix included 10 µl THUNDERBIRD™ Next SYBR® qPCR Mix (Toyobo), 2 µl forward primer (10 µM), 2 µl reverse primer (10 µM), 2 µl cDNA and 8.5 µl sterilised water. qPCR was carried out under the following thermocycling conditions: 95˚C for 60 seconds, followed by 3-step amplification of 40 cycles of 95˚C for 15 seconds, 55˚C for 30 seconds, and 72˚C for 60 seconds. One cycle of 95˚C for 10 seconds and 60˚C to 97˚C at 0.05˚C/s for dissociation. PCR primers were obtained from Integrated DNA Technologies (Singapore) with the following sequences: miR-125b forward, 5'-ACACTCCAGCTGGGTCCCTGAGACCCTTTAAC-3' and reverse, 5'-TGGTGTCGTGGAGTCG-3'; and U6 forward, 5'-CTCGCTTCGGCAGCACA-3' and reverse, 5'-AACGCTTCACGAATTTGCGT-3. These sequences were based on a study by Hu et al. (2018). The relative expression of miR-125b was determined using the 2-ΔΔCT analysis method, with U6 snRNA used as an internal reference.

Statistical analysis

Descriptive analysis was performed for all demographic variables, including age groups and ethnicity and clinical characteristics, including BC subtypes. Pearson's chi-square test was used to compare the BC subtypes in terms of demographic characteristics. The values of fold change (2-ΔΔCT) of miR-125b expression were confirmed to be not normally distributed. Non-parametric tests such as the Mann-Whitney-U test, were used to compare miR-125b expression between control tissues and cancer tissues, to assess the relationship between miR-125b expression across different age groups and ethnicities within the patient cohort. The Kruskal-Wallis's test was utilised to assess a relationship between miR-125b expression across different subtypes within the patient cohort. P-values less than 0.05 were considered to be statistically significant. All statistical tests were conducted using SPSS Statistics 29.0 (IBM, USA).

RESULTS

BC cases in Hospital Canselor Tuanku Muhriz, UKM for 2023

Data on the demographics and clinical characteristics of BC patients were collected at Hospital Canselor Tuanku Muhriz, UKM (HCTM). This included information on age, ethnic background and hormone receptor status. Table 1 shows that in 2023, there were a total of 241 BC cases at HCTM. The distribution of BC patients by age groups was 22.4% under 50 years old and 77.6% aged 50 and above. Ethnic distribution was 57.3% Malay, 33.2% Chinese,

Table 1

Frequency of BC incidence based on demographic data in 2023 at Hospital Canselor Tuanku Muhriz UKM (HCTM)

Category		Frequency (n=241)	Percentage (%)
Ethnicity	Malay	138	57.3
	Chinese	80	33.2
	Indian	13	5.4
	Other	10	4.1
Age (Years)	< 50	54	22.4
	≥ 50	187	77.6
Subtypes	Luminal A	107	44.4
	Luminal B	21	8.7
	HER2-enriched	21	8.7
	Triple-negative	33	13.7
	Not Available	59	24.5

Notes: Demographic and clinical distribution of BC cases diagnosed in 2023 at HCTM.

5.4% Indian and 4.1% classified as 'Other'. The subtype distribution was based on the hormone receptor status, luminal A comprised 44.4%, followed by triple-negative (13.7%), luminal B (8.7%), and HER2-enriched (8.7%). Due to incomplete data, about 24.5% of patients could not be categorised into any subtypes.

Association of BC subtypes and demographic characteristics

No statistically significant association was found between BC subtypes and demographic characteristics such as ethnicity (p = 0.255) and age (p = 0.344) as shown in Table 2.

Table 2

BC subtypes among patients at Hospital Canselor Tuanku Muhriz UKM (HCTM) in 2023 according to demographic data

Category		Subtypes										p*
		Luminal A		Luminal B		HER2-enriched		Triple-negative		Not Available		
		n	%	n	%	n	%	n	%	n	%	
Ethnicity	Malay	53	49.5	12	57.1	16	76.2	20	60.6	37	62.7	0.255
	Chinese	39	36.4	9	42.9	5	23.8	9	27.3	18	30.5	
	Indian	10	9.3	0	0.0	0	0.0	1	3.0	2	3.4	
	Other	5	4.7	0	0.0	0	0.0	3	9.1	2	3.4	
Age (Years)	< 50	20	18.7	8	38.1	6	28.6	8	24.2	12	20.3	0.344
	≥ 50	87	81.3	13	61.9	15	71.4	25	75.8	47	79.7	

*Notes: Distribution of BC subtypes by ethnicity and age. Percentages are reported within subtypes to reflect the distribution of age and ethnicity within each subtype. * Pearson chi-square test.*

miR-125b expression among control tissues and BC tissues

The relative expression of miR-125b was measured in control tissues and BC tissues. No significant difference was observed between two groups (p = 0.263), as presented in Table 3. Nevertheless, Figure 1(A) showed that the control tissues exhibited higher miR-125b expression compared to BC tissues.

Table 3

miR-125b expression in control tissues compared to BC tissues

Gene Expression	N = 20	Control Tissues Mean (SD)	Cancer Tissues Mean (SD)	p-value
miR-125b	20	100.250 (141.767)	0.273 (0.923)	0.263

Notes: Relative expression levels of miR-125b in control and BC tissues.

miR-125b expression and BC subtypes

miR-125b expression levels were assessed across the three main BC subtypes. Of the 18 samples, 27.8% were luminal A, 38.9% were HER-2-enriched, and 33.3% were triple-negative. Table 4 provides details on miR-125b expression levels among these subtypes and the number of samples in each category. No significant difference was found among the subtypes (p = 0.701) (Table 4). Figure 1(B) illustrates the variation in miR-125b expressions across the subtypes, with triple-negative showing the highest levels, followed by the luminal A and HER2-enriched.

miR-125b expression in BC patients and its association with age groups

miR-125b expression were analysed across two age groups: under 50 years old (28.6% of the sample size) and individuals 50 years old and above (71.4% of the sample size). Table 4 shows no significant difference in miR-125b expression between these age groups (p = 1.000). However, miR-125b expression was the highest in patients aged 50 and above, and followed by those under 50. Figure 1(C) illustrates the variation in miR-125b expression across different age groups.

miR-125b expression in BC patients among Malaysian ethnic groups

miR-125b expression was evaluated for Malay and Chinese ethnic groups, as no samples were available for Indian ethnicities. Figure 1(D) shows that miR-125b expression was higher in Malay individuals compared to Chinese individuals, despite having an equal number of samples. No significant difference was found in miR-125b expression between the two ethnic groups (p = 0.546) (Table 4).

Table 4

Summary table of miR-125b expression and demographic variables of 18 BC patients at Hospital Canselor Tuanku Muhriz UKM (HCTM)

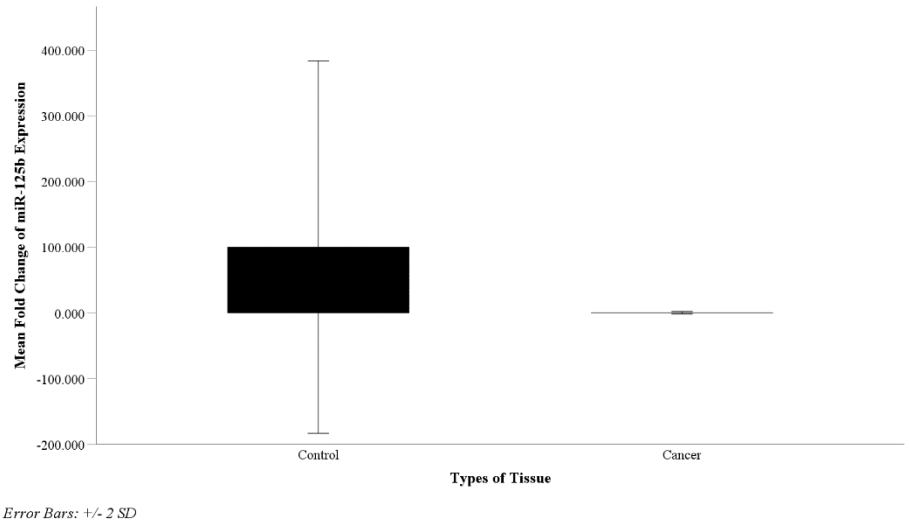
Category		N = 18	Mean (SD)	p-value
Ethnicity	Malay	9	0.528 (1.289)	0.546
	Chinese	9	0.018 (0.031)	
Age (Years)	< 50	4	0.078 (0.125)	1.000
	≥ 50	14	0.329 (1.046)	
Subtypes	Luminal A	5	0.107 (0.218)	0.701
	HER2-enriched	7	0.012 (0.016)	
	Triple-negative	6	0.718 (1.580)	

Notes: Expression levels of miR-125b categorised by ethnicity, age group and molecular subtype.

Figure 1

Mean fold change bar charts of miR-125b expression among 18 BC patients by: (A) control, (B) BC subtype, (C) age group and (D) ethnicity.

A

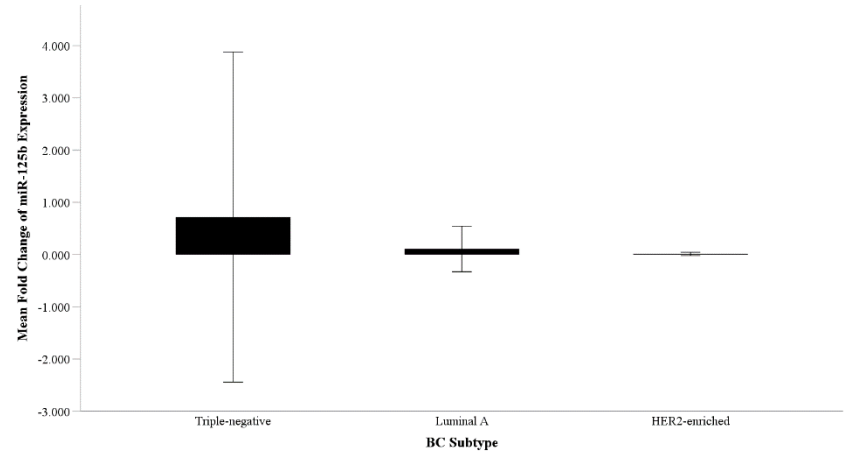


Notes: Figure 1 illustrates the mean fold change in miR-125b expression among 18 BC patients across various categories: (A) Comparison between control and cancer tissues demonstrates a general downregulation in cancer, though not statistically significant. (B) Among BC subtypes, triple-negative patients exhibited the highest variability and expression of miR-125b. (C) Patients aged ≥50 years exhibited relatively higher expression compared to those aged <50. (D) Malay patients had markedly higher miR-125b expression levels compared to Chinese patients.

Figure 1 (continued)

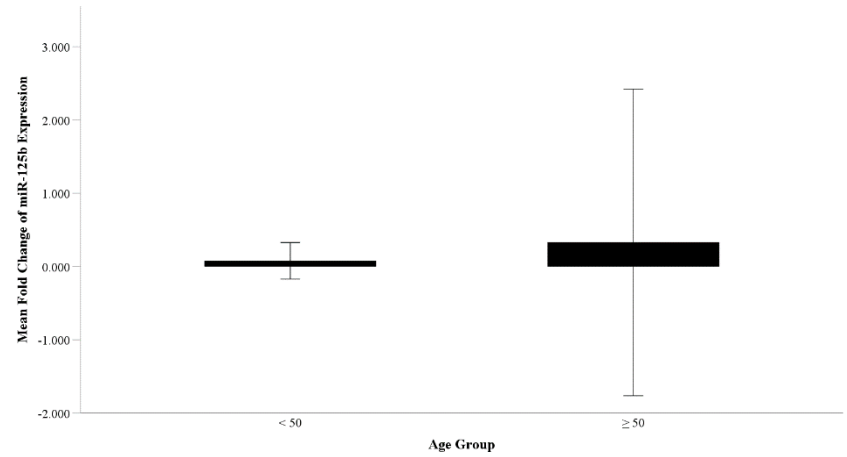
Mean fold change bar charts of miR-125b expression among 18 BC patients by: (A) control, (B) BC subtype, (C) age group and (D) ethnicity.

B



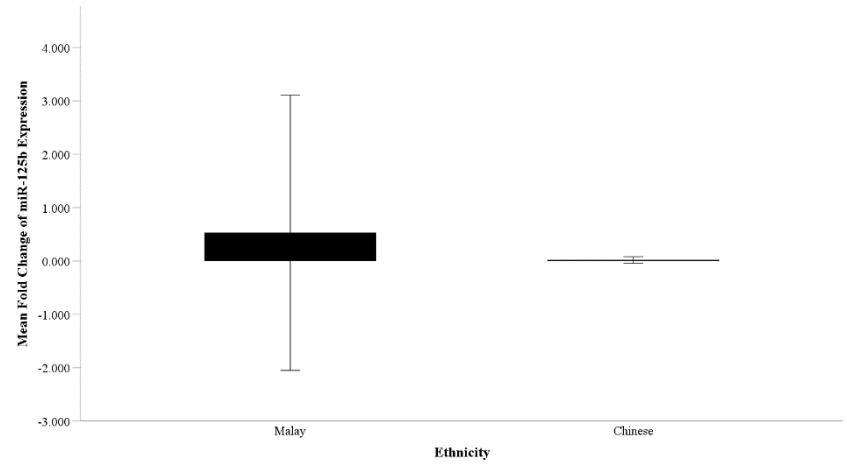
Error Bars: +/- 2 SD

C



Error Bars: +/- 2 SD

D



Error Bars: +/- 2 SD

Notes: Figure 1 illustrates the mean fold change in miR-125b expression among 18 BC patients across various categories: (A) Comparison between control and cancer tissues demonstrates a general downregulation in cancer, though not statistically significant. (B) Among BC subtypes, triple-negative patients exhibited the highest variability and expression of miR-125b. (C) Patients aged ≥50 years exhibited relatively higher expression compared to those aged <50. (D) Malay patients had markedly higher miR-125b expression levels compared to Chinese patients.

DISCUSSION

This study found no statistically significant association between BC subtypes and demographic characteristics such as ethnicity and age. These findings contrast with larger studies that demonstrate significant associations between BC subtypes and demographic factors like age and race (Llanos et al., 2015). These discrepancies may be attributed to the small sample size, as data were collected and analysed solely from BC cases in 2023.

No statistically significant difference was observed in miR-125b expression between BC tissues and control tissues. However, the relative expression (2-ΔΔCT) indicated that miR-125b expression was downregulated in BC tissues compared to controls. This observation aligns with studies reporting downregulation of miR-125b in BC tissues relative to normal adjacent tissues (Hu et al., 2018; Kolesnikov et al., 2019; Mar-Aguilar et al., 2013). These discrepancies in findings may be attributed to the small sample size, with only 18 BC tissues and two control tissues included in the study.

This study also revealed downregulation of miR-125b expression across all BC subtypes, although it did not reach statistical significance due to the limited sample size of 18 patients. An uneven subtype distribution (luminal A: 5 patients; triple-negative: 6 patients; HER2-enriched: 7 patients) may have contributed to the lack of significant results. A previous study with a larger cohort similarly found no significant differences in miR-125b expression among different subtypes but reported significant downregulation in cancer tissues compared to normal adjacent tissues, which supports these findings (Kolesnikov et al., 2019).

miR-125b has been implicated in regulating genes involved in apoptosis that influence the mitochondrial function, such as MCL-1 and HAX-1 and its dysregulation may contribute to resistance against chemotherapeutic agents like doxorubicin (Hu et al., 2018; Xie et al., 2015). Studies on miR-125b expression in BC produced varied results, which may be attributed to differences in molecular pathways and genes it influences. While some studies report consistent downregulation of miR-125b in BC chemo resistant cells (Hu et al., 2018), associating it with tumour suppressive roles (Kolesnikov et al., 2019), others find upregulation of miR-125b in triple-negative BC in modulating the epithelial-mesenchymal transition (EMT) (Nie et al., 2019), which aligns with this study's findings where the expression level of miR-125b was the highest in triple-negative BC. This highlights the diverse regulatory networks of miR-125b, which might explain the lack of significant findings in this study, particularly given the heterogeneous nature of the samples and methodologies employed such as tumour percentage of more than 10% in this study.

Malaysia's multi-ethnic composition provides an opportunity to study population-specific genetic variations. In this study, no significant difference in miR-125b expression was observed between Malay and Chinese BC patients. This aligns with findings for other miRNAs, such as miR-21, which showed no significant differences among Malaysia's three main ethnic groups (Malay, Chinese and Indian) (Wong et al., 2024). These consistencies reinforce these results, despite the limited sample size and representation of only two main ethnicities. Similarly, no significant difference was observed in miR-125b expression between age groups in the cohort (below 50 years: 4, above 50 years: 14), which could have skewed the results. A larger study also found no correlation between age groups and miR-21 expression in BC patients (Wong et al., 2024), suggesting the clinical significance of miR-125b should be further evaluated across all age groups. Considering Malaysian demographic and its influence on miR-125b expression, there is no clear association between age groups, ethnicities and subtypes. Therefore, based on this study's cohort, miR-125b expression appears to be independent, as it is downregulated in BC patients.

The sample size of 18 BC patients and 2 control samples represents a significant limitation, reducing the statistical power of the analysis, making it difficult to detect true differences or associations. Uneven subtype distribution and limited ethnic representation further constrain the reliability of conclusions. A larger cohort would provide more robust data, enhance statistical power and improve the reliability of findings regarding miR-125b expression across different subtypes and demographics.

While this study provides valuable insights into miR-125b expression in BC, further research is needed to explore its underlying regulatory pathways. Future studies should focus on miR-125b's involvement in mitochondrial function and apoptosis through microarray studies. Integrating miR-125b profiling with multi-omics approaches, such as transcriptomics and proteomics, would offer a more comprehensive understanding of its molecular mechanisms. Additionally, validating protein expression using Western blot analysis could confirm the downstream effects of miR-125b regulation.

Previous studies have demonstrated the downregulation of miR-125b in BC and its tumour suppressor potential, but these findings have primarily been derived from non-Malaysian populations (Hu et al., 2018; Mar-Aguilar et al., 2013; Xie et al., 2015). No prior studies have specifically investigated the miR-125b expression across BC subtypes and demographic factors in Malaysia. This study addresses the gap by exploring miR-125b expression within Malaysia's multi-ethnic population, considering its potential clinical relevance in local context. Although numerous miRNAs associated with specific subtypes (Arun et al., 2022), a single miRNA such as miR-125b, which is consistently downregulated in BC (Hu et al., 2018; Kolesnikov et al., 2019; Mar-Aguilar et al., 2013), could serve as a promising biomarker. Despite the lack of significance findings in this study, further investigation is needed to evaluate miR-125b's potential as a biomarker across various ethnicities, age groups and subtypes.

CONCLUSION

In conclusion, this study provides initial insights into miR-125b expression in BC, demonstrating consistent downregulation across age groups, ethnicities and subtypes, despite the lack of statistical significance. These findings align with previous studies, supporting the potential of miR-125b as a biomarker for BC. To validate these results, additional investigations involving larger cohorts are necessary. Furthermore, employing advanced techniques such as RNA sequencing or proteomics will be essential to further validate miR-125b as a potential biomarker for BC across all demographics and subtypes.

AUTHOR CONTRIBUTIONS

Norlizawati conceived the study, conducted the experiments, performed statistical analyses, interpreted the data and drafted the manuscript. Zhu Xiao Ning assisted in developing the experimental protocols. Lee Wen Xuan and Yeo Bann Siang contributed to data collection and assisted with the experiments. Tan Geok Chin guided the selection of FFPE samples. Cheah Yoke Kqueen supervised the study and provided critical feedback on the manuscript. All authors have read and approved the final manuscript.

ETHICS APPROVAL

This study was approved by Universiti Kebangsaan Malaysia Research Ethics Secretariat under protocol number JEP-2023-453 for the use of clinical tissues and data collection.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest in this work.

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