Breast Cancer: Targets and Therapy

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ORIGINAL RESEARCH

Prognostic Value of Vimentin in Triple Negative Breast Cancer Patients Depends on Chemotherapy Regimen and p53 Mutant Expression

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Purpose: To determine the prognostic value of vimentin in triple negative breast cancer (TNBC) patients, specifically in relation to chemotherapy regimen and p53 mutant expression.

Patient and Methods: We retrospectively analyzed the association of pre-treatment tumor expression of vimentin with 48-month overall survival (OS) of 72 all stages TNBC patients diagnosed between 2014 and 2018 in relation to chemotherapy regimen and expression of p53 mutant. Vimentin and p53 mutant expressions were examined using immunohistochemistry. Analysis was conducted on all patients collectively, then repeated on two cohorts divided according to the chemotherapy regimen. Sub-analysis was performed to determine the effect of p53 mutant expression on the prognostic value of vimentin.

Results: Vimentin was expressed in 43.1% of patients and was not associated with clinicopathologic characteristics. Vimentin was associated with improved 48-month OS in all patients in univariate analysis but not significant in multivariate analysis. When analyzed according to chemotherapy regimen, vimentin was independently associated with improved 48-month OS in patients receiving non-platinum-based chemotherapy (80% vs 15.8%; HR: 0.17, 95% CI: 0.05–0.58, *p*: 0.005). Other independent prognostic factors include T (HR: 6.18, 95% CI: 1.38–27.7, *p*: 0.017) and M (HR: 5.64, 95% CI: 1.2–26.33, *p*: 0.028). On subanalysis, vimentin was significantly associated with improved 48-month OS in patients expressing p53 mutant (69.2% vs 22.2%, *p*: 0.006) but was not significant in patients not expressing p53 mutant.

Conclusion: Vimentin expression was independently associated with improved 48-month OS in TNBC patients treated with non–platinum–based chemotherapy. Expression of p53 mutant significantly affected the prognostic value of vimentin.

Keywords: vimentin, p53 mutant, chemotherapy, platinum resistance, TNBC, prognostic factor

Introduction

Previously thought of as a singular disease, Perou et al, later expanded by Lehmann et al (Vanderbilt) and Burstein et al (Baylor), have elegantly demonstrated the genetic heterogeneity of triple negative breast cancer (TNBC), leading to the categorization of TNBC into subtypes of different characteristics and response towards systemic chemotherapy.[1–3] Both Vanderbilt and Baylor classifications share overlapping subtypes, namely basal-like, mesenchymal and luminal androgen.[3] Basal-like subtype is highly sensitive towards platinum-based chemotherapy due to its mechanism of action targeting homologous recombination deficiency and BRCA1/2 mutation, while treatment targeting androgen receptor in luminal androgen subtype have shown promising results.[4–8] Mesenchymal subtype has been observed to have worse

Received: 25 April 2023
Accepted: 19 July 2023
Published: 27 July 2023

prognosis and poor response towards chemotherapy, with no identified potential targetable molecule.[9] Very little is currently understood regarding the best treatment modality for mesenchymal TNBC.

Vimentin, an intermediate filament protein of mesenchymal cancer cell, is associated with more aggressive breast cancer, including in TNBC.[10,11] Vimentin is involved in epithelial-to-mesenchymal transition (EMT) in TNBC, a process associated with disease progression and metastasis, two of the main causes of mortality in TNBC.[12] Previous studies have shown conflicting results on the prognostic role of vimentin in TNBC, which among other variables, might be caused by implementation of different chemotherapy regimens, which was not analyzed in these studies.[10,13–15] Furthermore, the role of vimentin in relation to EMT process might be significantly influenced by p53 loss of function (p53 mutant).[16,17] This study aims to determine the prognostic value of vimentin in TNBC patients, specifically in relation to platinum-based and non-platinum-based chemotherapy, as well as p53 mutant expression.

Materials and Methods

Patient Populations

This was a retrospective observational study conducted at Dr. Sardjito Hospital, Yogyakarta, Indonesia, involving stage I–IV TNBC patients diagnosed between 2014 and 2018. We consecutively included all patients 18 years old or older, who received systemic chemotherapy, with Eastern Cooperative Oncology Group (ECOG) performance index of 0–1. We excluded patients with unretrievable formalin-fixed paraffin-embedded (FFPE) tissue for immunohistochemistry (IHC) and patients lost to follow up. Patient clinical data was extracted from medical record, while follow up status was prospectively recorded. This study has been approved by the IRB Ethics Committee Faculty of Medicine, Public Health, and Nursing, Gadjah Mada University/Dr. Sardjito Hospital, Yogyakarta, Indonesia with approval numbers KE/0286/03/2020 and KE/FK/0789/EC/2022.

Pathology Assessment

Tumor samples were obtained FFPE tissue stored at room temperature, protected from light, at the Department of Anatomical Pathology, Dr. Sardjito General Hospital, Yogyakarta, Indonesia.

Immunohistochemistry

Block paraffin samples were cut 3 μm in thickness to analyze the expression of vimentin and p53 mutant by IHC. Anti-vimentin monoclonal antibody (PRM 312 AA, dilution 1:50, Biocare Medical) was used to detect tumor expression of vimentin. Anti-p53 mutant antibody (ab32049, dilution 1:1000, Abcam) was used to detect tumor expression of p53 mutant. Vimentin and p53 mutant were considered positive if their expressions were detected in more than 10% of the tumor cells. Immunohistochemistry examination was performed using ImageJ software by a senior pathologist, blinded to the patient's survival status and clinical data, including which chemotherapy regimen was received.

Statistical Analysis

The association between vimentin and clinicopathologic characteristic was analyzed using chi-square test or Fisher's exact test as appropriate. Survival analysis was performed using Kaplan–Meier curve to determine the 48-month overall survival (OS). Univariate analysis of potential prognostic factors was conducted using Log rank test. Variables significant in univariate analysis were included in multivariate analysis using Cox proportional hazard. Analysis was conducted on all patients collectively, then repeated on two cohorts divided according to the chemotherapy regimen. Subanalysis was performed to determine the effect of p53 mutant expression on the prognostic value of vimentin. Significant p-value was set at <0.05. All statistical analyses were performed using IBM SPSS version 24 software.

Results

We consecutively detected 287 patients, 173 of which were excluded due to unretrievable FFPE tissue for IHC, 42 of which were excluded due to lost to follow up, leaving 72 patients eligible for analysis. The average age of diagnosis was

50.1 ± 11 years old, with a median of 49.5 (31–82) years. Most patients were diagnosed with advanced stage, 52 patients (72.2%) had T3-4 tumor, 51 patients (70.8%) had lymph node metastasis. Distant metastasis was detected in 10 patients (13.9%). Thirty-eight patients (52.8%) received platinum–based chemotherapy, while the remaining 34 patients (47.2%) received non–platinum–based chemotherapy. Vimentin was expressed in 31 patients (43.1%), and p53 mutant was detected in 31 patients (43.1%) (Table 1). There was no significant baseline patient characteristic difference according to vimentin expression (Table 2). At the end of the 48-month follow-up, 33 patients (45.8%) were still alive (48-month OS), with a median OS of 31 months.

Table 1 Patient Baseline Characteristic

Characteristic	Classification	N (%)	Mean (± SD)
Age (year)	< 40	11 (15.3)	50.1 ± 11
	≥ 40	61 (84.7)	
BMI (kg/m^2)	< 25	42 (58.3)	24.6 ± 4.6
	≥ 25	30 (41.7)	
T	T1-2	20 (27.8)	
	T3-4	52 (72.2)	
N	N (-)	21 (29.2)	
	N (+)	51 (70.8)	
M	M0	62 (86.1)	
	M1	10 (13.9)	
Chemotherapy Regimen	Platinum	38 (52.8)	
	Non-platinum	34 (47.2)	
Vimentin Expression	Negative	41 (56.9)	
	Positive	31 (43.1)	
p53 WT Expression	Negative	41 (56.9)	
	Positive	31 (43.1)	

Abbreviation: BMI, Body Mass Index.

Table 2 Patient Baseline Characteristic According to Vimentin Expression

Characteristic	Classification	Vimentin (+) (%) (n: 31)	Vimentin (-) (%) (n: 41)	*P*
Age (year)	< 40	3 (9.7)	8 (19.5)	0.331[a]
	≥ 40	28 (90.3)	33 (80.5)	
BMI (kg/m^2)	< 25	18 (58.1)	24 (58.5)	0.968[b]
	≥ 25	13 (41.9)	17 (41.5)	
T	T1-2	10 (32.3)	10 (24.4)	0.464[b]
	T3-4	21 (67.7)	31 (75.6)	

(*Continued*)

Table 2 (Continued).

Characteristic	Classification	Vimentin (+) (%) (n: 31)	Vimentin (-) (%) (n: 41)	*P*
N	N (-)	10 (32.3)	11 (26.8)	0.618[b]
	N (+)	21 (67.7)	30 (73.2)	
M	M0	27 (87.1)	35 (85.4)	1[a]
	M1	4 (12.9)	6 (14.6)	
p53 WT Expression	Negative	18 (58.1)	23 (56.1)	0.868[b]
	Positive	13 (41.9)	18 (43.9)	
Chemotherapy Regimen	Platinum	16 (51.6)	22 (53.7)	0.864[b]
	Non-platinum	15 (48.4)	19 (46.3)	

Note: [a]Fisher's exact test, [b]Chi-square test.
Abbreviation: BMI, Body Mass Index.

Expression of vimentin was associated with significantly improved 48-month OS, both in all patients (61.3% vs 34.1%, mean OS: 37.4 vs 29.5 months, *p*: 0.02), as well as in patients receiving non-platinum-based chemotherapy (80% vs 15.8%, mean OS: 42.3 vs 24.9 months, *p*: 0.000) (Figure 1). Larger tumor size was associated with worse 48-month OS, both in all patients (36.5% vs 70%, mean OS: 29.6 vs 41.3 months, *p*: 0.009), as well as in patients receiving non-platinum-based chemotherapy (30.4% vs 72.7%, mean OS: 27.7 vs 42.7 months, *p*: 0.018) (Figure 2). Similarly, distant metastasis was associated with worse 48-month OS, both in all patients (20% vs 50%, mean OS: 24.7 vs 34.2 months, *p*:

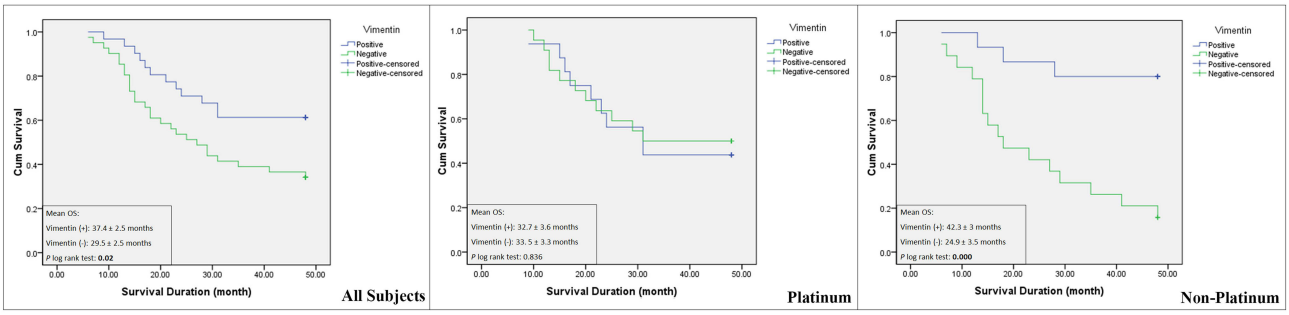

Figure 1 Kaplan – Meier curve showing 48-month OS according to vimentin expression in all patients (left), in patients receiving platinum – based chemotherapy (center), and in patients receiving non – platinum – based chemotherapy (right).

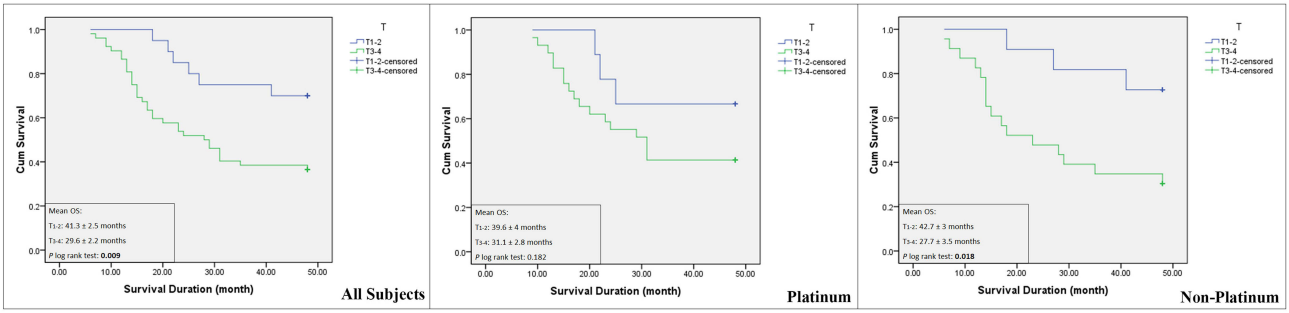

Figure 2 Kaplan – Meier curve showing 48-month OS according to tumor size (T) in all patients (left), in patients receiving platinum – based chemotherapy (center), and in patients receiving non – platinum – based chemotherapy (right).

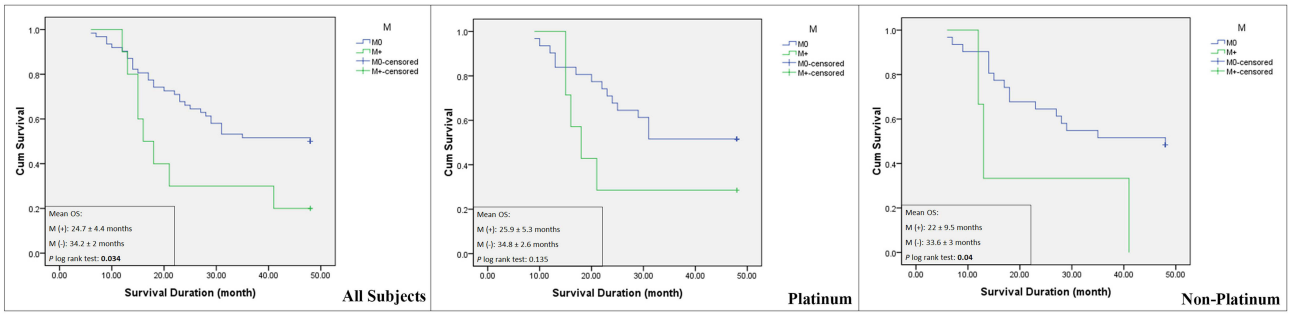

Figure 3 Kaplan – Meier curve showing 48-month OS according to distant metastasis (M) in all patients (left), in patients receiving platinum – based chemotherapy (center), and in patients receiving non – platinum – based chemotherapy (right).

0.034), as well as in patients receiving non-platinum-based chemotherapy (0% vs 48.4%, mean OS: 22 vs 33.6 months, *p*: 0.04) (Figure 3). No variable was significantly associated with 48-month OS in patients receiving platinum-based chemotherapy (Table 3). When analyzed according to vimentin expression, platinum-based chemotherapy was associated with worse 48-month OS in patients expressing vimentin (80% vs 43.8%, mean OS: 32.7 vs 42.3 months, *p*: 0.049). On the contrary, platinum-based chemotherapy was associated with improved 48-month OS in patients not expressing vimentin (50% vs 15.8, mean OS: 33.5 vs 24.9 months, *p*: 0.032) (Figure 4).

On multivariate analysis, independent prognostic factors in all patients were T (HR: 3.24, 95% CI: 1.34–7.81, *p*: 0.009) and M (HR: 2.3, 95% CI: 1.03–5.12, *p*: 0.042) (Table 4). Whereas in patients receiving non-platinum-based chemotherapy were T (HR: 6.18, 95% CI: 1.38–27.7, *p*: 0.017), M (HR: 5.64, 95% CI: 1.2–26.33, *p*: 0.028) and vimentin

Table 3 Log Rank Test for 48-Month OS According to Chemotherapy Regimen

Chemotherapy Regimen	Classification	Alive (%)	Deceased (%)	*P*	HR (95% CI)
All regimen (n: 72)	Vimentin (+) (n: 31)	19 (61.3)	12 (38.7)	**0.02**	2.2 (1.1–4.3)
	Vimentin (-) (n: 41)	14 (34.1)	27 (65.9)		
Platinum (n: 38)	Vimentin (+) (n: 16)	7 (43.8)	9 (56.2)	0.836	0.9 (0.4–2.2)
	Vimentin (-) (n: 22)	11 (50)	11 (50)		
Non-platinum (n: 34)	Vimentin (+) (n: 15)	12 (80)	3 (20)	**0.000**	7.3 (2.1–25.2)
	Vimentin (-) (n: 19)	3 (15.8)	16 (84.2)		
All regimen (n: 72)	Age < 40 years old (n: 11)	3 (27.3)	8 (72.7)	0.172	0.6 (0.3–1.3)
	Age ≥ 40 years old (n: 61)	30 (49.2)	31 (50.8)		
Platinum (n: 38)	Age < 40 years old (n: 5)	1 (20)	4 (80)	0.292	0.6 (0.2–1.7)
	Age ≥ 40 years old (n: 33)	17 (51.5)	16 (48.5)		
Non-platinum (n: 34)	Age < 40 years old (n: 6)	2 (33.3)	4 (66.7)	0.444	0.7 (0.2–2)
	Age ≥ 40 years old (n: 28)	13 (46.4)	15 (53.6)		
All regimen (n: 72)	BMI < 25 kg/m^2 (n: 42)	19 (45.2)	23 (54.8)	0.778	0.9 (0.5–1.7)
	BMI ≥ 25 kg/m^2 (n: 30)	14 (46.7)	16 (53.3)		
Platinum (n: 38)	BMI < 25 kg/m^2 (n: 25)	13 (52)	12 (48)	0.315	1.6 (0.6–3.9)
	BMI ≥ 25 kg/m^2 (n: 13)	5 (38.5)	8 (61.5)		

(*Continued*)

Table 3 (Continued).

Chemotherapy Regimen	Classification	Alive (%)	Deceased (%)	*P*	HR (95% CI)
Non-platinum (n: 34)	BMI < 25 kg/m^2 (n: 17)	6 (35.3)	11 (64.7)	0.157	0.5 (0.2–1.3)
	BMI ≥ 25 kg/m^2 (n: 17)	9 (52.9)	8 (47.1)		
All regimen (n: 72)	T1-2 (n: 20)	14 (70)	6 (30)	**0.009**	3 (1.2–7.1)
	T3-4 (n: 52)	19 (36.5)	33 (63.5)		
Platinum (n: 38)	T1-2 (n: 9)	6 (66.7)	3 (33.3)	0.182	2.2 (0.7–7.7)
	T3-4 (n: 29)	12 (41.4)	17 (58.6)		
Non-platinum (n: 34)	T1-2 (n: 11)	8 (72.7)	3 (27.3)	**0.018**	4 (1.1–13.7)
	T3-4 (n: 23)	7 (30.4)	16 (69.6)		
All regimen (n: 72)	N (-) (n: 21)	12 (57.1)	9 (42.9)	0.248	1.5 (0.7–3.2)
	N (+) (n: 51)	21 (41.2)	30 (58.8)		
Platinum (n: 38)	N (-) (n: 6)	4 (66.7)	2 (33.3)	0.326	2 (0.5–8.8)
	N (+) (n: 32)	14 (43.8)	18 (56.2)		
Non-platinum (n: 34)	N (-) (n: 15)	8 (53.3)	7 (46.7)	0.407	1.5 (0.6–3.8)
	N (+) (n: 19)	7 (36.8)	12 (63.2)		
All regimen (n: 72)	M (-) (n: 62)	31 (50)	31 (50)	**0.034**	2.3 (1–5)
	M (+) (n: 10)	2 (20)	8 (80)		
Platinum (n: 38)	M (-) (n: 31)	16 (51.6)	15 (48.4)	0.135	2.1 (0.8–6)
	M (+) (n: 7)	2 (28.6)	5 (71.4)		
Non-platinum (n: 34)	M (-) (n: 31)	15 (48.4)	16 (51.6)	**0.04**	3.4 (1–12)
	M (+) (n: 3)	0 (0)	3 (100)		
All regimen (n: 72)	p53 mutant (+) (n: 31)	13 (41.9)	18 (58.1)	0.607	0.8 (0.5–1.6)
	p53 mutant (-) (n: 41)	20 (48.8)	21 (51.2)		
Platinum (n: 38)	p53 mutant (+) (n: 16)	7 (43.8)	9 (56.2)	0.851	0.9 (0.4–2.2)
	p53 mutant (-) (n: 22)	11 (50)	11 (50)		
Non-platinum (n: 34)	p53 mutant (+) (n: 15)	6 (40)	9 (60)	0.598	0.8 (0.3–2)
	p53 mutant (-) (n: 19)	9 (47.4)	10 (52.6)		

Note: Bold: significant value.
Abbreviations: BMI, Body Mass Index; HR, Hazard Ratio; 95% CI, 95% Confidence Interval.

(HR: 0.17, 95% CI: 0.05–0.58, *p*: 0.005) (Table 5). On sub-analysis, vimentin expression was associated with significantly improved 48-month OS in p53 mutant expressing patients (69.2% vs 22.2%, mean OS: 40.9 months vs 25.1 months, *p*: 0.006), whereas vimentin was non-prognostic in p53 non-expressing patients (55.6% vs 43.5%, mean OS: 34.8 months vs 32.9 months, *p*: 0.538) (Figure 5 and Table 6).

Discussion

Our study has shown a significant difference in vimentin's prognostic value in relation to chemotherapy regimen, with significantly improved prognosis in patients receiving non-platinum-based chemotherapy and non-statistically significant

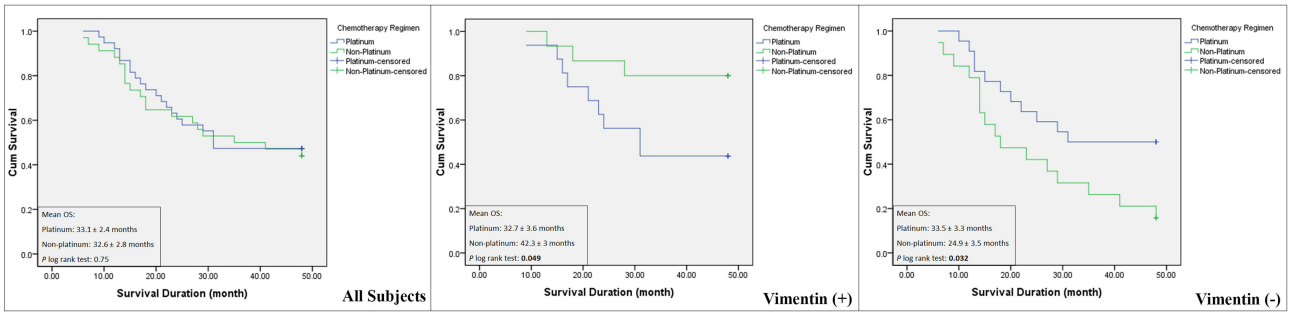

Figure 4 Kaplan – Meier curve showing 48-month OS according to chemotherapy regimen in all patients (left), in patients expressing vimentin (center), and in patients not expressing vimentin (right).

worse prognosis in patients receiving platinum-based chemotherapy (Figure 1). The positive prognostic value of vimentin in our study is similar to the study form Dine et al, which reported improved prognosis in patients receiving neoadjuvant chemotherapy (NAC).[13] On the contrary, Yamashita et al reported a negative prognostic value of vimentin, and non-prognostic results were reported by Schmidt et al and Kusinska et al[10,14,15] it was unclear whether the patients received systemic chemotherapy in studies conducted by Yamashita et al. Kusinska et al, whereas Schmidt et al did not specify the type of chemotherapy given to their patients, which might have contributed to the inconsistent results.

Table 4 Cox Proportional Hazard Result of All Patients

Variable	Classification	Subject	HR	95% CI	*P*
T	T1-2	20	3.24	1.34–7.81	**0.009**
	T3-4	52			
M	M (-)	62	2.3	1.03–5.12	**0.042**
	M (+)	10			
Vimentin Expression	Positive	31	0.5	0.25–1	0.052
	Negative	41			

Note: Bold: significant value.
Abbreviations: HR, Hazard Ratio; 95% CI, 95% Confidence Interval.

Table 5 Cox Proportional Hazard Result of Patients Receiving Non-Platinum-Based Chemotherapy

Variable	Classification	Subject	HR	95% CI	*P*
T	T1-2	11	6.18	1.38–27.7	**0.017**
	T3-4	23			
M	M (-)	31	5.64	1.2–26.33	**0.028**
	M (+)	3			
Vimentin expression	Positive	15	0.17	0.05–0.58	**0.005**
	Negative	19			

Note: Bold: significant value.
Abbreviations: HR, Hazard Ratio; 95% CI, 95% Confidence Interval.

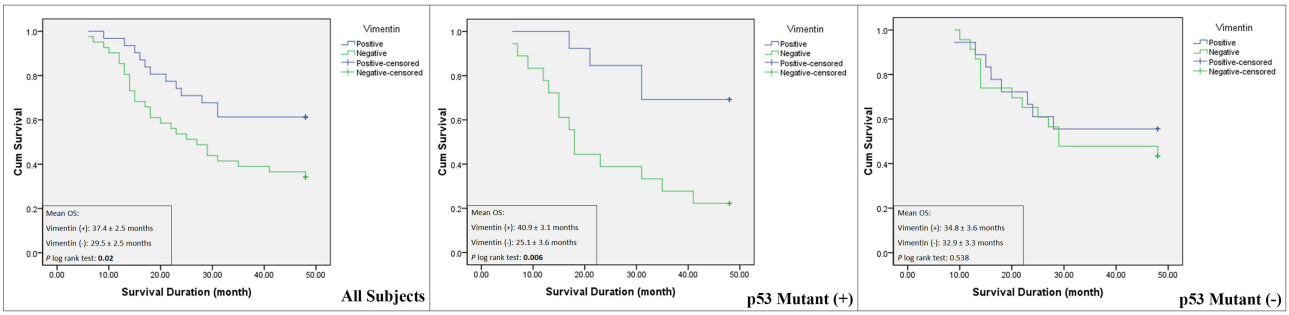

Figure 5 Kaplan – Meier curve showing 48-month OS according to vimentin regimen in all patients (left), in patients expressing p53 mutant (center), and in patients not expressing p53 mutant (right).

We demonstrated a dichotomous response of platinum-based chemotherapy, with worse prognosis observed in vimentin-expressing patients and improved prognosis in patients not expressing vimentin, suggesting platinum resistance in vimentin-expressing tumor (Figure 4). Currently, there is no clinical data on the response towards platinum-based and non-platinum-based chemotherapy in mesenchymal TNBC, especially concerning vimentin expression. A preclinical study reported mesenchymal TNBC cell line had lower sensitivity towards cisplatin compared to the epithelial TNBC cell line.[18,19] Genomic analysis using the GeneWeaver database observed cisplatin resistance associated with vimentin expression, which was hypothesized due to decreased import and increased export of cisplatin to tumor cells.[20]

Mutation of p53 is frequently found in TNBC, with reported frequency as high as 80% of all TNBC cases.[21–23] The prognostic value of p53 mutant in breast cancer remains inconsistent, depending on the cancer subtype and treatment.[24] The detrimental effect of p53 mutation is closely related to EMT, resulting in the acquisition of stemness characteristic of mesenchymal cells.[17] Mutation of p53 did not result in significant prognostic difference (Table 3) but affected the prognostic significance of vimentin in our study. Vimentin was associated with improved prognosis in patients expressing p53 mutant, while non-prognostic in patients without p53 mutant expression (Figure 5). The result of our study suggested that p53 mutation might not directly affect patient prognosis but was dependent on the progression of EMT.

Similar to previous studies, increased tumor size and distant metastasis were independent poor prognostic factors in our patients.[25–27] Patients in our study presented with significantly more advanced stage compared to previous studies, which translated into worse OS.[25,28,29] Improvement in this scenario can only be made by earlier cancer detection through improving the implementation of breast cancer screening, which is still currently ineffective in Indonesia.[30] Furthermore, NAC is still very rarely implemented in Indonesia, which in combination with high proportion of T3-4 patients in our cohort, might have contributed to suboptimal tumor resection and worse survival. Our study is the first to demonstrate the different prognostic values of vimentin according to p53 mutant expression and chemotherapy regimen in TNBC patients, which at least partially explains the inconsistent prognostic value of vimentin from previous studies.

Table 6 Log Rank Test for 48-Month OS According to p53 Mutant Expression

p53 Mutant Expression	Classification	Alive (%)	Deceased (%)	*P*	HR (95% CI)
All patients (n: 72)	Vimentin (+) (n: 31)	19 (61.3)	12 (38.7)	**0.02**	2.2 (1.1–4.3)
	Vimentin (-) (n: 41)	14 (34.1)	27 (65.9)		
p53 Mutant (+) (n: 31)	Vimentin (+) (n: 13)	9 (69.2)	4 (30.8)	**0.006**	4.2 (1.4–12.7)
	Vimentin (-) (n: 18)	4 (22.2)	14 (77.8)		
p53 Mutant (-) (n: 41)	Vimentin (+) (n: 18)	10 (55.6)	8 (44.4)	0.538	1.3 (0.5–3.2)
	Vimentin (-) (n: 23)	10 (43.5)	13 (56.5)		

Note: Bold: significant value.
Abbreviations: HR, Hazard Ratio; 95% CI, 95% Confidence Interval.

We also demonstrated the dichotomy of chemotherapeutic response according to vimentin expression, suggesting the potential role of vimentin as a marker for choosing the best chemotherapy regimen in TNBC patients. The main limitations of our study are the small sample size and its retrospective design. The REMARK Checklist has been completed by the authors for this case report (Table S1).

Conclusion

In summary, the expression of vimentin was independently associated with improved 48-month OS in TNBC patients treated with non-platinum-based chemotherapy. Expression of p53 mutant significantly affected the prognostic value of vimentin.

Data Sharing Statement

The dataset analysed during the current study is available in Table S2.

Ethics Approval and Informed Consent

Written informed consent was obtained from the patients involved, including permission to use clinical data and reexamination of tissue specimen. This study was conducted in accordance with the Declaration of Helsinki. Ethical clearance was approved by the IRB Ethics Committee Faculty of Medicine, Public Health, and Nursing, Gadjah Mada University/Dr. Sardjito Hospital, Yogyakarta, Indonesia with approval numbers KE/0286/03/2020 and KE/FK/0789/EC/2022.

Acknowledgments

The authors express gratitude to Sardjito General Hospital for providing the necessary assistance during data procurement for this publication.

Funding

This research was funded by Dana Masyarakat, Faculty of Medicine, Public Health, and Nursing, Gadjah Mada University, Yogyakarta, Indonesia.

Disclosure

Dr Ibnu Purwanto reports grants from Faculty of Medicine, Public Health, and Nursing, Gadjah Mada University/Dr Sardjito Hospital, Yogyakarta, Indonesia, during the conduct of the study. The authors report no other conflicts of interest in this work.

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