 doi:10.20944/preprints202109.0348.v1

Article

p53 Antibodies as a Diagnostic Marker for Cancer: a Metanalysis

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Abstract: Importance: p53 is an unequivocal tumor suppressor altered in half cancers. The immune system produces systemic p53 autoantibodies (p53 Abs) in many cancer patients. **Objective**: The focus of this systemic review and meta-analysis is on the prognostic value of p53 Abs expressed in the serum of patients with solid tumors. **Data Sources**: All the clinical investigations were searched on PubMed, MBase and Cochrane from 1993 reporting the first study until May 2021. **Study Selection**: Studies were included that met the following criteria: 1) participants with cancer; 2) outcome results expressed in relation to the presence of a p53 antibody; 3) a primary outcome (disease free survival, overall survival or progression free survival) expressed as hazard ratio (HR). The following exclusion criteria were used: 1) insufficient data available to evaluate outcomes; 2) animal studies; 3) studies with less than 10 participants. 1333 potentially relevant articles; studies as duplicates, non-patients studies or reviews were excluded. After viewing the titles and abstracts of the 52 remaining studies, the full texts of 34 studies were retrieved and 12 studies were included in the analysis. **Data Extraction and Synthesis:** PRISMA guidelines were used for abstracting and assessing data quality and validity by three independent observers. The summary estimates were generated using a fixed-effect model (Mantel–Haenszel method) or a random-effect model (DerSimonian–Laird-method) depending on the absence or presence of heterogeneity (I^2). **Main Outcome(s) and Measure(s)**: The primary study outcome was to determine the prognostic value of p53 Abs from a large population size of patients with solid tumors, as determined before data collection. **Results:** In total 12 clinical studies and of which 2094 patients were included and it was determined that p53-wt Abs expression in the serum significantly correlated with a worse survival of cancer patients (95% CI 1.48 [1.24, 1.77]; p<0.00001). On the contrary, data from literature indicated that there was a potential association between p53-mut Abs antibodies with better survival. **Conclusions and Relevance:** This is the first meta-analysis proving the diagnostic utility of p53-Abs for cancer patients, predicting a worse outcome. The serum-p53 value (s-p53-value) could be useful for future theranostics.

Keywords: Meta-analysis; p53 wild type antibodies; p53 mutant antibodies; cancer survival prognostic factor

1. Introduction

P53 is an unequivocal tumor suppressor mutated in almost half of human cancers[1–4]. P53 is auto-regulated by MDM2, an E3 ubiquitin ligase[5,6].

Mice lacking MDM2 show embryonic lethality, while the double knockout of p53 and MDM2 can rescue the lethality [7]. The p53 mutation in cancer (p53-mut) does not activate the

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expression of the E3 ligase. Consequently, degradation of p53 protein is not down-modulated[8]. High expression of p53 by cells recapitulates in T-cells the production of antibodies against mutant or wild-type p53[8].

Prognostic biomarkers have a crucial role in medicine to measure the progression of a disease from samples of patients, such as metastasis in cancer, and they can aid clinicians to intervene with more precise medical interventions. In addition to the common notion that in humans loss of p53 increases genomic instability, stem-cell likeness, which ultimately leads to a highly aggressive cancers, with invasive and metastatic properties. p53 antibodies (s-p53-Abs) are stably expressed in cancer patients serum and could have an important prognostic application. Many clinical studies have assessed in cancer patients the correlation between the expression of s-p53-Abs with tumor invasiveness grades, metastasis and prognosis.

Since 20-40% of p53-mut cancer patients have s-p53-Abs[9], we performed a meta-analysis of the current literature, investigating the role of s-p53-Abs as a prognostic factor and a predictor of response to anti-cancer treatments.

2. Material and Methods

The studies were identified according to the following inclusion criteria: 1) participants with cancer; 2) outcome results expressed in relation to the presence of a p53 antibody; 3) a primary outcome (disease free survival, overall survival or progression free survival) expressed as hazard ratio (HR). The following exclusion criteria were used: 1) insufficient data available to evaluate outcomes; 2) animal studies; 3) studies with less than 10 participants.

Two independent researchers revised the included studies, all disputes were evaluated with the corresponding author.

The summary estimates were generated using a fixed-effect model (Mantel–Haenszel method)[17] or a random-effect model (DerSimonian–Laird-method)[18] depending on the absence or presence of heterogeneity (I^2). A subgroup analysis was performed to highlight any differences between studies in terms of Overall Survival (OS), Disease Free Survival (DFS), Progression Free Survival (PFS), as summarized in **Table 1**.

When we used the keywords “p53 antibodies in early cancer“,”p53 antibodies in metastatic cancer”, “p53 antibodies impact on cancer progression”, the PubMed search yielded 1375 potentially relevant articles; studies as duplicates or reviews were excluded. After viewing the titles and abstracts of the 52 remaining studies, the full texts of 34 studies were retrieved and 12 studies [19–26] were included in the analysis (**Table 1** and **Table 2**) as summarized in the flow chart of **Figure 1**.

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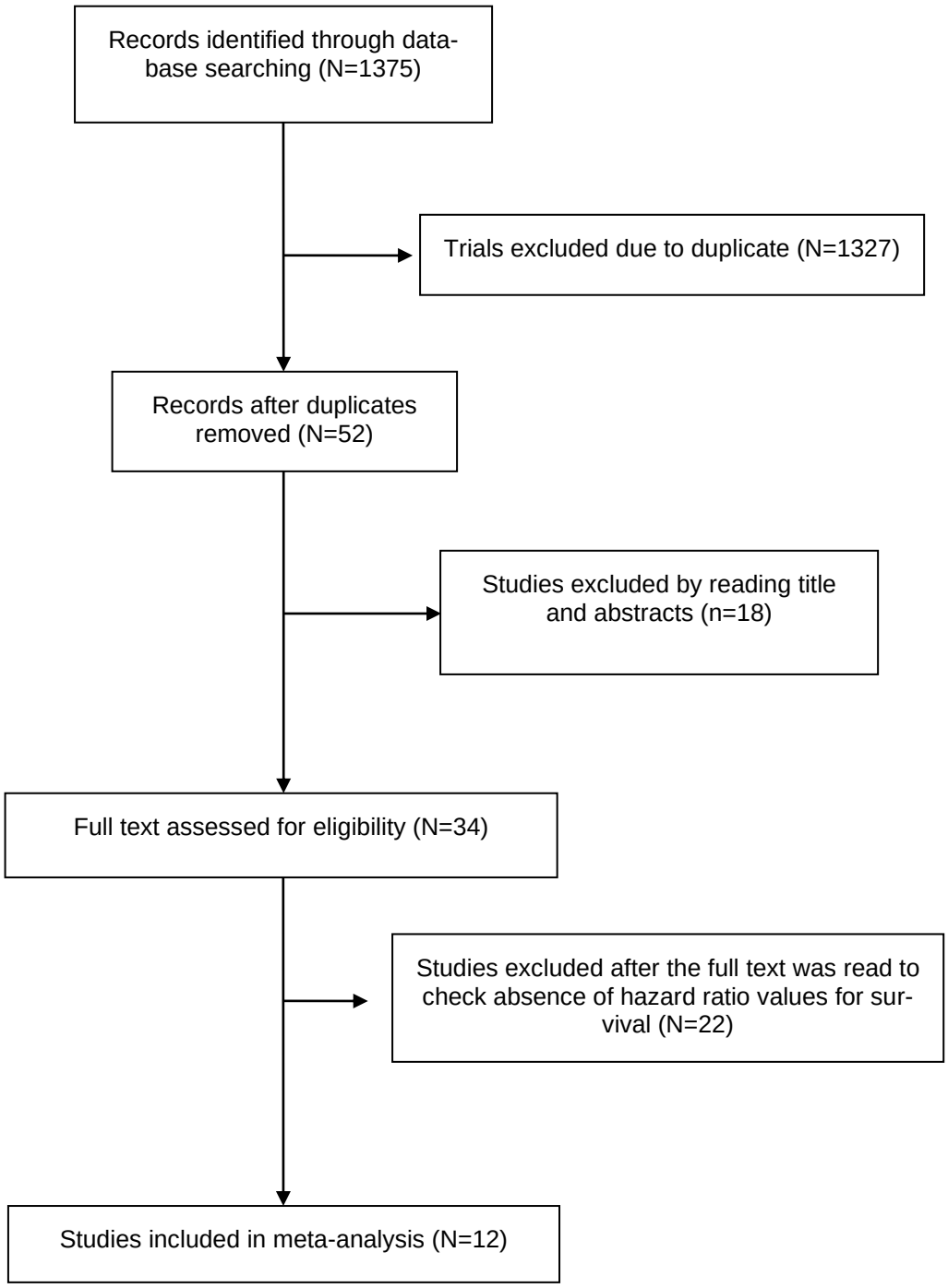

Figure 1. Flowchart of literature research strategy.

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Table 1. Clinical investigations of p53-wt antibodies in cancer. Main characteristics of clinical investigations for prognostic evaluation of serum p53-wt antibodies in cancer patients.

Study Reference	Patients	Methods	*Inclusion/Exclusion criteria*	*Intervention*	*Follow-up time*	*Prognostic value of s-p53-Abs*	Type of Study
21	76 patients with transitional urinary bladder cell carcinoma.	S-p53-Abs ELISA. Antibodies for p53-wt 184 CRC patients	Inclusion: transitional cell urinary bladder cancer Exclusion: secondary organ cancer; immunodeficiency state; ages over 90; other urinary bladder tumours.	Surgery (TUR) Surgery + chemotherapy + radiotherapy (advanced stage)	34 months	There was an association between the presence of s-p53-Abs and tumor p53 gene overexpression (p = 0.001).	Prospective
22	184 CRC patients. Dukes' stage: A (n= 31); B (n= 84); C (n= 41); D (n=28)	S-p53-Abs ELISA. Antibodies for p53-wt 184 CRC patients	Inclusion: primary colon cancer	Routine Biopsy Surgery	96 months	p53-Abs correlated with shorter survival (p = 0.02).	Retrospective
23	170 CRC patients	S-p53Ab, CEA ELISA. Antibody for p53-wt	Inclusion: primary colon cancer Exclusion: previous radiotherapy or chemotherapy	Surgery (resected tumour specimen)	93.6 months (median value)	Positivity for s-p53Ab in CRC did not correlate with overall survival. Kaplan-Meier analysis revealed significant differences between patients with elevated s-p53Ab and CEA and those with elevated levels of either one or neither of these factors (p < 0.001).	Retrospective
24	208 GC patients	S-p53Ab	Inclusion: Histologically	Surgery	34 months	Did not observe any	Retrospective

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		Detected with anti-p53 detection kit MESACUP anti-p53 Test Antibody for p53-wt	confirmed GC Exclusion: previously chemotherapy, radiotherapy and those who died within 30 days after surgery			significant correlation between S-p53Ab in GC and overall survival (hazard ratio(HR) = 2.052; 95% confidence interval(CI) = 0.891–4.726; p = 0.091). Conversely, Cox regression analysis revealed that a high level of CA19-9 was an independent prognostic factor for GC (hazard ratio(HR) = 3.864; 95% confidence interval(CI) = 1.248–11.959; p = 0.019).	
[25]	231 SCLC patients	S-p53-Abs ELISA. Antibodies for p53-wt	Inclusion: primary SCLC	Surgery Chemotherapy (227 out of 231 patients)	3 months (at least)	High levels of p53-Abs correlated with worse survival compared to patients with lower levels of the antibodies (p = 0.02).	Retrospective
[26]	80 HCC patients	S-p53-Abs ELISA. Antibodies for p53-wt	Inclusion: Cytohistological of AFP level-based diagnosis of HCC	Percutaneous injection (21) Surgery (15) Radiofrequency interstitial ablation (10) Chemotherapy (4) TACE (8) Combinational treatment (5) No treatment (17)	36 months	Anti-p53 was not useful as a prognostic factor.	Retrospective
[27]	244 CRC pa-	CEA, CA19-9, S-	Inclusion: preoperative	Surgery (colectomy plus	33.8 months	S-P53Ab had no power	Retrospective

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	tients	P53Ab Antibody for p53-wt	CEA, CA-19 and S-P53Ab. Primary tumour diagnosis	lymph nodes dissection) Chemotherapy (in case of CRC recurrence)	(median)	to predict the prognosis (p = 0.786). Combined CEA and CA19-9 positivity was an exclusive independent prognostic factor (p = 0.034).	
28	97 SCLC patients	S-p53-Abs ELISA. Antibodies for p53-wt	Inclusion: newly and proven diagnosed lung cancer	Bronchial biopsy Chemotherapy (cisplatin, etoposide, doxorubicin, cyclophosphamide) Radiotherapy for those with brain metastasis	18.1 months (median)	Patients with limited-stage SCLC and p53-Ab had a median survival time of 10 months, whereas limited-stage SCLC patients without p53-Ab had a 17-month median survival time (p = 0.014).	Prospective
29	133 esophageal squamous cell carcinoma (ESCC) patients	S-p53Ab, SCC-Ag, CEA Antibody for p53-wt	Inclusion: histologically confirmed ESCC Exclusion: patients who died after 30 days after treatment and those who had preoperative radiotherapy	Surgery	36 months (median)	S-p53Ab was detected in 39.1% (52 out of 133) of patients with ESCC, including 40.0% (20 out of 50) of patients with early-stage ESCC (p = 0.009)	Retrospective
7	201 lung cancer patients	S-p53 antibodies by ELISA	Inclusion: Primary lung cancer	Surgery Chemotherapy (Stage IIIB and IV) Radiotherapy (if required)	63 months	Patients with lower levels of p53Abs survived significantly longer than patients with higher levels of p53Abs (p = 0.049).	Retrospective
30	1487 esophageal squamous cell carcinoma	S-p53 antibodies by ELISA	Inclusion: radical surgery with no neoadjuvant treatment	Esophagectomy	42 months (median)	s-p53-Ab positive status was not significantly associated with poor overall survival	Retrospective
31	160 hepatocel-	Six hepatocellular	Inclusion: histologically	Surgery	60 months	.The positivity for the	Retrospective

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	lular carcinoma	carcinoma-associated antigens, including Sui1, p62, RalA, p53, NY-ESO-1, and c-myc antibodies by ELISA (TAA Panel)	proven HCC Exclusion: coexisting or metachronous cancer within 5 disease-free years			TAA panel was independently associated with poor prognosis (P = 0.030)	
[32]	72 gastric cancers	S-p53 antibodies by ELISA	Inclusion: primary gastric cancer Exclusion: previous chemotherapy; coexisting cancer	Surgery	32 months (median)	overall survival was not associated with the antibodies	Retrospective
[33]	105 esophageal squamous cell carcinoma	S-p53 antibodies by ELISA	Inclusion: primary oesophagal squamous cell carcinoma Exclusion: metastatic disease; neoadjuvant therapy	Surgery	35 months (median)	While seropositive patients did not demonstrate significant poor overall survival, high-titer patients demonstrated significant poor overall survival based on the multivariate analysis (P < 0.001).	Retrospective

Abbreviations: CRC, Colorectal Carcinoma; GC, Gastric Cancer; SCLC, Small Cell Lung Carcinoma; HCC, Hepatocellular Carcinoma; TACE, chemoembolization with epidoxorubicin and lipiodol; TUR, Transuteral Resection of the Tumor.

Table 2. Clinical investigations of p53-mut antibodies in cancer. Main characteristics of clinical investigations for prognostic evaluation of serum p53-mut antibodies in cancer patients.

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Study Reference	Patients	Methods	*Prognostic value of s-p53-Abs*	Type of Study	Inference
[24]	111 gastric carcinoma patients	S-p53-Abs Levels of p53-mut were determined with a selective, quantitative ELISA kit	The survival time of serum-positive patients was significantly longer than that of patients with low/negative serum levels, with a survival rate of 41.2% and 14.9%, respectively, over 48 months ($p < 0.05$).	Retrospective	Significant correlation seen between levels of S-p53-mut Abs and patient survival rate
[25]	104 ovarian cancer patients	S-p53-Abs ELISA. Antibodies against p53K132Q (c.394A > C).	Overall survival (OS) was significantly higher for patients with antibodies to mutant p53 when compared with patients without p53 antibodies ($P = .01$).	Retrospective	OS is significantly increased in advanced stage ovarian cancer patients with antibodies to p53
[17]	134 lung cancer patients	S-p53-Abs by Immunofluorescence. Antibodies against p53 R273H (c.818G > A) by ELISA.	Presence of anti-p53 autoantibodies is almost exclusively linked to the presence of malignant disease.	Retrospective	Presence of anti-p53 Abs had a significant correlation with shorter survival in NSCLC.

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[26]	50 BC patients	S-p53-Abs ELISA. Antibodies against p53R273H (c.818G > A).	s-p53-Abs were higher in BC patients with high risk vs. patients with low risk. The difference was not statistically significant (p = 0.15).	Retrospective	Presence of s-p53-Abs showed higher risk for BC patients.

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3. Results

A total of 2094 patients were included. The solid cancer patients were were treated with adjuvant chemotherapy (such as cyclophosphamide, docetaxel, fluorouracil, epirubicin, methotrexate, vinorelbine), anti-HER2 (trastuzumab, pertuzumab or lapatinib), endocrine therapy (such as goserelin, tamoxifen), combination of these treatments, Herceptin, chemotherapy, nonsteroidal anti-inflammatory drug celecoxib, including radiotherapy or a surgical component in some cases (**table 1**). The pooled analysis revealed that s-p53-Abs is a negative prognostic factor (HR: 148 [1.24, 1.77]; p<0.0001, **Figure 2**) in cancers. The analysis was performed using a random-effects model heterogeneity (I^2=19%).

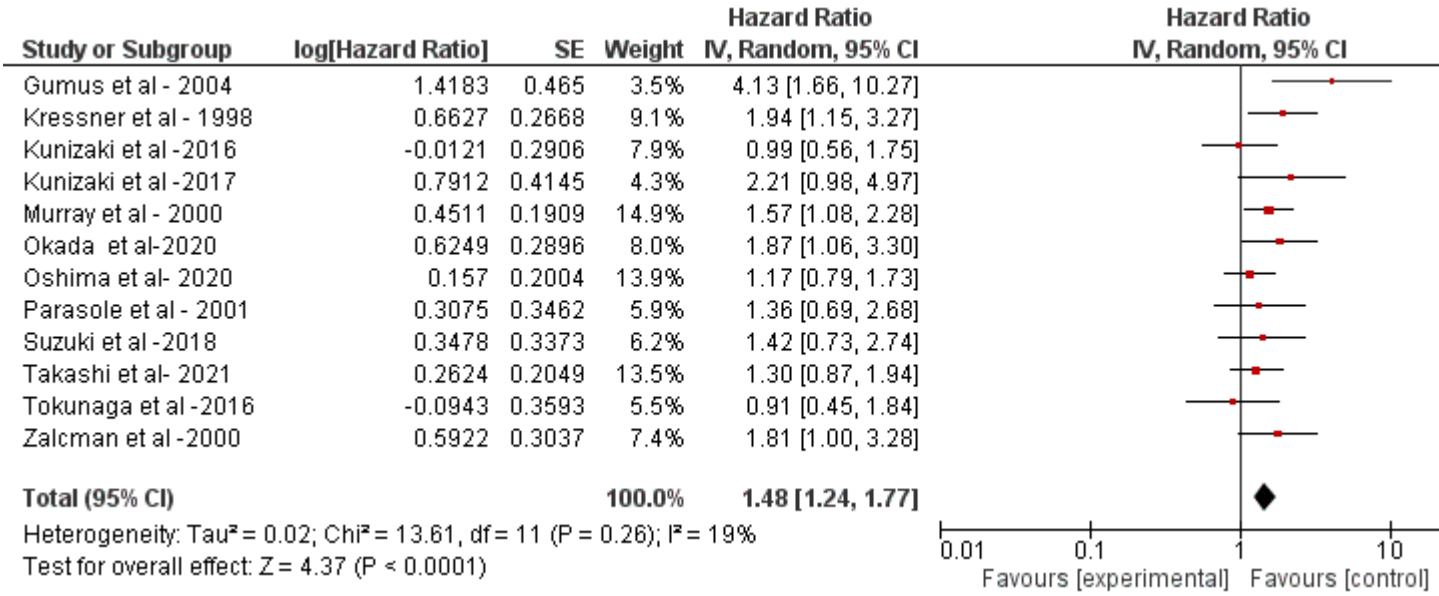

Figure 2. Matanalysis of serum p53-antibodies. The prognostic value of p53 antibodies in serum of cancer patients from eight clinical investigations was investigated in this metanalysis.

The funnel plot (**Figure 3**) of the included studies showed symmetric funnel plot and no significant publication bias was identified.

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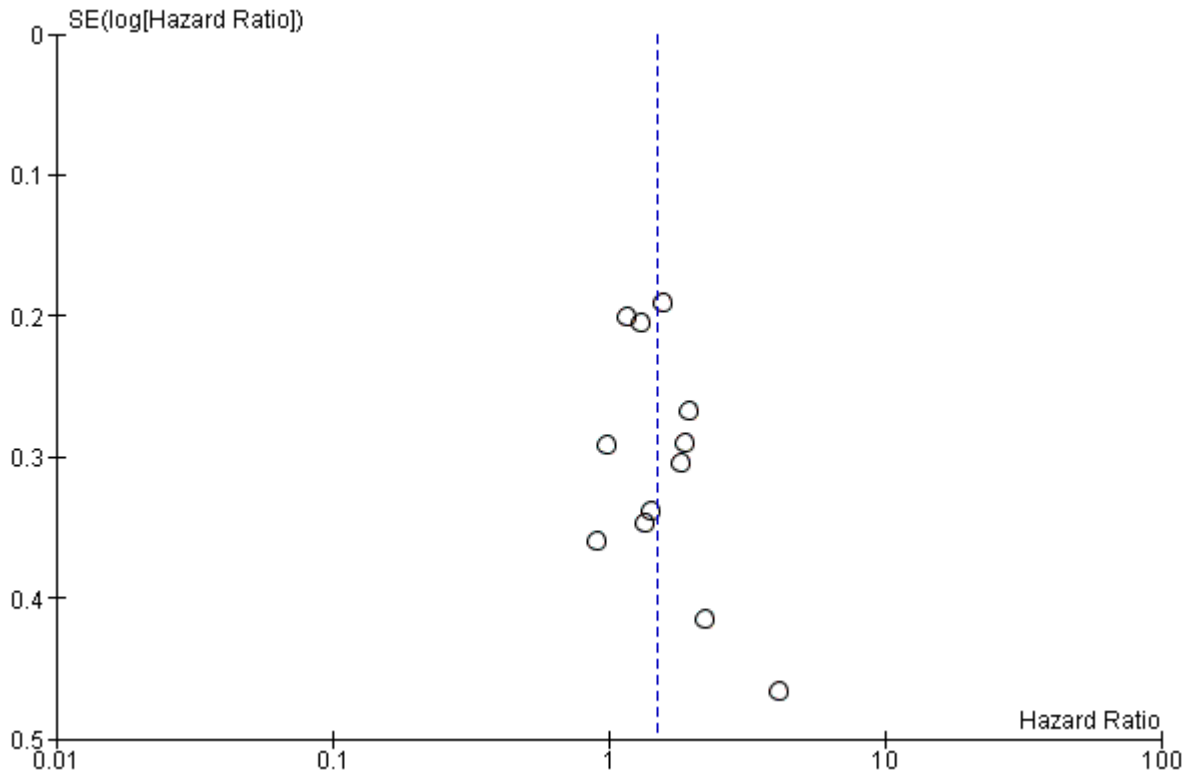

Figure 3. The funnel plot of included studies

4. Discussions and conclusions

The metanalysis showed that high levels of p53 antibodies significantly correlated with worse clinical outcomes. Our study has some limitations. First of all the retrospective nature of the study is intrinsically susceptible to biases. Moreover, different forms of solid tumors were included pre- or post-treatment with various type of therapies as the typology requires at different stages. These variables could ultimately had affected the results.

In our analysis patients were looked independently of treatment and tumor because of the relatively lower number of randomized studies at our disposal. As medicine unfolds more knowledge, a larger number of patients could help to evaluate the impact of our finding and treatment response.

In summary it is known that p53-wt cancers have a better prognosis compared to p53-mut. Our data is not in contradiction with this notion. We observed that serum antibodies generated in the blood of cancer patients against p53 are deleterious. Serological 53 antibodies as biomarker for cancer survival since they can be easily detected with an ELISA method from blood samples, as summarized in a simple workflow in **Figure 4**, constitute a robust method to be implanted to predict outcome of cancer patients in response to current or future therapies.

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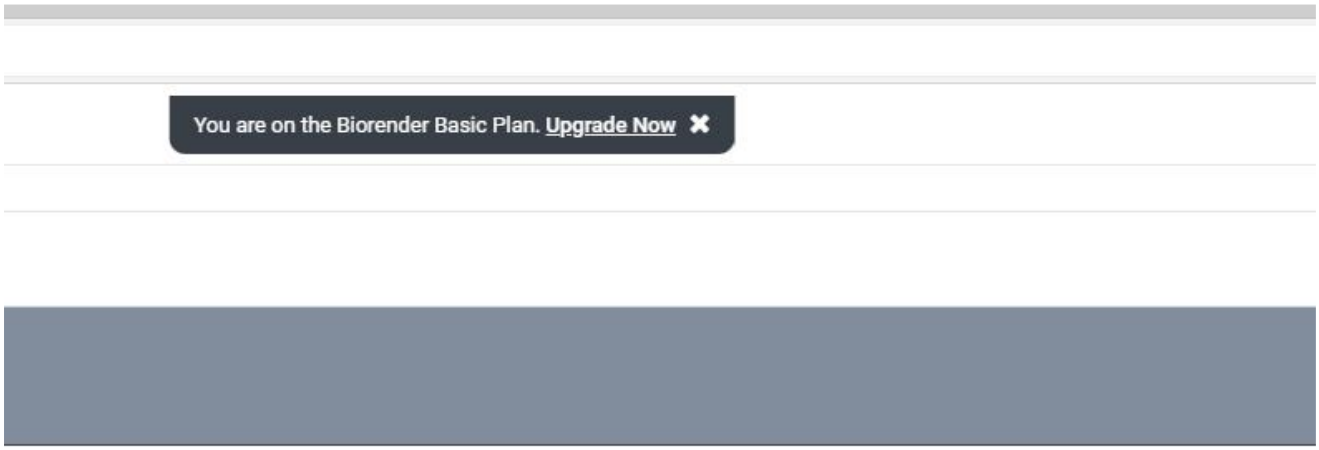

Figure 4. Schematic representation of the significance of serological biomarker p53 antibodies (p53Abs) in prediction of cancer survival.

5. Competing interests

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties. No writing assistance was utilized in the production of this manuscript.

Contributions of Authors: GR and NS conceived, designed and planned the study. GR and NS acquired data and produced original draft and figures. GR conducted statistical analysis of the data. All authors helped interpret the results and drafting the manuscript. GR and NS drafted the manuscript. PKN revised and improved manuscript's content and visualization. All authors revised and reviewed this article, and all authors gave their final approval of the submitted manuscript.

Funding Information: Not applicable.

Ethics approval: This article does not contain any studies with human participants or animals performed by any of the authors.

Availability of data and material: All relevant data are within the paper.

Acknowledgments: Supported by MEDnoTE through the Mozart Program with unconditional support by Novartis.

Conflicts of interest: The authors declare that they have no conflict of interest.

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