Highly expressed IMP3 and GLUT-1 in combination with the loss of BAP1 expression is useful for differentiating malignant mesothelioma from reactive mesothelial hyperplasia

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Research

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Abstract

Background Our study aims to evaluate how IHC staining of BRCA1 associated protein-1 (BAP1), insulin-like growth factor mRNA binding protein 3 (IMP3), and glucose transporter-1 (GLUT-1) can help to differentiate MM from reactive mesothelial hyperplasia (RMH).

Methods The expression levels of BAP1, IMP3, and GLUT-1 were investigated using immunohistochemistry (IHC) in 38 MMs and 32 RMHs.

Results BAP1 was lost in 20 (52.6%) of the 38 MMs. IMP3 and GLUT-1 were positive in 26 (68.4%) and 25 (65.8%), respectively, of the 38 MMs. The results of IHC analyses of BAP1, IMP3, and GLUT-1 indicated that these markers were characterized by a 100% specificity with sensitivities of 52.63, 68.42, and 65.79%, respectively. In addition, BAP1, IMP3, and GLUT-1 combined showed 100% specificity and the highest sensitivity (81.58%). Meanwhile, loss of BAP1 expression is related to a better prognosis.

Conclusions Overexpressed IMP3 and GLUT-1 in combination with the loss of BAP1 showed high specificity to MM that was different from that in RMH and improved diagnostic accuracy, especially in MM.

Background

Malignant mesothelioma (MM) is the most common mesothelioma with a poor prognosis and a median survival of 9.2–11.2 months [1–3]. Unlike MM, reactive mesothelial hyperplasia (RMH) is a self-limiting disease often caused by injury to the mesothelial surface; therefore, it is important to differentiate the two conditions to be able to accurately treat the patient and provide a prognosis. Although RMH is a benign condition, in some cases, especially in small biopsy tissues and effusion, it is difficult to identify benign from malignant mesothelial cells [4]. Current guidelines on pathology and cytology recommend the use of immunohistochemistry (IHC) and molecular detection for a differential diagnosis [5, 6]. Although IHC's usefulness has been fully demonstrated, the specificity and sensitivity of IHC markers are different. Some IHC markers, such as IMP3 [7–9] and GLUT-1 [9–12] have become the most popular of antibodies because of their relatively high diagnostic performance. In recent years, the loss of BAP1 expression in mesothelial cells has also become a marker with high specificity of malignant tumors.

BAP1 encodes BRCA1-related protein 1 (BAP1), which is a nuclear localization deubiquitinase that regulates gene expression, transcription, and DNA repair and plays a role in tumor inhibition by enhancing the inhibition of BAP1-mediated cell proliferation [13]. The deletion or inactivation of BAP1 may be caused by a chromosome deletion in BAP1 locus at 3p21.1 or by the sequence variation in BAP1, which has been proved to be associated with various tumors, including MM [14].

IMP3 is a carcinoembryonic, cancer-specific protein involved in embryogenesis, and its expression is associated with many malignant tumors related to aggressive and advanced cancers; it is not expressed

in benign tissues [15–17]. IMP3 has also been shown to promote the proliferation, invasion, and metastasis of tumor cells and may play an important role in the diagnosis of MM [18–20].

GLUT-1 is a glucose transporter with a high affinity and low capacity and is found mainly in the plasma membrane and usually expressed in red blood cells [21, 22], peripheral nerves [23], renal tubules [24], the blood-brain barrier [25], and placental tissues [26]. Although not expressed in most normal epithelial cells or epithelial benign tumors, GLUT-1 is expressed in epithelial malignancies in various organs [27–29]. Using IHC to detect GLUT-1 has shown great potential in differentiating MM from RMH [11].

The purpose of this study was to evaluate how IHC staining (i.e., immunostaining) of BAP1, IMP3, and GLUT-1 cells can help to differentiate MM from RMH.

Materials And Methods

Case selection

Tissue samples from 38 patients with MM and 32 with RMH who were treated from January 2000 to December 2016 at the Affiliated Hospital of Nantong University, China, were collected from the hospital's pathology department. All of the selected cases had identical diagnostic opinions and a definite diagnosis by two pathologists. Patients having an inconsistent diagnosis were excluded from the study. The Human Research Ethics Committee of the hospital was informed of the content of this investigation and approved the study. All samples used were anonymous archival specimens, and informed consent was not required for this study.

IHC procedures and evaluation of BAP1, IMP3, and GLUT-1 expression

IHC staining was conducted using the following antibodies: anti-BAP1 mouse monoclonal antibody (clone C-4; Santa Cruz Biotechnology, Santa Cruz, CA, USA; 1:100 dilution), anti-IMP3 rabbit monoclonal antibody (clone EP286; Maixin, Fuzhou, China; 1:100 dilution), and anti-GLUT-1 mouse monoclonal antibody (clone SPM498; Thermo Fisher Scientific, Kalamazoo, MI; 1:200 dilution). Nonmesothelial cells that were immunoreactive to BAP1 (e.g., inflammatory cells such as histiocytes and lymphocytes, fibroblasts, pneumocytes, and endothelial cells) served as internal positive controls for each staining protocol. Analysis of BAP1 after IHC revealed staining in the nucleus, and BAP1 loss in the tumor cells was defined as nuclear staining at an intensity lower than that of the internal positive control [30].

We set the cutoff value at 50% for IHC analysis of BAP1 as previously described [31]. IMP3 cytoplasmic/membranous staining and GLUT-1 membranous staining in ≥ 10% of the target cells were considered positive. Lymphoid cells for IMP3 and red blood cells for GLUT-1 served as the positive internal controls [32].

Statistical analyses

Fisher's exact test was used to evaluate the staining differences in BAP1, IMP3, and GLUT-1 among the MM and RMH cells. The corresponding receiver operating characteristic (ROC) curves were plotted for different combinations of immunostains, and the areas under these correlated ROC curves (AUCs) were compared using the nonparametric approach of DeLong et al [33]. The survival curve was calculated using the Kaplan-Meier method. $P < 0.05$ was considered statistically significant. Statistical analyses were performed using SPSS ver. 24 (IBM Corp., Armonk, NY, USA).

Results

Clinicopathological characteristics

Among the 38 patients with MM, 30 were males (M:F = 15:4). The average age was 61.87 years (range, 35–82 years). Thirty-eight MM specimens comprised 20 that were surgically excised, 12 that were biopsied, and 6 that were identified as pleural effusion cell masses. There were 32 cases of RMH, 24 of which were benign pulmonary mesothelial reactive hyperplasia, and 8 that were among the pleural effusion cell mass specimens (28 males and 4 females; average age 56.16 years; range, 21–76 years).

IHC results

The results of IHC staining of BAP1, IMP3, and GLUT-1 are summarized in Table 1. BAP1 was lost in 20 (52.6%) of the 38 MMs. IMP3 and GLUT-1 were positive in 26 (68.4%) and 25 (65.8%), respectively, of the 38 MMs. There was no IMP3 or GLUT-1 expression in any of the 32 cases of RMH.

Table 1
Diagnostic application of detection assays to differentiate malignant mesothelioma from reactive mesothelial hyperplasia.

		MM(n = 38)	RMH(n = 32)
BAP1 IHC	R	18	32
	L	20	0
GLUT1 IHC	P	25	0
	N	13	32
IMP3 IHC	P	26	0
	N	12	32
BAP1/GLUT1	L/ P	28	0
	R/ N	10	32
BAP1/ IMP3	L/ P	28	0
	R/ N	10	32
BAP1/GLUT1/ IMP3	L/ P/ P	31	0
	R/ N/ N	7	32
MM: malignant mesothelioma; RMH: reactive mesothelial hyperplasia; R: Retained; L:Loss;			
P: Positive; N: Negative.			

Sensitivity and specificity of detection assays for discriminating MM from RMH

Representative hematoxylin and eosin (H&E) stains of BAP1, IMP3, and GLUT-1 IHC assays of the MM and RMH samples are shown in Figs. 1 and 2. The sensitivity and specificity of each detection assay for discriminating MM from RMH samples are summarized in Table 2. All IHC assays of BAP1, IMP3, and GLUT-1 showed 100% specificity with sensitivities of 52.63, 68.42, and 65.79%, respectively. IHC assays for all combinations of BAP1, IMP3, and GLUT-1 also showed 100% specificity. The sensitivity of BAP1 alone was low with IHC, but increased when combined with other markers, and the combination of BAP1, IMP3, and GLUT-1 gave the highest sensitivity at 81.58% (Fig. 3A).

Table 2
Sensitivity and Specificity of IHC in malignant mesothelioma and reactive mesothelial hyperplasia.

	Sensitivity (95% CI)	Specificity (95% CI)	AUC (95% CI)
BAP1	52.63 (35.8–69.0)	100 (89.1–100.0)	0.763 (0.646–0.857)
GLUT1	65.79 (48.6–80.4)	100 (89.1-100.4)	0.829 (0.720–0.908)
IMP3	68.42 (51.3–82.5)	100 (89.1-100.5)	0.842 (0.735–0.918)
B&G&I	81.58 (65.7–92.3)	100 (89.1-100.3)	0.908 (0.815–0.964)
B&G&I: BAP1& GLUT1 &IMP3.			

The ROC curves for the IHC markers

AUCs (95% confidence interval [CI]) for BAP1, IMP3, and GLUT-1 were 0.763 (0.646–0.857), 0.842 (0.735–0.918), and 0.829 (0.720–0.908), respectively. AUC (95% CI) for BAP1, IMP3, and GLUT-1 combined was 0.908 (0.815–0.964) (Table 2, Fig. 3B).

Survival analyses

Kaplan-Meier analysis showed that loss of BAP1 expression is associated with a better prognosis in MM (P = 0.0217; Fig. 4A). The prognosis was not statistically different for IMP3, and GLUT-1 in MM (P = 0.187, P = 0.332; Fig. 4B,C).

Discussion

This study demonstrated the IHC assays and analyses of BAP1, IMP3, and GLUT-1 that can be used to differentiate MM from RMH. BAP1 is a newly identified diagnostic marker whose loss is specific to MM [34, 35]. Previous studies have found BAP1 loss in 27–67% of MM [30, 31, 36], more commonly in epithelioid MM (68–77%) than in sarcomatoid/desmoplastic MM (0–22%) [37–39]. The results of our study showed that BAP1 was lost in 20 (52.6%) of the 38 MMs, which is similar to the previous findings in that the loss of BAP1 expression is usually not seen in RMH proliferation [37]. Previous studies have observed, together with ours, 100% specificity for BAP1 after the IHC assay in MM with a sensitivity of 52.63%. In addition, AUC for BAP1 was 0.763 (0.646–0.857). Meanwhile, BAP1 mutation or loss of BAP1 expression has been shown to be associated with a better prognosis in MM [3]. Of course, our study came up with the same results.

IMP3 was first identified in a screening for pancreatic carcinoma–specific markers [40] and was noted to be highly expressed in both MMs and lung carcinomas [8, 41]. Positive levels of IMP3 were reported to have a wide range from 53 to 93%. Our study showed that IMP3 positivity was 68.4% in MM. The sensitivity and specificity of IMP3 from IHC staining results distinguishing between MMs and benign

mesothelial proliferations were reported as ranging from 36 to 91% and 73 to 100%, respectively. We observed that the sensitivity and specificity of IMP3 were 68.42 and 100%, respectively; therefore, our results are consistent with those of previous reports. AUC of IMP3 (0.842) was higher than that for other individual markers.

GLUT-1 is a high-affinity glucose transporter that is expressed in normal human tissues, including red blood cells, the endothelia of the blood-brain barrier, and the placenta [42, 43]. GLUT-1 also appears to be upregulated in certain types of malignancies, including those of lung [44], breast [45], head and neck (squamous) [46], and ovary [47]. In our study, we found that GLUT-1 was expressed in 25 of the 38 cases of MM. Lagana et al.[48] have found that 73/135 (54%) of malignant tumors were positive for GLUT-1. In our study and those of Kato et al. [11] and Lagana et al.,[48] GLUT-1 did not test positive in the RMH specimens. Previous studies have reported that GLUT-1 sensitivity ranged from 40 to 100%, while its specificity ranged from 63 to 100% in MMs [8, 9, 11, 32]. In our study, GLUT-1 sensitivity and specificity were 65.79 and 100%, respectively, and AUC of GLUT-1 was 0.829.

Conclusions

In the present study, we examined the results of IHC assays of BAP1, IMP3, and GLUT-1 and related these to their levels in MM and RMH. We hypothesized that evaluating all markers together could improve sensitivity. Our study showed that using a BAP1, IMP3, and GLUT-1 panel improved sensitivity by up to 81.58%, and that the sensitivity of the combined BAP1, IMP3, and GLUT-1 was significantly higher than that in any other combination of stains. Meanwhile, we also found that AUC of the combined BAP1, IMP3, and GLUT-1 was the highest at 0.908 ($P < 0.05$).

Overexpressing IMP3 and GLUT-1 in combination with BAP1 loss was highly specific in differentiating MM from RMH. Combining BAP1, IMP3, and GLUT-1 improved diagnostic accuracy, especially that in MM.

Study Limitations

There were some limitations to the present study. First, the study comprised a relatively small number of cases. Second, the expression of these markers in different types of MM was not analyzed. Third, although several studies have demonstrated that BAP1 loss is associated with better survival and is an independent prognostic factor, we did not study the correlation between the expression of the markers and the prognosis of patients with MM. The shortcomings of our study are the result of the small number of cohorts; a study with a larger cohort is needed to draw more definitive conclusions.

Abbreviations

MM: Malignant mesothelioma; BAP1: BRCA1 associated protein-1; IMP3: insulin-like growth factor mRNA binding protein 3; GLUT-1: glucose transporter-1; RMH: reactive mesothelial hyperplasia

Declarations

Acknowledgements

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Authors' contributions

HZ, QH designed the study and drafted the manuscript. DJ participated in data analysis. HH performed the evaluation of the IHC stains. JZ and JL provided tissue specimens. BT and YL financed the study and participated in evaluation of the IHC stains. All authors reviewed the manuscript for important intellectual content. All authors read and approved the final manuscript.

Availability of data and materials

Is available upon request from the corresponding author.

Ethics approval and consent to participate

Ethics approval and consent to participate was given by all patients in writing (ethics approval was given by the Ethics Committee of Affiliated Hospital of Nantong University).

Competing interests

The authors declare that they have no competing interests.

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Figures

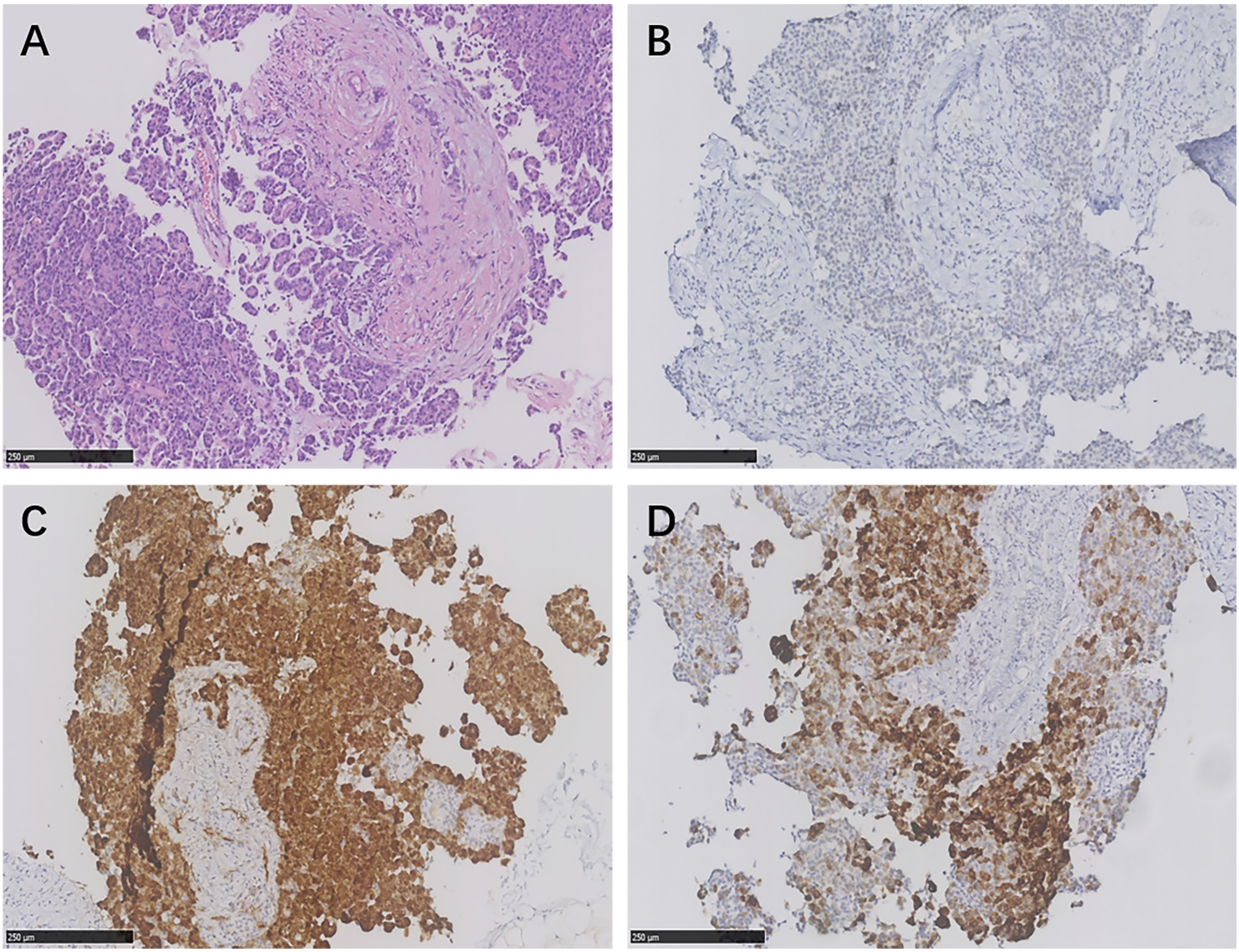

Figure 1

Representative examples of H&E staining (A) and BAP1 (B), IMP3 (C), and GLUT-1(D) immunostaining in MM. Original magnifications×200 (A-D). (A): epithelioid MM, (B): loss BAP1 expression, (C): high IMP3 expression (cytoplasmic/ membranous staining), (D) high GLUT-1 expression (membranous staining).

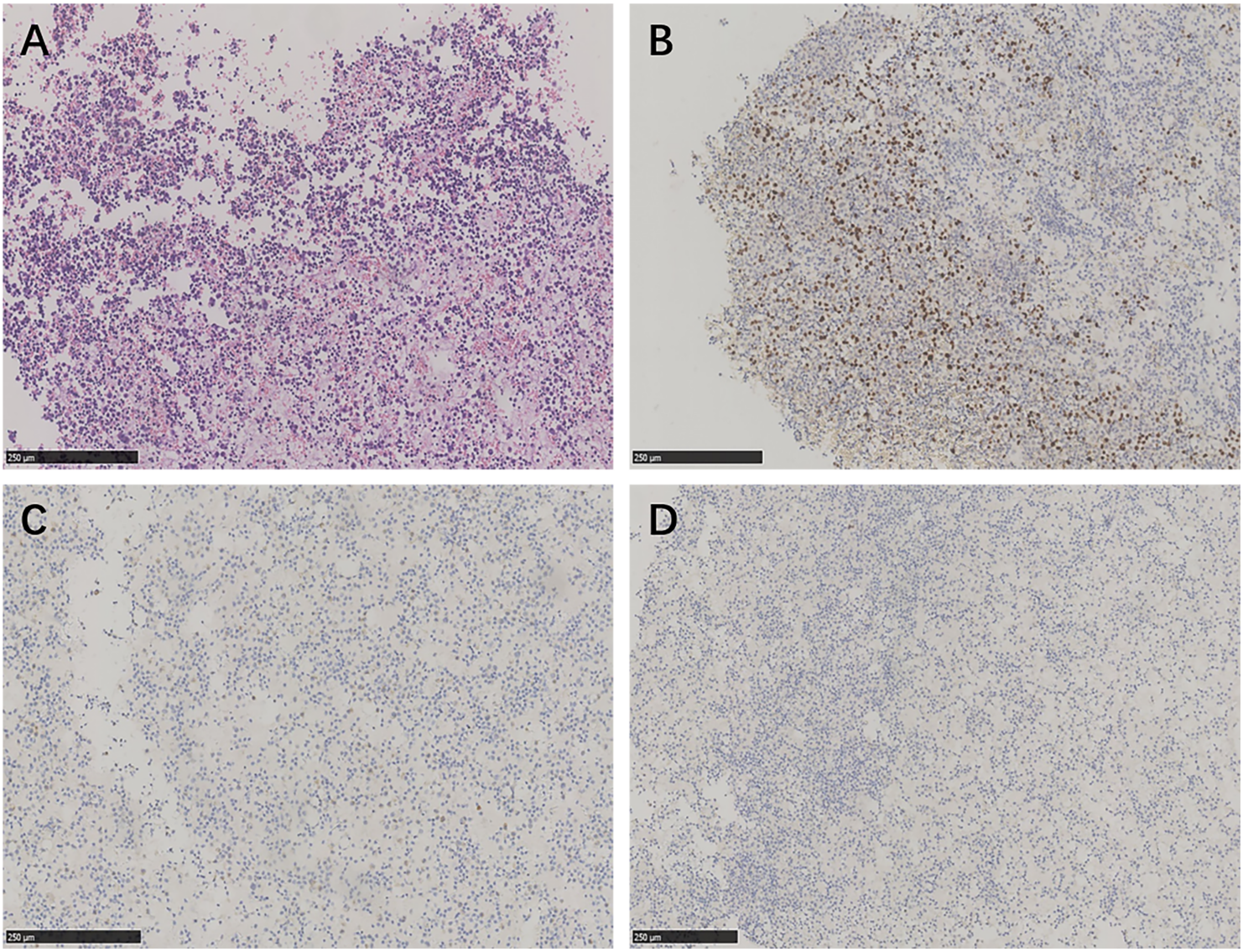

Figure 2

Representative examples of H&E staining (A) and BAP1 (B), IMP3 (C), and GLUT-1(D) immunostaining in RMH. Original magnifications×200 (A-D). (A): Reactive mesothelial hyperplasia, (B): retained BAP1 expression, (C): negative IMP3 expression, (D) negative GLUT-1 expression.

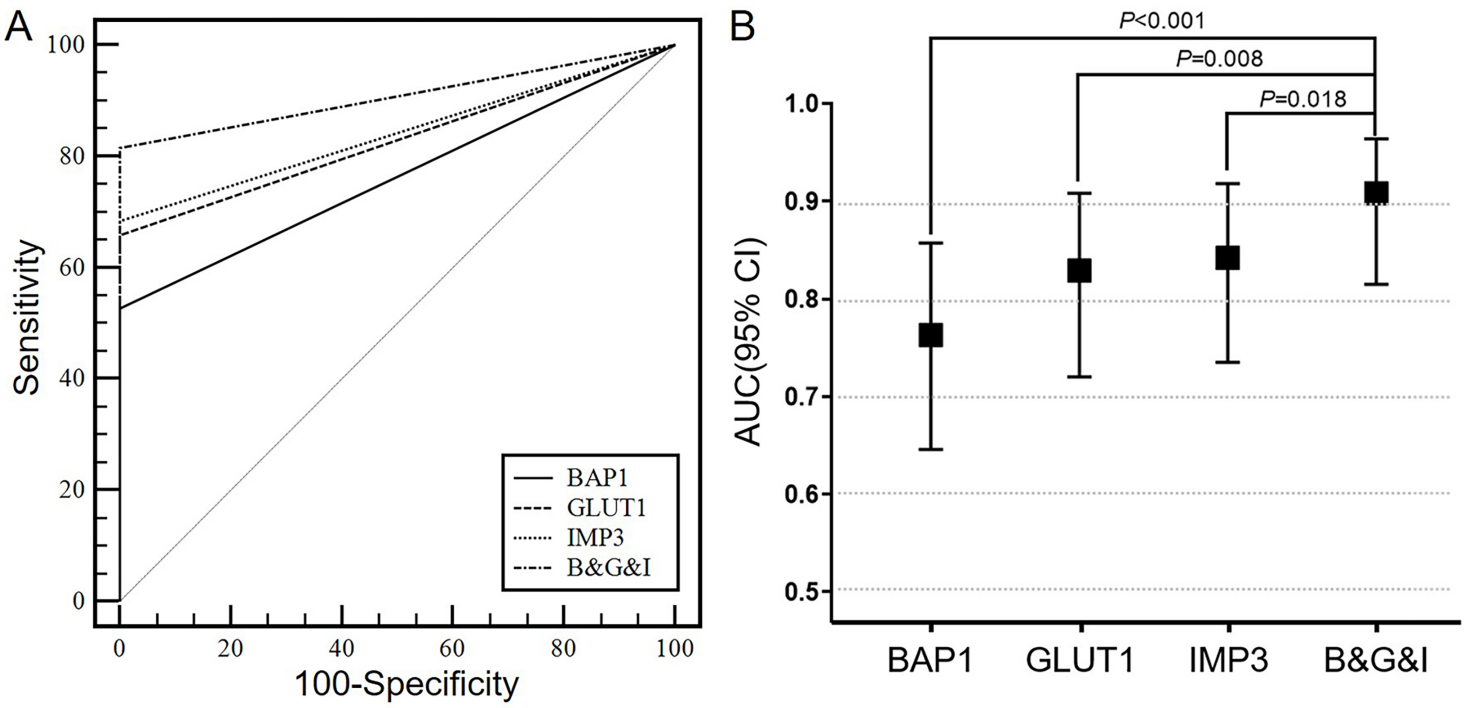

Figure 3

The ROC curves for the IHC markers. (A): Sensitivity and specificity of BAP1, GLUT1, IMP3, BAP1& GLUT1 &IMP3 for discriminating MM from RMH, (B): AUC (95% CI) of BAP1, GLUT1, IMP3, BAP1& GLUT1 &IMP3 for discriminating MM from RMH.

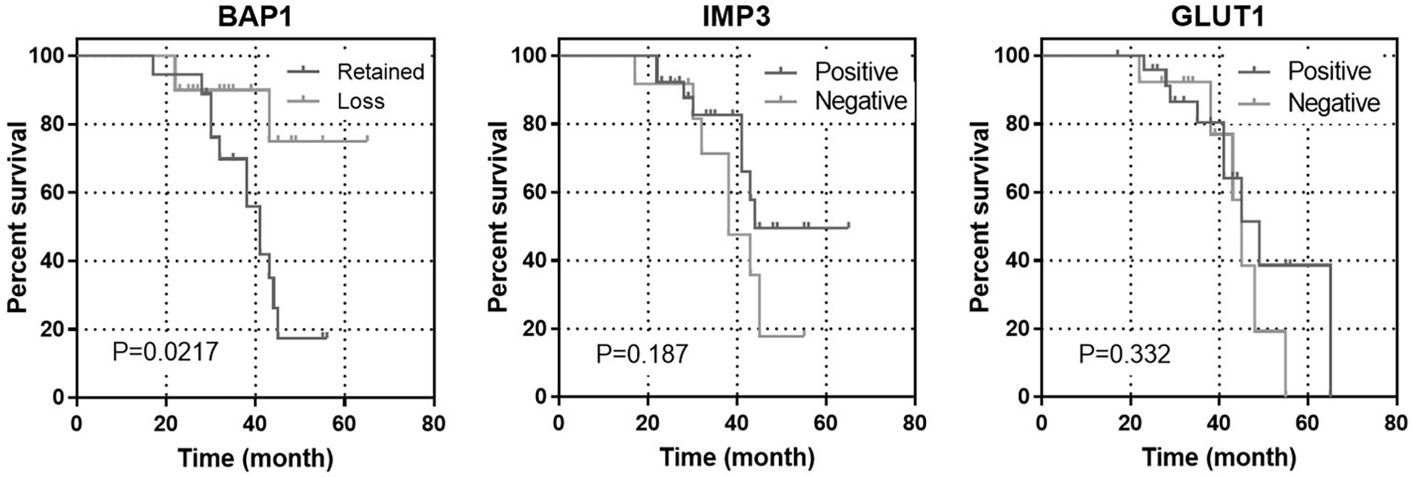

Figure 4

Overall survival (OS) curves for patients with MM. (A): BAP1 status, (B): IMP3 status, (C): GLUT-1 status.