miR-223 Overexpression is Associated with Increased Expression of EGFR and Worse Prognosis in Indonesian TNBC Patients

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Background

Triple negative breast cancer (TNBC) is associated with more aggressive disease and worse survival compared to other breast cancer subtypes. We aim to analyze the role of oncogenic microRNA-223 (miR-223) as a possible negative driving factor in TNBC through its association with clinicopathologic characteristic and prognostic value.

Methods

We retrospectively analyzed the association of pre-treatment miR-223 expression with clinicopathologic characteristics and 3-years overall survival (OS) of TNBC patients treated in a tertiary center during 2014-2017. miR-223 level of tumor tissue was measured using quantitative real-time polymerase chain reaction (qRT-PCR). Cutoff value for miR-223 was determined using Receiver Operating Curve (ROC). Chi-square and Fisher's exact tests were used to analyze the association between categorical variables, while Kaplan-Meier curve was used for survival analysis.

Results

Fifty-three stage I-IV TNBC patients were included in the analysis (Table 1). The optimal cutoff value for miR-223 was 23.435 (Figure 1, Table 2) and was used to classify miR-223 expression into over- and under-expressed groups. miR-223 overexpression was associated with increased expression of Epidermal Growth Factor Receptor (EGFR) (69.7% vs. 35%, p: 0.022) and lower 3-years OS (33.3% vs. 70%; median OS±SE (months): 25.66±1.58 vs. 30.23±1.99; p log rank: 0.029) as seen in Figure 2. No significant association was observed between miR-223 expression with other clinicopathologic characteristics (age, BMI, stage, tumor size, nodal status, distant metastasis, and CK5/6 expression).

Characteristics		MiR-223 Underexpressed (N: 20)	Mir-223 Overexpressed (N: 33)	*p* - Value
Age	<50 y.o	6	17	p: 0.126
	≥50 y.o	14	16	
BMI	<25	11	23	p: 0.279
	≥25	9	10	
Stage	Early	3	4	p: 0.209
	LABC	16	22	
	Metastatic	1	7	
Tumor Size (T)	< 5 cm	4	9	p:0.555
	≥ 5 cm	16	24	
Nodal Status (N)	Positive	12	24	p: 0.336
	Negative	8	9	
Distant Metastasis (M)	Present	1	7	p: 0.113
	Absent	19	26	
CK5/6	Positive	10	20	p: 0.57
	Negative	10	13	
EGFR	Positive	7	23	**p: 0.013**
	Negative	13	10	

Table 1. Patient Clinicopathologic Profile According to MiR-223 Expression.

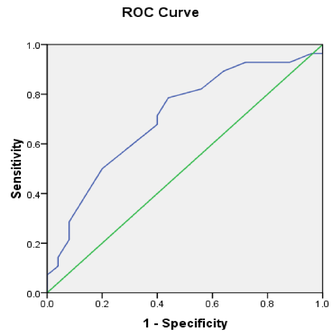

Figure 1. Area under curve (AUC): 0.706, 95%CI: 0.565-0.848; p: 0.01; Sensitivity: 78.6%; Specificity: 56%.

Area	Std. Error	p value	95% Confidence Interval	
			Lower Bound	Upper Bound
0.706	0.072	0.010	0.565	0.8484

Table 2. AUC value of miR-223 ROC.

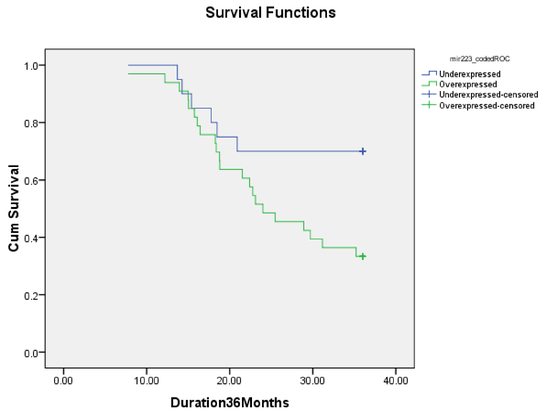

Figure 2. 3-years OS based on miR-223 expression (p log rank: 0.029).

Discussion

MiR-223 is known to have pleiotropic effect in malignancy, meaning it can act both as an oncogenic-microRNA (oncomiR) or as a tumor suppressor, depending on the context.[1] In our cohort, miR-223 was observed to have oncogenic effect which is consistent with the only existing clinical study which showed elevated level of serum miR-223 in relapsing TNBC patients compared to non-relapsing group.[2] Our finding, however, differs from published preclinical studies which considered miR-223 as tumor suppressor in TNBC cell lines.[3,4] Further analysis is required understand the mechanism behind the negative prognostic effect of miR-223 in our cohort.

Conclusion

Pre-treatment miR-223 level of expression in Indonesian TNBC patients is correlated with poor survival and increased of EGFR expression. Thus, targeting miR-223 becomes a potential therapeutic strategy for TNBC patients. However, further study is needed to validate this result.

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The authors declare no conflicts of interest.

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