BAP1, Wilms' tumor 1, and calretinin in predicting survival and response to chemotherapy in patients with malignant pleural mesothelioma.

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Aim

BAP1, Wilms' tumor 1 (WT1), and calretinin are useful immuno-histochemical (IHC) biomarkers in diagnosis of diffuse pleural mesothelioma (DPM). In a limited number of studies, BAP1, WT1, and calretinin expression in tumor tissue are associated with prognosis.

This study aims to evaluate the role of BAP1, WT1, and calretinin IHC staining results in FFPE tumor tissue samples in predicting prognosis and chemotherapy response in DPM patients treated with only chemotherapy.

Methods

107 DPM patients treated with pemetrexed-platinum in the first-line setting were included.

Nuclear and cytoplasmic staining was required for calretinin positivity (retain), and nuclear staining was required for WT-1 or BAP1 positivity.

The IHC staining findings were evaluated concerning clinical variables with appropriate statistical methods.

Results

The clinical characteristics of the 107 DPM patients are shown in Table 1.

Tabe 1. Clinical characteristics of the patients.

Characteristics	Value	Characteristics	Value
Age, yr, X±SD (min-max),	63.83±9.63 (30-81)	Stage, n (%)	
Gender, n (%)		IA	7 (6.5)
Male	68 (63.6)	IB	11 (10.3)
Female	39 (36.4)	II	5 (4.7)
Histopathology, n (%)		IIIA	14 (13.1)
Epithelioid	74 (69.1)	IIIB	55 (51.4)
Biphasic	25 (23.4)	IV	15 (14.0)
Sarcomatoid	8 (7.5)	Response rate, n (%)	
		Progressive disease	45 (42.1)
		Stable disease	36 (33.6)
		Partial response	25 (23.4)
		Complete response	1 (0.9)

The IHC staining status of the patients is shown in Figure 1.

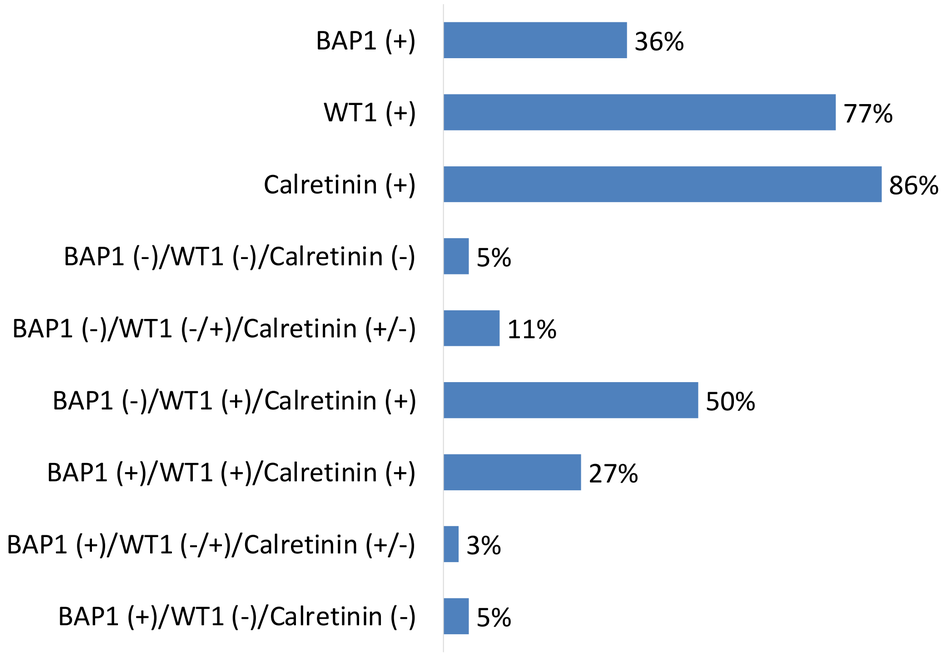

Figure 1. Distribution of immunohistochemical staining status in patients. If there is a stain expression, this situation is indicated as (+); if there is no expression, it is indicated as (-).

Immunohistochemical staining expression status and chemotherapy response:

While the loss of expression of BAP1 did not differ significantly according to chemotherapy response (progressive disease, stable disease, objective response: 57.8%, 63.9%, and 76.9%; p=0.266), the rate of WT1 expression presence was significantly higher in objective responders (71.1%, 77.1%, 95.8%; p=0.054). Similarly, the calretinin expression rate was significantly higher in objective responders (75.0%, 94.3%, 100.0%; p=0.003).

The distribution of response to chemotherapy in the panels formed according to the immunohistochemical staining combinations is shown in Figure 2.

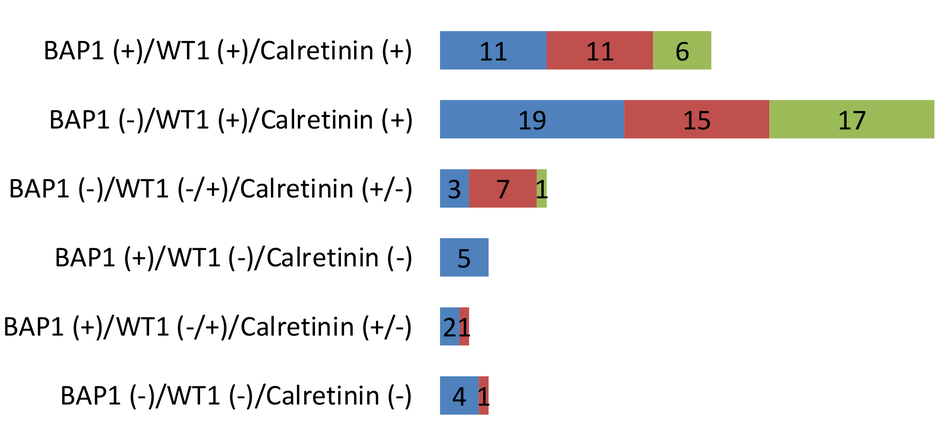

Figure 2. Distribution of response to chemotherapy according to the immunohistochemical staining combinations.

The progressive response rate was 84.6% (11/13) in patients with BAP1 expression and loss of expression in one or both of the other two markers or in patients with loss of expression in all three markers (***unfavorable status***). In the remaining two patients, stable disease was observed.

Progressive response to treatment was observed in 33 (36.7%) of 90 patients in the presence of expression of the three markers or the presence of expression of one or both of the other two markers with loss of BAP1 (***favorable status***). Objective response was recorded in 24 patients (26.7%) (p=0.001).

Immunohistochemical staining expression status and survival:

One hundred six patients had died at the analysis date (99.1%). The median survival time of the patients was 12.0±1.3 (9.5-1.5) months.

The survival times, comparisons, and curves of the patients according to their immunohistochemical staining status are given in Figure 3.

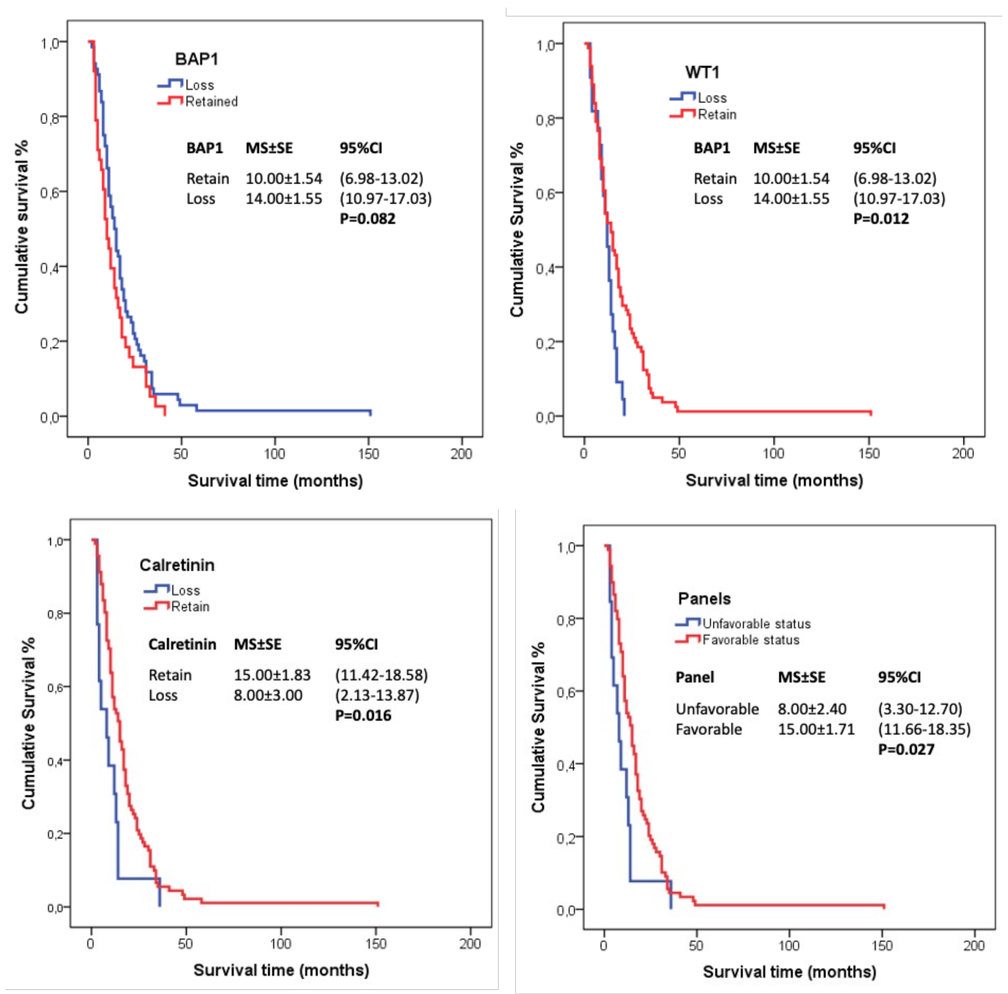

Figure 3. Survival times of the patients.

The results of univariate and multivariate Cox regression models that determine the risks associated with the survival time of the patients are presented in Figure 4.

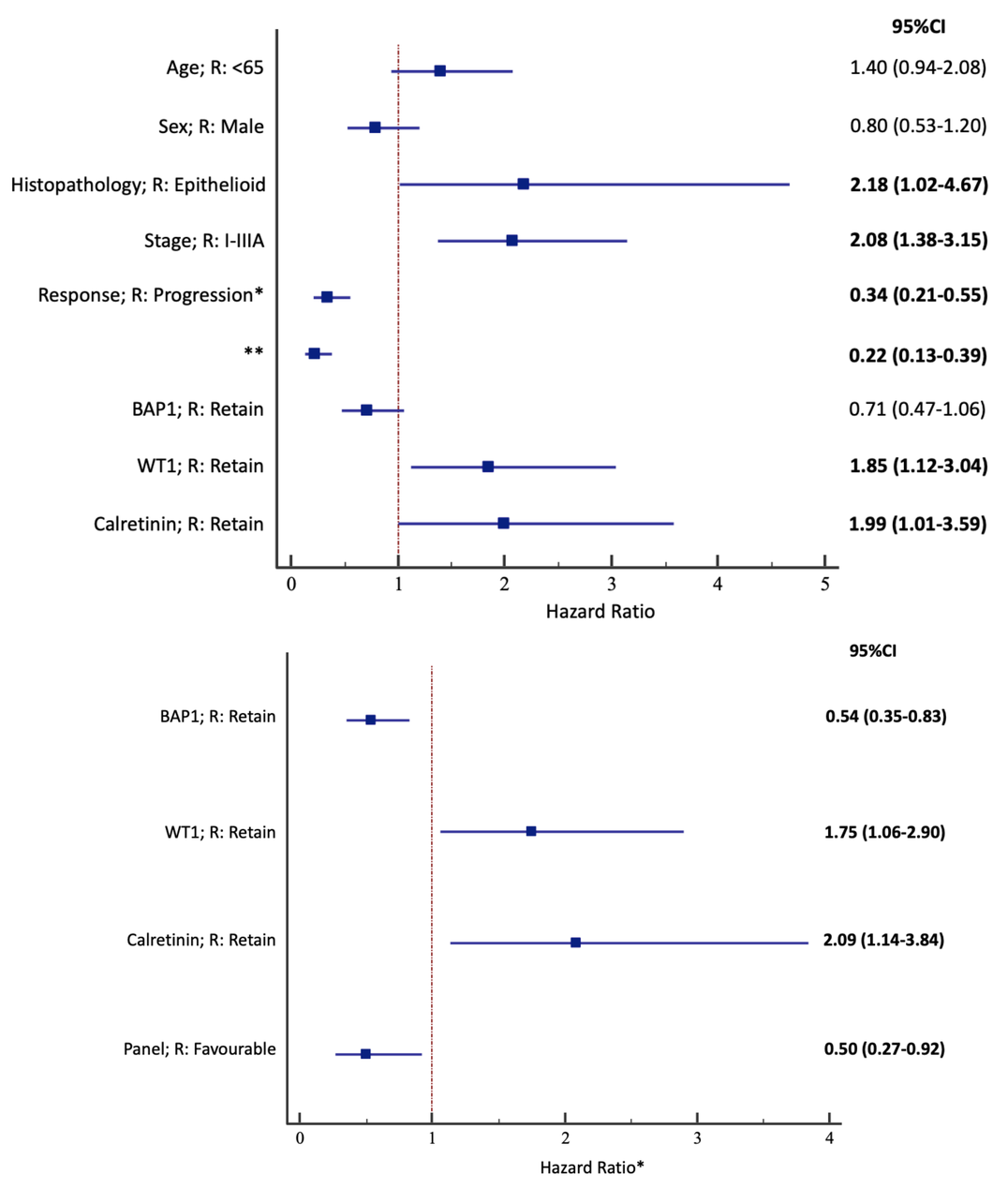

Figure 4. The results of univariate and multivariate Cox regression models.
**: Adjusted probability with histopathology and stage.*

Conclusion

- The presence of BAP1 loss or WT1 or calretinin expression in tumor tissue of DPM patients, determined by IHC, is not useful in determining the response to chemotherapy.
- The loss of BAP1, the presence of WT1 and calretinin are useful in predicting patients with a better prognosis.
- The panels formed by BAP1, WT1, and calretinin expression status, and defined as ***favorable*** and ***unfavorable status,*** show useful and promising results in predicting the response to chemotherapy and prognosis.