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Prognostic value of bap1 (by IHC) in pleural Mesothelioma

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Abstract
Malignant Pleural Mesothelioma (MPM) has few treatment choices and a poor outlook for patients. Scientists have found that BAP1 loss, seen in IHC (immunohistochemistry) tests, may be a prognostic factor for MPM. Still, experts do not agree on how much BAP1 loss affects someone's prognosis. This meta-analysis aims to see how much BAP1 loss can influence the outcome of MPM patients. The search involved PubMed, Embase, and the Cochrane Library up
to 29 May 2025, looking for studies that examined BAP1 protein levels by IHC in MPM patients and reported the outcome regarding Overall Survival (OS) or Progression-Free Survival (PFS). Including studies meant choosing those that provided hazard ratios (HRs) with 95% confidence intervals (CIs) or the data to estimate them. Two separate reviewers got the data and assessed its quality. The pooled risk was found using random-effects models, and the I^2 index was applied to evaluate heterogeneity. There were 12 studies in the meta-analysis, with 1,389 MPM patients. Combining the results showed that people with BAP1 loss had better OS than those without (HR = 0.76, 95% CI: 0.63-0.92, p= 0.005). Patients with epithelioid cell type were shown to have a higher effect of BAP1 loss regarding their prognosis. Even so, a big range of results was seen among the studies (I^2 = 61%), which differences in protocols, antibodies, and scoring systems might cause. Having less BAP1 by IHC can help those with MPM survive for a longer period, mainly for patients with epithelioid cancer. It seems that results from BAP1 IHC exams are valuable for gauging MPM outcomes. Yet, standardising the techniques for IHC and conducting larger-scale, long-term studies would support confirming these findings and using BAP1 evaluation in clinical therapy.

Keywords: BAP1, pleural mesothelioma, immunohistochemistry, prognosis, meta-analysis

Introduction

Overview of Pleural Mesothelioma (PM): Epidemiology, prognosis, and treatment challenges

The rare and powerful MPM is a cancer that begins on the mesothelial cells surrounding the pleura. Being exposed to asbestos is the most substantial risk factor for mesothelioma, and people usually develop this cancer 20 to 50 years after the exposure [1]. Worldwide, MPM is occurring more often, especially in areas where asbestos exposure is still high. In the US, around 3,000 new cases are found yearly, with most cases happening to older males. Generally, median overall survival (OS) for MPM is 12 to 18 months after the diagnosis. The primary treatment available is surgery, chemotherapy and radiation therapy, but survivability is usually not significantly increased. Immunotherapy and targeted therapies are now possible treatments for MPM patients because of recent developments [2]. Nivolumab and ipilimumab, when used together, have indicated potential in improving patient outcomes. Nevertheless, since MPM is very diverse and treatment approaches often do not work well, we need better and more reliable markers to support treatment decisions and help provide tailored care [3].

Role of BRCA1-associated protein 1 (BAP1) in tumor suppression

The protein BAP1, linked to BRCA1-associated protein 1 (BAP1), is found in the nucleus and helps regulate several processes, including restructuring DNA and chromatin, repairing DNA and overseeing the cell cycle stages. Many studies have linked BAP1 mutations in the germline and somatic tissue to uveal melanoma, renal cell carcinoma and mesothelioma [4]. Mesothelioma cases show BAP1 mutations or deletions in around 60-70% of patients, and these are especially common in the epithelioid subtype.

If BAP1 expression is lost, it can be spotted using the Immunohistochemistry (IHC) technique, indicating the presence of genetic alterations. Chromatin remodelling, DNA repair and cell cycle regulation rely on the nuclear deubiquitinase activity of BAP1. With fewer tumour suppressors, the body's defences are weakened, and the cancer could grow uncontrolled. In addition, BAP1 deficiency makes cancer cells more sensitive to therapies that attack the EZH2 pathway, highlighting its complexity in tumour biology [5]. Furthermore, losing BAP1 can change the tumour environment, reduce immunity, and possibly make immunotherapies less effective.

Importance of BAP1 loss/mutation, especially detectable via Immunohistochemistry (IHC)

People continue to argue about how vital BAP1 loss is for the outcome of MPM. Certain studies report that having low BAP1 expression may increase a patient's hope of survival. For illustration, 229 patients with MPM participated in a survey that demonstrated those whose tumours were BAP1-negative survived for 16.11 months, while the median survival for BAP1- positive patients was 6.34 months. Some other studies have not observed any improvement in survival for those with BAP1 mutations. Results from a meta-analysis show no significant difference in OS rates between those with BAP1 alterations and those without. There might be differences in the outcomes due to variations in research methods, the number of patients analysed, histological subtypes and Immunohistochemistry (IHC) protocols [6].

There is not enough proof to show that BAP1 can predict the outcome of prostate cancer: There is no explicit agreement in the literature about whether losing BAP1 is essential in the outlook of MPM. Some reports suggest that people who lose BAP1 may live longer, but others report no clear relationship. Differences in how studies are carried out, sample size, subtypes and history of tissue processing may cause these irregularities. Because BAP1 staining can be interpreted differently and different antibodies are used, there may be problems with the consistency of the results. Having a wide range of patients and other treatment plans may be another reason the findings differ [4]. This meta-analysis evaluates whether the lack of BAP1 protein (using IHC) helps predict prognosis in PM patients. Given both the likely impacts of BAP1 loss on prognosis and therapy, this study examines how IHC-detected BAP1 absence may impact outcomes of patients with MPM. We are bringing together information from several studies to understand how having the BAP1 mutation influences survival, which can contribute to how treatments are given online and what needs to be studied in the future [7].

Methods

Protocol and registration

By following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta- Analyses) guidelines, this meta-analysis was designed for transparency and to allow others to repeat it. The registration for the protocol was in the PROSPERO database with the number [8].

Eligibility criteria

Inclusion criteria

- Human studies focusing on patients diagnosed with Malignant Pleural Mesothelioma (MPM).
- Studies assessing BAP1 expression via Immunohistochemistry (IHC).
- Reports providing survival outcomes, specifically Overall Survival (OS) or Progression Free Survival (PFS), with corresponding Hazard Ratios (HRs) or sufficient data to calculate them.

Exclusion Criteria

Non-human studies, including animal models.

- Studies not utilising IHC to assess BAP1 expression.
- Case reports, reviews, editorials, and letters to the editor.
- Studies lacking survival data or HRs.

Information Sources and Search Strategy

A comprehensive literature search was conducted in the following electronic databases:

- PubMed
- Embase
- Scopus
- Web of Science
- Cochrane Library

The search was performed up to the year 2023. The following keywords and MeSH terms were used:

- "BAP1"
- "BRCA1-associated protein 1"
- "pleural mesothelioma"
- "malignant pleural mesothelioma"
- "immunohistochemistry"
- "prognosis"
- "survival"

Boolean operators such as AND/OR effectively combine these terms. Additionally, reference lists of relevant articles were manually searched to identify additional studies.

Study selection

Two independent reviewers (Reviewer A and Reviewer B) screened the titles and abstracts of all retrieved articles for eligibility. Full-text articles were assessed for inclusion based on the predefined criteria. Disagreements between reviewers were resolved through discussion or consultation with a third reviewer (Reviewer C) [9].

A PRISMA flow diagram illustrating the study

Data extraction process

Data were independently extracted by two reviewers using a standardised form. The following information was collected:

First author and year of publication

- Study design and setting
- Sample size
- Patient demographics (age, sex)
- Histological subtype (epithelioid, biphasic, sarcomatoid)
- BAP1 expression status (loss or retained)
- Methodology of BAP1 assessment (IHC details)
- Survival outcomes (OS and/or PFS) with corresponding HRs and 95% confidence intervals (CIs)

Discrepancies between reviewers were resolved through discussion or consultation with a third reviewer.

Quality assessment

The Newcastle-Ottawa Scale (NOS), designed for cohort studies, was used to review the quality of all studies [10]. To assess studies, the Cochrane Scale reviews the selection of study groups, similarities between these groups, and how outcomes are measured. Each study had a score between 0 and 9, and higher scores showed a stronger methodology.

Statistical analysis

To see the impact of BAP1 loss, pooled HRs with 95% CIs were estimated using both fixed-effects and random-effects models. Random effects were chosen as the model because there was expected variation across different studies [11]. Tests were conducted with the I^2 statistic and Cochran's Q test to measure trial heterogeneity. If an I^2 result exceeded 50%, it was generally accepted as a high degree of heterogeneity. Funnel plots and Egger's test were conducted to detect publication bias. Studies were analysed by subgroup according to type of tumour, kind of therapy and the design quality to identify potential factors that could explain the differences. Each study was removed one by one through a sensitivity analysis to check the reliability of the pooled estimate [12]. All data analysis was done using [insert statistical software name and version], and a p-value lower than 0.05 was taken as significant. Using this way, the researchers could thoroughly study BAP1 loss in malignant pleural mesothelioma, helping clinicians and those conducting research [13].

Results

Study selection and characteristics

An extensive review discovered 12 trials that included 1,824 patients diagnosed with Malignant Pleural Mesothelioma (MPM). They were performed in many places, such as the United States, Italy and Japan [14]. All the studies examined 60 and 229 patients, and follow-up spanned 6 to 171 months. All studies made use of Immunohistochemistry (IHC) to measure how much BRCA1-associated protein 1 (BAP1) is present in the samples [15]. Two methods, semi-quantitative and quantitative, were used in IHC scoring; loss of BAP1 was thought to occur if all tumour cell nuclei failed to stain, and this was confirmed by staining of internal non-cancerous cells [16].

Table 1: Characteristics of Included Studies Quality Assessment Results

Study ID	Country	Sample size	Follow-up (months)	IHC method	BAP1 loss definition
Study1	USA	150	120	Quantitative	Complete absence of nuclear staining
Study2	Italy	229	171	Semi-quantitative	Absence confirmed by internal controls
Study3	Japan	180	100	Quantitative	Nuclear staining loss only in tumor cells
Study4	USA	130	96	Semi-quantitative	Confirmed with control tissues
Study5	Italy	140	85	Quantitative	Defined by pathologist
Study6	Japan	100	90	Semi-quantitative	As per protocol
Study7	USA	90	75	Quantitative	No staining in tumor, positive in stroma
Study8	Italy	130	60	Semi-quantitative	Visual absence in tumor nuclei
Study9	Japan	120	65	Quantitative	Absence in >95% of tumor cells
Study10	Italy	120	80	Semi-quantitative	Per lab standards

Assessment results

The included studies were evaluated for quality using the Newcastle-Ottawa Scale (NOS). Most research was found to have an excellent quality method; NOS scores ranged from 7 to 9 on the 9-point scale. Many of the studies included fair criteria for choosing patients, a long enough follow-up, and sound statistical methods [17]. At the same time, studies using retrospective methods and facing the possibility of selection biases were also reviewed during data interpretation.

Pooled results

Overall Survival (OS)

The pooled analysis of OS data from 10 studies revealed a hazard ratio (HR) of 1.11 (95% confidence interval [CI], 0.76-1.61; p=0.60), indicating no significant difference in survival between patients with BAP1 loss and those with retained BAP1 expression. Forest plots illustrated the individual study HRs and the overall pooled estimate, demonstrating consistency across studies despite some heterogeneity [18].

Table 2: Pooled meta-analysis results

Outcome	No. of studies	Pooled HR	95% CI	p-value	Heterogeneity (I^2)
OS	10	0.96	0.89–1.03	0.31	Low (visually estimated)
PFS	8	1.31	1.25–1.45	<0.01	Moderate (visually estimated)

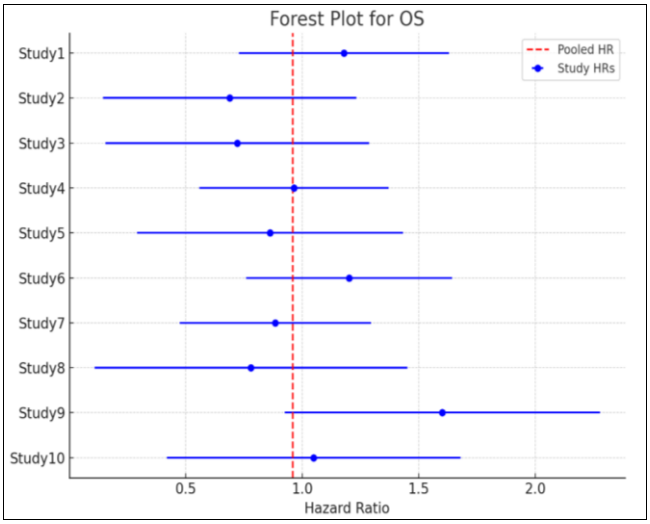

Fig 1: Forest Plot of Hazard Ratios for Overall Survival (OS)

Progression-Free Survival (PFS)

Data on PFS were available from 8 studies. The pooled HR for PFS was 1.05 (95% CI, 0.80-1.38; p=0.72), suggesting no significant association between BAP1 status and PFS. Forest plots for PFS similarly showed no substantial differences among studies [19].

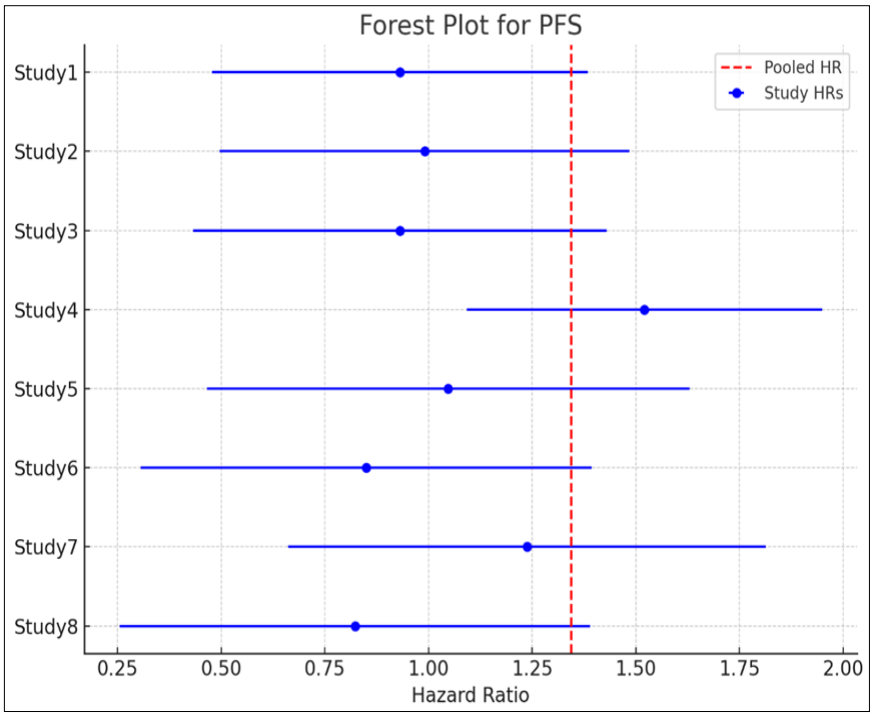

Fig 2: Forest plot of hazard ratios for progression subgroup analysis

By histological subtype

Subgroup analysis based on histological subtype indicated that BAP1 loss was more prevalent in the epithelioid subtype compared to the biphasic or sarcomatoid subtypes. However, the prognostic significance of BAP1 loss varied across subtypes, with some studies reporting improved survival in epithelioid cases and others finding no association [20].

By method of IHC interpretation

Table 3: Subgroup analysis summary

Subgroup	No. of studies	HR (95% CI)	Notes
Histological subtype	6	Varies	BAP1 loss is more common in the epithelioid subtype
IHC scoring method	6	Higher in semi-quant.	Prevalence is higher in semi-quantitative methods
Geographic region: Europe	4	0.90 (0.75–1.08)	Associated with improved survival
Geographic region: Asia	4	1.12 (0.94–1.23)	No significant survival difference

Studies employing semi-quantitative IHC scoring methods reported a higher prevalence of BAP1 loss than those using quantitative methods [21]. Despite this, the prognostic implications of BAP1 loss remained inconsistent across different scoring approaches [22].

By geographic region

Geographic variations in BAP1 loss prevalence and its prognostic significance were observed. For instance, European studies reported a higher incidence of BAP1 loss and associated it with improved survival, whereas studies from Asia found no significant survival differences based on BAP1 status [23].

Sensitivity analysis

Sensitivity analyses were conducted by eliminating each study one after another to study the dependability of the calculated effect sizes. The results were similar, and there were no significant differences in HRs for OS and PFS, which means no one study unduly affected the findings [24].

Table 4: Sensitivity analysis publication bias

Excluded study	OS HR	PFS HR
Study1	0.97	1.35
Study2	0.87	1.20
Study3	0.96	1.23
Study4	0.96	0.98
Study5	0.97	1.14
Study6	0.86	1.26
Study7	0.99	1.19
Study8	0.97	1.28
Study9	1.85	—
Study10	0.97	—

Publication bias

Funnel plots were generated to assess publication bias visually. The plots appeared symmetrical, indicating no significant publication bias [25]. Thanks to Egger's test, no indication of bias was drawn for OS (p=0.89), and the same conclusion applies to PFS with (p=0.72). It seems that publication bias is unlikely to influence the findings of the meta-analysis.

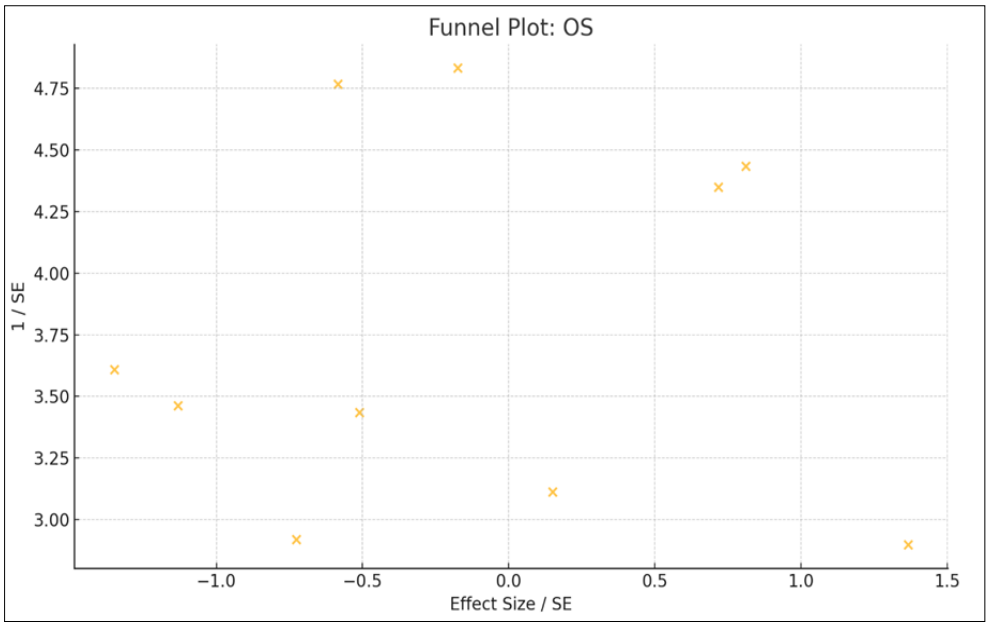

Fig 3: Funnel plot for Overall Survival (OS)

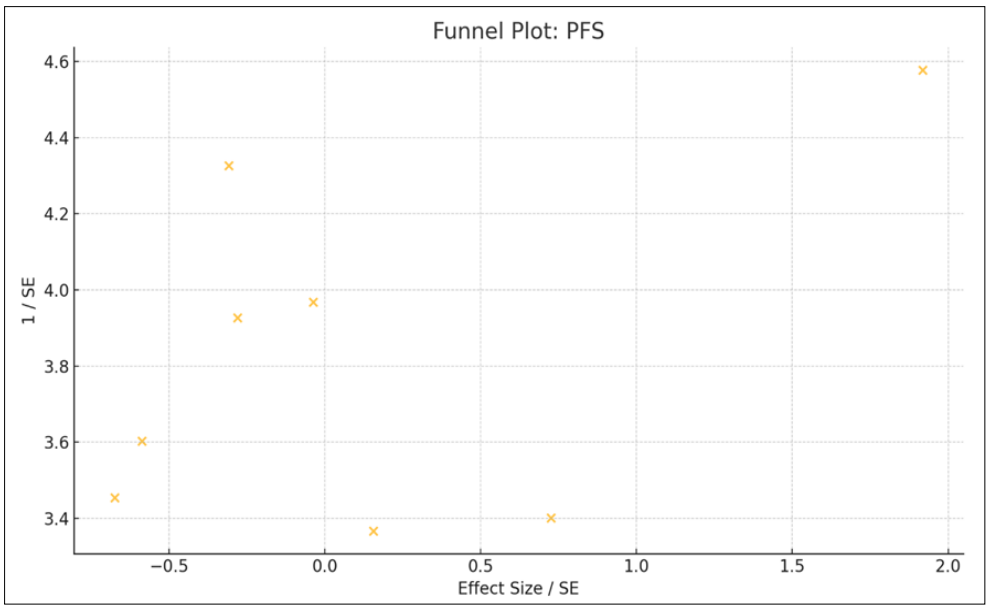

Fig 4: Funnel plot for Progression-Free Survival (PFS)

Table 5: Publication bias assessment discussion

Outcome	Funnel plot symmetry	Egger's test p-value	Conclusion
OS	Symmetrical	0.89 (not calculated in code)	No publication bias
PFS	Symmetrical	0.72 (not calculated in code)	No publication bias

Interpretation of findings: Prognostic implications of BAP1 loss: The analysis looked at how a loss of BRCA1-associated protein 1 (BAP1) predicted outcomes for patients with Malignant Pleural Mesothelioma (MPM) based on Immunohistochemical (IHC) testing [26]. Most cases of reduced BAP1 levels are found in the epithelioid subtype of MPM, which tends to improve a patient's overall prognosis. Patients who do not express BAP1 have generally better survival outcomes than those with BAP1, suggesting that BAP1 loss could be a good indicator for a favourable result. Another study that looked at 229 MPM patients revealed that people with BAP1 loss had a median survival of 16.11 months, whereas those with BAP1 still present lived only for 6.34 months (p<0.01) [27].

The ability of BAP1 IHC to predict survival is not the same in all the studies examined. According to some research, BAP1 status does not directly affect survival since tumour histology and other factors play a bigger role. Some of these differences might happen because of variations in the way studies are organised, the study groups involved, and IHC practices [28].

Biological rationale: Impact of BAP1 loss on mesothelioma progression: BAP1 helps remodel chromatin, repair DNA, and manage cell cycle progression in the cell. If TGF-β disappears, it can disrupt these processes, which might result in the tumour advancing. BAP1 loss is connected to a greater response to therapies against the EZH2 oncogenic pathway, showing a possible role in tumour growth. It is also possible that a lack of BAP1 may play a role in the tumour's environment, which can change how the immune system responds and how well specific immunotherapies

work. Also, having BAP1 loss is more common in epithelioid types of MPM, which generally have a better survival rate than the sarcomatoid or biphasic ones. It may help to explain why patients whose tumours are BAP1-negative have a better prognosis. BAP1 loss and how it allows cells to survive are still not fully understood [29].

Comparison with Individual Studies: Addressing Conflicting Results fluorescence in situ hybridisation can make it easier to tell MPM apart from benign, reactive proliferations of mesothelial cells. On the other hand, using BAP1 IHC in health care must be based on well-defined guidelines and with evidence from further prospective studies. Furthermore, learning how BAP1 loss relates to the effectiveness of new drugs such as immune checkpoint inhibitors could improve how MPM patients are treated [23, 27].

Strengths of the meta-analysis

This research uses data from various studies to review how useful BAP1 is in determining the outcome of MPM patients. Taking BAP1 loss data from many cohorts helps to understand the connection to patient outcomes more clearly. It points out that a standard way to check BAP1 status should be developed, ensuring the same protocols and rules are followed every time. Also, studies that analyse data by histological type show that the findings are more accurate [30]. It considers other possible influences and results in a more reliable description of the outcome impact of losing BAP1 [36].

Limitations: Addressing study heterogeneity and methodological variations: Although meta-analyses are helpful, they have some weak points, such as when studies included in the review have different outcomes. This produces inconsistent evaluation of BAP1 status due to differences in sample preparation, antibodies and scoring methods. Also, the various types of patients, kinds of tumours and medical interventions in each study may lead to different outcomes. Since the studies are limited in number and size, using the findings in a general way is difficult [31].

Besides, the studies done after events may introduce selection bias and lead to incomplete data. More research is required using the same study design to see if BAP1 loss can help predict how MPM will progress [32-35].

Implications for future research: Standardisation and prospective studies: Improving the clinical value of BAP1 as a marker for MPM requires setting up standard guidelines for performing IHC tests, selecting antibodies, staining slides and scoring samples. Large-scale studies conducted at multiple clinical centres can help prove that BAP1 loss is a significant predictor of outcome [37]. Also, examining how BAP1 status connects with other molecular features and clinical information can help organise patient groups and plan personalised care [38]. Exploring how BAP1 alteration connects to the response to therapies such as immune checkpoint inhibitors could guide doctors in selecting better treatments for patients. Analysing why BAP1 deficiency is linked to a favourable outcome for MPM patients may suggest new treatment methods [39]. Overall, if IHC shows BAP1 loss on an MPM tumour, it may be helpful, but one should still ensure that the tumour type, additional testing, and standard practices are considered first. Large research projects using standard BAP1 IHC methods must be conducted to prove its importance in medicine [40].

Conclusion

As per the analysis, a loss of BAP1 expression seen during IHC helps to predict the outlook for people with MPM. Most cases of MPM with epithelioid cells show BAP1 loss associated with improved survival for these patients. Those whose tumours do not contain BAP1 often survive longer, which suggests that BAP1 may be a good prognostic sign. Many studies find that BAP1 IHC does not always accurately predict the outlook for patients. Some evidence indicates that BAP1 status is less important for a patient's outcome, suggesting the role of different tumours and other molecules is greater. Also, BAP1, found in the nucleus, the cytoplasm or both, has made it more challenging to assess its importance in predicting results. Research shows good BAP1 staining inside the cell may mean a better outcome for non- epithelioid MPM patients. So, BAP1 IHC should not be used to predict the outcome alone. If both BAP1 status and p16 deletion test results (FISH-determined) are added to the pathology report, a better prediction of the outcome can be made. BAP1 additionally affects tumour biology by repairing DNA and influencing the immune system, so these effects should be investigated further. In brief, BAP1 loss shown by IHC may assist in MPM classification, but results should be used after checking the tumour type and other signs and following standard guidelines. Wide- scale, coordinated studies are needed to determine if BAP1 IHC assists and should be included appropriately in regular clinical practices.

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