Prognostic and diagnostic significance of serum p53 antibody levels in patients with surgically treated pancreatic cancer

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Abstract. Serum p53 antibody (s-p53-Ab) levels increase in patients with various cancer types; however, their clinicopathological relevance in pancreatic ductal adenocarcinoma (PDAC) is not well defined. The present study aimed to assess the prognostic value of s-p53-Ab status in PDAC. The present retrospective study included 124 patients who underwent surgery for PDAC between January 2012 and December 2023. Patients were categorized into s-p53-Ab(+) and s-p53-Ab(-) groups using a cutoff value of 1.3 U/ml. Prognostic significance was examined using univariate and multivariate analyses. A total of 25 patients (20%) were s-p53-Ab-positive. The isolated s-p53-Ab positivity rates in stage I and II disease were 10 and 8%, respectively. The s-p53-Ab(+) group exhibited significantly worse overall survival (P=0.038) and relapse-free survival (P=0.037) than the s-p53-Ab(-) group. Multivariate analysis revealed that s-p53-Ab(+) independently predicted poorer relapse-free survival (P=0.044) and overall survival (P=0.048). s-p53-Ab was occasionally positive in stage I/II PDAC and was associated with more aggressive disease behavior. The present study was registered as a clinical trial in the University Hospital Medical Information Network Clinical Trials Registry (registration number, UMIN000014530; date of registration, 2011/07/11).

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is an aggressive malignancy with one of the poorest outcomes among all cancers, reflected in a 5-year survival rate of only 9% (1,2). Although early detection allows for curative surgical resection, approximately 85% of cases are diagnosed at advanced or metastatic stages due to the disease's subtle onset and rapid progression (3). Consequently, the development of novel, preferably noninvasive biomarkers with high sensitivity and specificity is essential for facilitating early diagnosis, increasing resectability, and improving survival outcomes.

Carbohydrate antigen 19-9 (CA19-9) remains the most widely used tumor marker for PDAC. However, its diagnostic performance is limited, with median sensitivity and specificity of 79 and 82%, respectively (4-9), and sensitivity dropping below 50% for tumors ≤2 cm (10). Moreover, individuals who lack Lewis antigens may exhibit false-negative CA19-9 results, further reducing its clinical utility (10-13). These limitations underscore the pressing need for complementary or alternative biomarkers.

The p53 protein is a key tumor suppressor frequently mutated across many cancer types. Mutant p53 accumulates in tumor cells, increasing immunogenicity and leading to serum autoantibody production in a subset of patients. Thus, serum p53 antibody (s-p53-Ab) positivity may function as an indirect marker of p53 mutation and tumor burden (14). Our research group have previously demonstrated the diagnostic relevance of s-p53-Ab in several solid tumors, including esophageal (15), gastric (16), colorectal (17), hepatocellular (18), and breast cancers (19), and has also explored the value of multi-autoantibody panels (17,18,20). Despite ongoing interest, reports on s-p53-Ab in PDAC are limited to five studies with small cohorts (22-82 cases), showing positivity rates of 5-28% (21-25). Importantly, no prior studies have focused solely on resectable PDAC cases or examined the prognostic implications of s-p53-Ab status.

Considering these gaps, this study aimed to clarify the clinicopathological features and prognostic significance of s-p53-Ab positivity in patients with PDCA.

Materials and methods

Patients. This study was registered as UMIN000014530. Preoperative serum samples were collected from 124 patients with PDAC who underwent surgery at Omori Medical Center, Toho University School of Medicine, between January 2012 and December 2023. The cohort included 63 men (51%) and 61 women (49%), with a median age of 72 years (range,

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33-87 years). Patients with active coexisting malignancies-defined as synchronous cancers or metachronous cancers occurring within 5-year disease-free intervals were excluded. PDAC staging was determined pathologically according to the eighth edition of the International Union Against Cancer tumor-node-metastasis classification system (26). Preoperative assessment, surgical procedures, and postoperative follow-up adhered to established clinical practice guidelines for pancreatic cancer. Tumors presenting with distant metastasis, including peritoneal dissemination, were classified as unresectable.

Data collection and serum tumor marker analyses. Clinicopathological data, s-p53-Ab, CA19-9, and CEA levels were analyzed. Preoperative variables, pathological findings, postoperative outcomes, and survival data were compiled in a spreadsheet and transferred to a dedicated database. The prognostic significance and clinical utility of s-p53-Ab in PDAC were assessed. Overall survival (OS) and relapse-free survival (RFS) were defined from the date of surgery to death or October 2025.

The cutoff value for s-p53-Ab was set at 1.3 U/ml based on the manufacturer's instructions (27). CEA and CA19-9 cutoff values were 5.0 ng/ml and 37 U/ml, respectively, according to the assay kit guidelines.

Statistical analysis. Statistical analyses were conducted using JMP version 13 (SAS Institute, Cary, NC, USA). Clinicopathological variables and recurrence sites were analyzed using Fisher's exact probability test. OS was estimated using the Kaplan-Meier method, and survival differences were assessed using the log-rank test. Significant predictors were identified through univariate and multivariate analyses using Cox proportional hazard models, with hazard ratios and 95% confidence intervals calculated. A P-value <0.05 was considered statistically significant.

Results

Clinicopathological significance of s-p53-Ab status. No significant differences were observed between the s-p53-Ab (+) and (-) groups in demographic factors (age and sex), tumor location, tumor size, lymph-node involvement, histological grade, or other pathological features (Table I). Among the 124 patients, 25 (20%) were s-p53-Ab (+). Seropositivity appeared even in early disease stages, including 19% (10/53) of stage I and 21% (10/48) of stage II cases, indicating that elevated s-p53-Ab levels occur even in the initial phase of PDAC progression. Furthermore, several patients were solely positive for s-p53-Ab in stages I (n=5) and II (n=4) (Fig. 1). These findings suggest that combining s-p53-Ab with other tumor markers improve diagnostic sensitivity.

Prognostic significance of s-p53-Ab status. Kaplan-Meier survival analysis showed that patients with s-p53-Ab (+) had significantly worse RFS (P=0.037) and OS (P=0.038) than those who were s-p53-Ab (-) (Figs. 2 and 3). Among CA19-9 (+) patients, those who were also s-p53-Ab (+) showed significantly poorer RFS than CA19-9 (+)/s-p53-Ab (-) patients (P=0.032). Multivariate Cox analysis further identified s-p53-Ab (+) as an independent prognostic factor for reduced RFS [hazard ratio (HR)=1.683, 95% confidence interval (CI): 1.102-2.693, P=0.047] and OS (HR=1.758, 95% CI: 1.036-2.915, P=0.048) (Tables II and III).

Comparison of recurrence sites between s-p53-Ab positive and negative group. The s-p53-Ab (+) group demonstrated a significantly higher rate of lymph-node recurrence (P=0.013) and peritoneal dissemination (P=0.045) than the s-p53-Ab (-) group (Table IV).

Discussion

This study examined the clinicopathological and prognostic significance of s-p53-Ab (+) in 124 patients with PDAC and demonstrated that 20% were s-p53-Ab (+), a status significantly associated with poorer RFS and OS.

No clear relationship was observed between s-p53-Ab positivity and clinicopathological variables, consistent with findings in other malignancies (14-18). Notably, the positivity rate in stage I (19%) and stage II (21%) patients were comparable to the overall cohort, aligning with previous reports in gastric (28), esophageal (29), colorectal (30), and hepatocellular cancers (18). Although s-p53-Ab alone was positive in 10% of stage I and 8% of stage II cases, CEA positivity was far lower (2 and 4%, respectively). These results suggest that s-p53-Ab is a supplementary diagnostic marker, particularly for early-stage PDAC, and we propose as a high-specificity 'confirmatory' adjunct to CA19-9, given the low sensitivity.

Regarding the prognostic significance of s-p53-Ab (+), it was identified as an independent poor prognostic factor for both RFS and OS in PDAC, suggesting that s-p53-Ab reflects the tumor's biological aggressiveness. The HRs for RFS and OS were comparable, with the HR for OS approximately 1.13 times that for RFS-similar to ratios observed with CA19-9 (x1.18) and CEA (x1.17). This suggests that patients positive for s-p53-Ab have a resistance to post-recurrence treatments comparable to those positive for CA19-9 or CEA.

Although preoperative s-p53-Ab (+) was not associated with lymph-node metastasis at surgery, it was significantly associated with postoperative lymph-node recurrence. Among patients with pathologically confirmed lymph-node metastasis, those with preoperative s-p53-Ab (+) had a markedly higher rate of lymph-node recurrence than s-p53-Ab (-) patients (8/14 vs. 8/52, P=0.028). This implies that elevated s-p53-Ab levels indicate early dissemination of cancer cells to extra-regional lymph nodes, possibly explaining the poorer RFS observed in s-p53-Ab (+) patients. s-p53-Ab might be a more sensitive indicator of occult micro-metastasis than current pathological staging.

Despite these promising results, several limitations must be acknowledged. First, the retrospective nature and single-institution design may introduce selection and information biases. Second, the unavailability of immunohistochemical analyses of tumor tissues by costs. Serum autoantibodies and expression in tumor tissue may be correlated (14). Since micro heterogeneity of p53 expression may affect induction of autoantibodies, further precise immunohistochemical analysis should be performed. Third, the biological mechanisms linking s-p53-Ab positivity to

Table I. Comparison of clinicopathological characteristics between the s-p53-Ab(+) group and the s-p53-Ab(-) group in patients with pancreatic cancer.

Variables	No. of patients (n=124)	s-p53-Ab(+), n (%) (n=25)	s-p53-Ab(-), n (%) (n=99)	P-value[a]
Sex				0.302
Male	63	15 (60)	48 (48)	
Female	61	10 (40)	51 (52)	
Age, years				0.970
<70	50	10 (40)	40 (40)	
≥70	74	15 (60)	59 (60)	
Tumor location				0.374
Ph	79	14 (56)	65 (66)	
Pb-t	45	11 (44)	34 (34)	
CRP, mg/dl				0.342
≤0.2	89	16 (64)	73 (74)	
>0.2	35	9 (36)	26 (26)	
Albumin, g/dl				0.421
>3.5	97	21 (84)	76 (77)	
≤3.5	27	4 (16)	23 (23)	
Tumor size, mm				0.599
<25	44	10 (40)	34 (34)	
≥25	80	15 (60)	65 (66)	
Tumor classification				0.552
Well, moderate	113	22 (88)	91 (92)	
Poor	11	3 (12)	8 (8)	
Lymphovascular invasion				0.982
Negative	25	5 (20)	20 (20)	
Positive	99	20 (80)	79 (80)	
Perineural invasion				0.623
Negative	60	11 (44)	49 (49)	
Positive	64	14 (56)	50 (51)	
Tumor depth				0.598
T1	25	6 (24)	19 (19)	
T2, 3, 4	99	19 (76)	80 (81)	
Nodal status				0.755
Negative	58	11 (44)	47 (47)	
Positive	66	14 (56)	52 (53)	
CEA, ng/ml				0.982
≤5.0	99	20 (80)	79 (80)	
>5.0	25	5 (20)	20 (20)	
CA19-9, U/ml				0.686
≤37	49	9 (36)	40 (40)	
>37	75	16 (64)	59 (60)	
Neoadjuvant chemotherapy				0.556
Yes	8	1 (4)	7 (7)	
No	116	24 (96)	92 (93)	

[a]Fisher's exact probability test. Pb-t, pancreatic body-tail; Ph, pancreatic head; s-p53-Ab, serum p53 antibody.

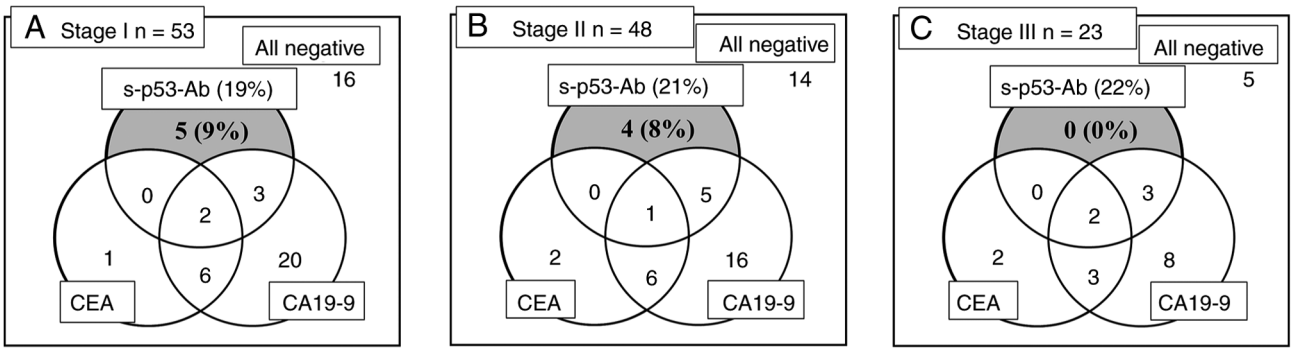

Figure 1. Relationship between positive serum tumor markers. (A) Stage I, (B) stage II and (C) stage III patients. s-p53-Ab, serum p53 antibody.

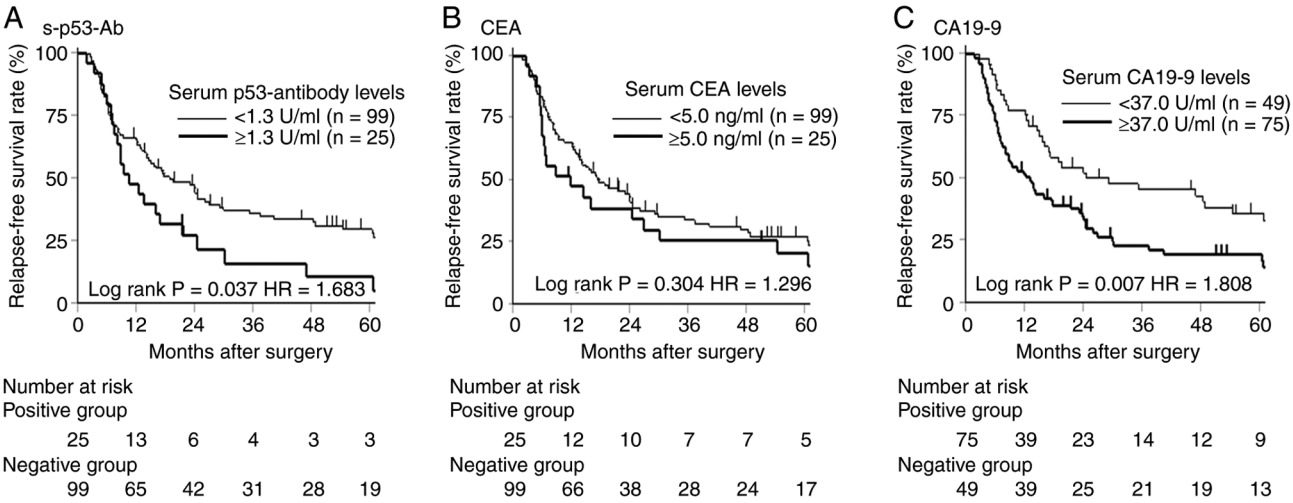

Figure 2. Comparison of relapse-free survival based on tumor marker status. (A) s-p53-Ab. (B) CEA. (C) CA19-9. HR, hazard ratio; s-p53-Ab, serum p53 antibody.

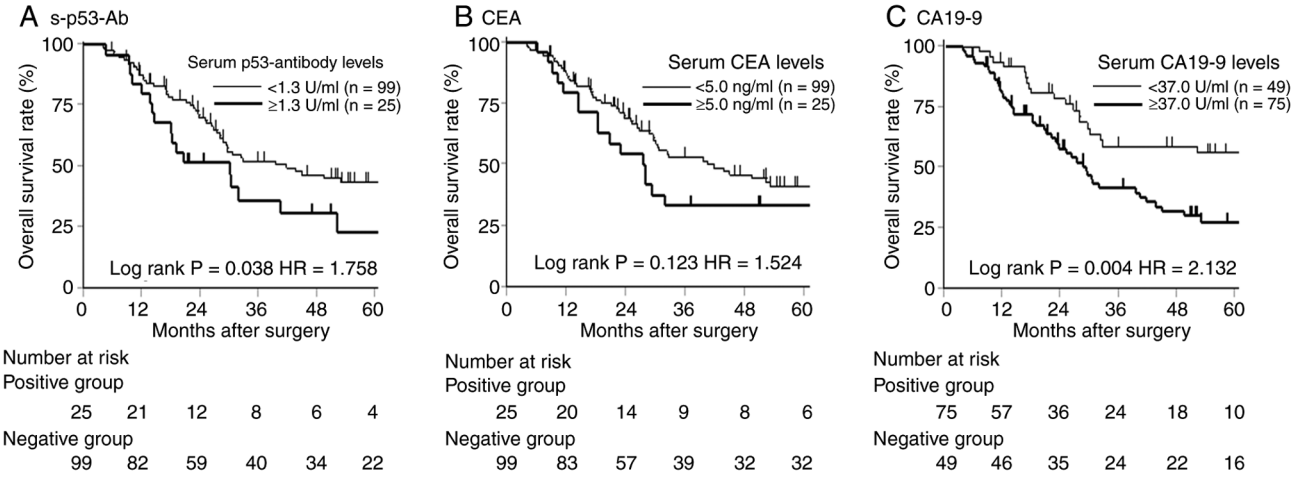

Figure 3. Comparison of overall survival based on tumor marker status. (A) s-p53-Ab. (B) CEA. (C) CA19-9. HR, hazard ratio; s-p53-Ab, serum p53 antibody.

aggressive tumor behavior remain unclear; it is unknown whether s-p53-Ab simply reflects tumor immunogenicity or actively influences tumor progression or the host immune response. Further molecular and translational studies are needed to clarify this relationship. Forth, although a standardized cutoff value for s-p53-Ab (1.3 U/ml) was applied, the optimal threshold may vary depending on population characteristics, assay sensitivity, and clinical application (diagnosis vs. prognosis). Therefore, external validation in independent, multi-institutional cohorts is essential before routine clinical use. Future prospective research should confirm these findings and assess the value of incorporating

Table II. Univariate and multivariate analysis of risk factors for relapse-free survival in patients with pancreatic cancer.

Variables	No. of patients (n=124)	Univariate analysis P-value[a]	Multivariate analysis		
			HR[b]	95% CI[c]	P-value[d]
Sex					
Male	63	0.908			
Female	61				
Age, years					
<70	50	0.410			
≥70	74				
Tumor location					
Ph	79	0.627			
Pb-t	45				
CRP (mg/dl)					
≤0.2	89	0.003	1		0.107
>0.2	35		1.468	0.918-2.307	
Albumin (g/dl)					
>3.5	97	0.809			
≤3.5	27				
Tumor classification					
Well, moderate	113	0.982			
Poor	11				
Lymphovascular invasion					
Negative	25	0.079			
Positive	99				
Perineural invasion					
Negative	60	0.124			
Positive	64				
Tumor depth					
T1	25	0.459			
T2, 3, 4	99				
Nodal status					
Negative	58	0.002	1		0.087
Positive	66		1.481	0.944-2.348	
s-p53-Ab, U/ml					
≤1.3	99	0.037	1		0.047
>1.3	25		1.683	1.102-2.693	
CEA, ng/ml					
≤5.0	99	0.303			
>5.0	25				
CA19-9, U/ml					
≤37	49	0.006	1		0.042
>37	75		1.598	1.106-2.447	
Neoadjuvant chemotherapy					
Yes	8	0.172			
No	116				
Resection margin					
R0	96	<0.001	1		0.011
R1	28		1.972	1.175-3.234	

[a]Log-rank test. [b]Adjusted HR. [c]Adjusted 95% CI. [d]Cox regression analysis. HR, hazard ratio; Pb-t, pancreatic body-tail; Ph, pancreatic head; s-p53-Ab, serum p53 antibody.

Table III. Univariate and multivariate analysis of risk factors for overall survival in patients with pancreatic cancer.

Variables	No. of patients (n=124)	Univariate analysis P-value[a]	Multivariate analysis HR[b]	95% CI[c]	P-value[d]
Sex					
Male	63	0.915			
Female	61				
Age, years					
<70	50	0.885			
≥70	74				
Tumor location					
Ph	79	0.763			
Pb-t	45				
CRP, mg/dl					
≤0.2	89	0.003	1		0.050
>0.2	35		1.700	0.999-2.836	
Albumin, g/dl					
>3.5	97	0.911			
≤3.5	27				
Tumor classification					
Well, moderate	113	0.322			
Poor	11				
Lymphovascular invasion					
Negative	25	0.241			
Positive	99				
Perineural invasion					
Negative	60	0.452			
Positive	64				
Tumor depth					
T1	25	0.676			
T2, 3, 4	99				
Nodal status					
Negative	58	0.003	1		0.097
Positive	66		1.566	0.921-2.711	
s-p53-Ab, U/ml					
≤1.3	99	0.038	1		0.048
>1.3	25		1.758	1.036-2.915	
CEA, ng/ml					
≤5.0	99	0.123			
>5.0	25				
CA19-9, U/ml					
≤37	49	0.004	1		0.028
>37	75		1.808	1.066-3.157	
Neoadjuvant chemotherapy					
Yes	8	0.086			
No	116				
Resection margin					
R0	96	0.002	1		0.126
R1	28		1.579	0.874-2.764	

[a]Log-rank test. [b]Adjusted HR. [c]Adjusted 95% CI. [d]Cox regression analysis. HR, hazard ratio; Pb-t, pancreatic body-tail; Ph, pancreatic head; s-p53-Ab, serum p53 antibody.

Table IV. Comparison of recurrence sites between the s-p53-Ab(+) group and the s-p53-Ab(-) group (n=91).

Variables	Recurrent patients, n (%) (n=91)	s-p53-Ab(+) group, n (%) (n=22)	s-p53-Ab(-) group, n (%) (n=69)	P-value[a]
Multiple organ recurrence	20 (22)	4 (18)	16 (23)	0.984
Initial recurrence site				
Liver	28 (31)	4 (18)	24 (35)	0.364
Lymph nodes	26 (29)	10 (45)	16 (23)	0.013
Local	20 (22)	1 (5)	19 (28)	0.037
Peritoneum	18 (20)	7 (32)	11 (16)	0.045
Lung	12 (13)	3 (14)	9 (13)	0.667
Recurrence within 1 year	49 (54)	13 (59)	36 (52)	0.156

[a]Fisher's exact probability test. s-p53-Ab, serum p53 antibody.

s-p53-Ab into multi-marker panels or risk models to enhance pancreatic cancer management.

In conclusion, this study shows that serum s-p53-Ab is present in a subset of patients with resectable PDAC and that its positivity independently predicts poorer prognosis. s-p53-Ab may serve as a valuable adjunct biomarker for early detection and outcome prediction in PDAC.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

RO conceived the study. RO designed the study. YO, YK, YM and YI acquired data. RO and HS confirm the authenticity of all the raw data. RO and YO were involved in quality control of data and algorithms. RO, YO and HS analyzed and interpreted data. RO performed statistical analysis. RO prepared the manuscript. RO and HS edited the manuscript. All authors reviewed the manuscript. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

All study participants provided consent for future analyses of their blood samples for research. The protocol for the present study was approved by the Ethics Committee of the Toho University (approval nos. T2024-2081, M22211, M21038_20197_19213 and A18103_A17052_A16035_A16001_26095_25024_24038_22047_22112; Ota-ku, Tokyo, Japan). Patients provided written informed consent before enrolment. The study was registered in the UMIN Clinical Trials Registry (UMIN000014530) and was conducted in accordance with The Declaration of Helsinki and the Japanese Ethical Guidelines for Clinical Research.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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