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Immune checkpoint blocking impact and nomogram prediction of COVID-19 inactivated vaccine seroconversion in patients with cancer: a propensity-score matched analysis

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ABSTRACT

Background Patients with cancer on active immune checkpoint inhibitors therapy were recommended to seek prophylaxis from COVID-19 by vaccination. There have been few reports to date to discuss the impact of progression cell death-1 blockers (PD-1B) on immune or vaccine-related outcomes, and what risk factors that contribute to the serological status remains to be elucidated. The study aims to find the impact of PD-1B on vaccination outcome and investigate other potential risk factors associated with the risk of seroconversion failure.

Methods Patients with active cancer treatment were retrospectively enrolled to investigate the interaction effects between PD-1B and vaccination. Through propensity score matching of demographic and clinical features, the seroconversion rates and immune/vaccination-related adverse events (irAE and vrAE) were compared in a head-to-head manner. Then, a nomogram predicting the failure risk was developed with variables significant in multivariate regression analysis and validated in an independent cohort.

Results Patients (n=454) receiving either PD-1B or COVID-19 vaccination, or both, were matched into three cohorts (vac+/PD-1B+, vac+/PD-1B-, and vac-/PD-1B+, respectively), with a non-concer control group of 206 participants. 68.1% (94/138), 71.3% (117/164), and 80.5% (166/206) were seropositive in vac+/PD-1B+cohort, vac+/PD-1B- cohort, and non-cancer control group, respectively. None of irAE or vrAE was observed to be escalated in PD-1B treatment except for low-grade rash.The vaccinated patients with cancer had a significantly lower rate of seroconversion rates than healthy control. A nomogram was thus built that encompassed age, pathology, and chemotherapy status to predict the seroconversion failure risk, which was validated in an independent cancer cohort of 196 patients.

Conclusion Although patients with cancer had a generally decreased rate of seroconversion as compared with the healthy population, the COVID-19 vaccine was generally well tolerated, and seroconversion was not affected in patients receiving PD-1B. A nomogram predicting failure risk was developed, including age, chemotherapy status, pathology types, and rheumatic comorbidity.

INTRODUCTION

The contraction of coronavirus disease 2019 (COVID-19, SARS-CoV-2 virus) in patients with cancer proved catastrophic to clinical outcomes due to altered immune status and diminished care provided. Previous reports showed markedly elevated risk of intubation, intensive care unit admission, and death in patients with cancer in active treatment.[1] Although there has been no current recommendation in guidelines of cancer-related prophylactic plans in China, many world organizations, including American Society of Clinical Oncology, National Comprehensive Cancer Network, and European Society for Medical Oncology, have unequivocally advocated for active immunization for patients receiving cancer treatments based on the efficacy and safety data of the approved vaccine.[2–4] The currently approved vaccine type in China includes 2-dose inactivated (Sinovac and SinoPharm) and 1-dose adenovirus-based vaccine (Ad5-nCoV). Both vaccines showed promising immunogenicity and moderate adverse events in healthy populations in phase I/II trials, in which, however, patients with compromised immune status have not been included.[5–7] Patients with cancer, especially those on active immunotherapies, are of particular concern because of unknown drug-vaccine interaction that could potentially manifest with different serological results and drug safety issues.

Current data, although sparse, showed relative safety and successful seroconversion in patients with cancer, although the approved vaccine achieved less than 80% of seroconversion.[8] The preliminary results from the prospective Vax-On study by Nelli *et al* found relative safety and efficacy of

mRNA-BNT162b2 vaccine in patients with cancer.[9] One systemic review of 621 patients with cancer found adequate seroconversion in patients with cancer, but the antibody titer response was significantly lower than that of non-cancer controls.[10] Although the response may not be satisfactory enough, the protecting effects against severe or fatal cases would be crucial to patients with compromised immune systems. Further discussion into the use of an inactivated vaccine in patients with cancer may provide added real-world evidence for future trials on populations with altered immune status. What other factors contributed to decreased seroconversion, and how to predict the vaccination-related adverse events (vrAE) and serological status, require further investigation in order to give more individualized prophylactic plans in cancer treatment.

The systematic treatment of cancers, on the other hand, has evolved from pure chemotherapy into biological agent-dominated regimens. In the past decades, immune checkpoint inhibitors (ICI) have revolutionized the landscape of multiple types of malignancies.[11] The inert immune cells become activated against tumor cells, but the systemic, immune-related adverse events (irAE) caused by immune dysregulation could also happen.[12–14] Due to the mass application of ICI-based regimens in clinical practice, the interaction between the inactivated vaccine and ICI should be discussed, investigated, and handled properly in the context of active cancer treatment.

In this retrospective, multicenter study, an initial attempt was made to investigate the impact of ICI therapy on seroconversion rate and adverse events of inactivated vaccination. As a secondary goal, the incidence of irAE and vrAE were also followed up in the process. Then, a nomogram was thus built to predict the risk of seroconversion failure in all patients with cancer.

METHODS

Participants and design

The study retrospectively reviewed and enrolled consecutive patients with active cancer treatment who received COVID-19 inactivated vaccine in a multicenter cancer registry database including the following centers from January 2021: Sun Yat-sen University Cancer Center, Affiliated Cancer Center of Shantou University Medical College (SU), First Affiliated Hospital of Zhengzhou University, and Hainan Hospital of PLA General Hospital. The study primarily investigated the seroconversion, and secondarily, the interaction between vaccination and progression cell death-1 blockers (PD-1B). Therefore, we first reviewed all patients with both PD-1B and vaccination in the database and another three groups of control were matched by treatment or demographic status to alleviate selection bias. Vaccinated patients who were not on PD-1B therapy were selectively included to match patients on PD-1B therapy with chemotherapy usage and comorbid conditions. Patients with cancer on PD-1B therapy, yet not receiving the vaccine, were also included as the control group. A group of non-cancer control group was recruited in the metropolitan communities of the four medical centers (Guangzhou, Zhengzhou, Sanya, and Shantou). Therefore, a total of four groups were included in the study, including patients with PD-1B and the vaccine (PD-1B+/vac+), patients with the vaccine but without PD-1B (PD-1B-/vac+), patients with PD-1B but without the vaccine (PD-1B+/vac-), and vaccinated non-cancer control group.

The qualitative serological status and the quantitative antibody titers of the COVID-19 antibody were tested 1–3 weeks after the first dose, and was retested 1 and 2 weeks after the second dose if the first result was negative. Patients were tested for serological status 2–3 weeks after the second dose, if applicable. Sera were analyzed at one third-party laboratory in Zhengzhou, Henan Province, China for antibody testing. For qualitative Test, the S-specific IgG were detected using the chemiluminescence qualitative kit (Auto Biotechnology, Zhengzhou, China). For quantitative testing, the anti-RBD chemiluminescence kit (BioScience Biotechnology, Tianjin, China) was applied (See supplementary materials for details of testing and seroconversion definition).

All patients reviewed in the study must agree to the investigation and follow-up of the results before inclusion into the study. Electronic medical records of the included patients were reviewed to include clinical and demographic characteristics: age, gender, the current status of chemotherapy, Eastern Cooperative Oncology Group-Performance Score (ECOG-PS), pathology type, comorbidity with rheumatic disease. A standard questionnaire was constructed to follow-up treatment-related adverse events of both PD-1B (irAE) and the inactivated vaccine (vrAE) within 2 months of vaccination.[15] The following irAE specific to PD-1B were followed up: increase in liver function test, pneumonitis, and diarrhea/colitis. The following vrAE were followed up: fatigue, fever, headache, lymphadenopathy, and nausea. Adverse events potentially related to both PD-1B and vaccination included rash and arthralgia. The irAEs were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (V.4.03).[16]

Statistics and nomogram development

To further alleviate potential bias across geographically different medical centers, participants in each group were matched by propensity scores to reach head-to-head comparison to minimize selection and confounding bias.[17] propensity score-matched analysis was carried out through a multivariate conditional logistic regression model with a caliper width of 0.03.[18] Factors included in the regression model included all demographic and clinical variables. To evaluate the matching performance in minimizing potential bias, the standardized difference (SD) was calculated for each of the matched variables. According to Austin PC, an SD over (√ ((n1 +n2)/n1*n2))*1.96 is regarded as imbalanced matching of

confounding covariates, where n1 and n2 stands for the sample size of the two groups.[18]

After determining the interaction between effects of PD-1B and vaccination, a nomogram was constructed to predict the failure risk of serological conversion. Potential risk factors were first examined by multivariate logistic regression analysis, and significant factors were applied in nomogram development. The performance of the nomogram was measured by concordance index (C-index) and assessed by comparing nomogram-predicted vs observed risk. Bootstraps with 1000 resamples were applied in the performance assessment. For external validation of the nomogram, an independent cohort of vaccinated patients with cancer was recruited from October, 2021 in The Second Affiliated Hospital of Shantou University Medical College.

Categorical variables were compared with the χ^2 test or Fisher exact test, and continuous variables were compared with paired t-test in a head-to-head comparison. The nomogram was constructed by using R statistics, V.4.1.0. The significance threshold was set at $p<0.05$ for paired tests and the χ^2 test. The statistical method used in propensity score matching included the nearest matching method and were carried out in the FUZZY extensions of SPSS V.26.0 software, with a minimum attempt (bootstrap) of 1000 times (Python Essentials).[17] The power (1-β) of the comparison of propensity score-mached groups were calculated based on the sample size and were performed on PASS software (V.15.0).[19] Each statistical test was based on pre-specified statistical hypothesis, and the type I error is 0.05 for each test.

RESULTS

Baseline characteristics of the derivation groups

A total of 476 patients receiving active treatment were reviewed in the medical records with either PD-1B or vaccination, in which 17 patients did not have serology tested, 5 patients did not consent to the participation of the study. Therefore, the study included 454 patients with cancer (116 males and 338 females, mean age 50.28±11.15, table 1). No patients had been infected with the COVID-19 virus. No patients developed the disease or had positive PCR virology during the follow-up period from January to October. The PD-1B types included nivolumab in 51 patients, pembrolizumab in 49 patients, sintilimab in 76 patients, toripalimab in 44 patients, tislelizumab in 31 patients, and camrelizumab in 39 patients. Pathology types were grouped into three categories: gastrointestinal epithelial cancers (GI, 196 patients), head and neck cancers (HN, 101 patients), and non-small cell lung cancers (NSCLC, 157 patients). a total of 111 patients were on active chemotherapy regimen cycles, and 51 patients were diagnosed as metastatic cancers in the entire cohorts. The chemotherapy courses ranges from 1 to 3 cycles, and the specific regimen were subject to the attending oncologists and were used concurrently with or without PD1-B therapies. As for ECOG-PS status,

Table 1 Baseline characteristics of the patients with cancer and non-cancer control

Factor		PD-1B+/Vac+	PD-1B-/Vac+	PD-1B+/Vac-	Total patients with cancer	Non-cancer control
Age (years), mean (SD)		49.78 (11.38)	51.17 (10.42)	49.87 (10.66)	50.28 (11.15)	49.93 (12.28)
Gender	Male	34 (24.6%)	44 (26.8%)	38 (25.0%)	116 (25.6%)	51 (24.7%)
	Female	104 (75.4%)	120 (73.2%)	114 (75.0%)	338 (74.4%)	155 (75.2%)
Pathology	NSCLC	48 (34.8%)	54 (32.9%)	55 (36.2%)	157 (34.6%)	—
	GI	62 (44.9%)	72 (43.9%)	62 (40.8%)	196 (43.2%)	
	HN	28 (20.3%)	38 (23.2%)	35 (23.0%)	101 (22.2%)	
Chemotherapy	Yes	28 (20.3%)	42 (25.6%)	41 (27.0%)	111 (24.4%)	—
	No	110 (79.7%)	122 (74.4%)	111 (73.0%)	343 (75.6%)	
ECOG-PS	0	92 (66.7%)	120 (73.2%)	107 (70.4%)	319 (70.3%)	—
	1	46 (33.3%)	44 (26.8%)	45 (29.6%)	135 (29.7%)	
ICI duration (weeks), mean (SD)		6.54 (2.30)	—	6.49 (2.31)	—	—
Metastasis	Yes	10 (7.2%)	12 (7.3%)	29 (19.1%)	51 (11.2%)	
	No	128 (92.8%)	152 (92.7%)	123 (80.9%)	403 (88.8%)	—
Dose of vaccine	1	58 (42.0%)	72 (43.9%)	—	130 (43.0%)	99 (48.0%)
	2	80 (58.0%)	92 (56.1%)		172 (57.0%)	107 (52.0%)
Comorbidity with rheumatic disease	Yes	32 (23.2%)	40 (24.4%)	30 (19.7%)	102 (22.5%)	40 (19.4%)
	No	106 (76.8%)	124 (75.6%)	122 (80.3%)	352 (77.5%)	166 (89.6%)

ECOG-PS, Eastern Cooperative Oncology Group-Performance Score; GI, gastrointestinal cancers; HN, head and neck cancers; ICI, immune checkpoint inhibitor; NSCLC, non-small cell lung cancer; PD-1B, progression cell death-1 blocker; SD, standard deviation; Vac, vaccine.

319 patients were rated as '0', and 135 patients were rated as '1'. A total of 206 vaccinated healthy control were recruited to match commodities in vaccinated patients with cancer.

Impact of PD-1B treatment on vaccination outcome

The first head-to-head matching by propensity scores was carried out in the vaccinated PD-1B group (PD-1B+/vac+) and vaccinated non-PD-1B group (PD-1B-/vac+) to see the impact of PD-1B treatment on vaccination outcome. The matching yielded a total of 268 patients (134 pairs), with a mean propensity score of 0.46±0.05. The matched variables included age, gender, pathology, chemotherapy status, ECOG-PS, metastatic status, vaccine doses, and rheumatic comorbidity (table 2). The balance test showed that the SD of the baseline variables were within the range of 0.23 (see online supplemental table 1). There was a total of 90 serologically positive cases in the PD-1B+/vac +group (67.16%), and 95 serologically

Table 2 Propensity score-matched comparison of vaccine in patients with cancer with and without PD-1B (N=134 pairs)

Factor		PD-1B	No PD-1B	P value
Matched baseline variables				
Age, mean (SD)		50.92 (10.45)	50.94 (10.57)	0.99
Gender	Male	34 (25.4%)	35 (26.1%)	0.89
	Female	100 (74.6%)	99 (73.9%)	
Pathology	NSCLC	46 (34.3%)	45 (33.6%)	0.97
	GI	60 (44.8%)	62 (46.3%)	
	HN	28 (20.9%)	27 (20.1%)	
Chemotherapy	Yes	28 (20.9%)	28 (20.9%)	1
	No	106 (79.1%)	106 (79.1%)	
ECOG-PS	0	92 (68.7%)	97 (72.4%)	0.43
	1	42 (31.3%)	37 (27.6%)	
Metastasis	Yes	10 (7.5%)	9 (7.7%)	0.81
	No	124 (92.5%)	125 (93.3%)	
Dose of vaccine	1	57 (42.5%)	54 (40.3%)	0.71
	2	77 (57.5%)	80 (59.7%)	
Comorbidity with rheumatic disease	Yes	32 (23.9%)	30 (22.4%)	0.77
	No	102 (76.1%)	104 (77.6%)	
Follow-up variables				
Serological status	+	90 (67.2%)	95 (70.9%)	0.51
	–	44 (32.8%)	39 (29.1%)	
Antibody titers (U/mL), mean (SD)		434.82 (507.34)	415.79 (460.65)	0.75
Fatigue	Yes	19 (14.2%)	26 (19.4%)	0.25
	No	115 (85.8%)	108 (80.6%)	
Fever	Yes	12 (9.0%)	9 (6.7%)	0.50
	No	122 (91.0%)	125 (93.3%)	
Lymphadenopathy	Yes	15 (11.2%)	15 (11.2%)	1.00
	No	119 (88.8%)	119 (88.8%)	
Nausea	Yes	15 (11.2%)	15 (11.2%)	1
	No	119 (88.8%)	119 (88.8%)	
Headache	Yes	13 (9.7%)	13 (9.7%)	1
	No	121 (90.3%)	121 (90.3%)	
Rash	Yes	35 (26.1%)	10 (7.5%)	<0.01
	No	99 (73.9%)	124 (92.5%)	
Arthralgia	Yes	18 (13.4%)	15 (11.2%)	0.58
	No	116 (85.6%)	119 (88.8%)	

ECOG-PS, Eastern Cooperative Oncology Group-Performance Score; GI, gastrointestinal cancers; HN, head and neck cancers; NSCLC, Non-small cell lung cancer; PD-1B, formance Scor-1 blockers; SD, standard deviation.

positive cases (70.90%) in the PD-1B-/vac +group. The comparison results showed that there was no significant difference in serological status (p=0.51). As the seroconversion rate of the PD-1B-/vac+ patient was 71% and the sample size was 134 in both groups after matching, the power was 73% to detect a effect size of 15% in the statistical test. Therefore, the beta was 17%.

The anti-SARS-CoV-2 S-spike titers of the PD-1B+/vac+ group and the PD-1B-/vac+ group was 434.34±507.34 and 415.79±460.65, respectively, and there was no significant difference of antibody titers between the two groups (p=0.75, table 2). We also quantitatively compared the antibody titers of the seropositive participants. The antibody titers of all serologically positive patients were compared between the two groups, and there were also no significant difference (online supplemental figure 1A). However, there was significant difference between all vaccinated patients with cancer with seropositive status (N=166) and the non-cancer control group with seropositive status (N=211, online supplemental figure 1B). Also, age was found negatively correlated with the titers in the cancer patient, regardless of PD-1B regimens (Pearson r=−0.71, p<0.001, online supplemental figure 2A). In the PD-1B+/vac +group, we also interrogated whether the duration of PD-1B treatment may affect seroconversion. The mean time of ICI treatment duration was 6.32±2.39 weeks in seronegative patients, and 6.65±2.26 weeks in seropositive patients. There was also no significant difference of ICI treatment duration between the two groups (p=0.43). Also, an ROC analysis was applied to evaluate the relationship between the duration and the seroconversion status (online supplemental figure 2B).

The vrAEs were moderate for both PD-1B+/vac+ and PD-1B-/vac+ groups and no significance was found in these adverse events (table 2). In potential adverse events for both PD-1B and vaccination, the rash was found significant (p<0.01). There were 35 cases of reported rash in the PD-1B+group, and the reported rash cases range from grade 1 (51.4%) to grade 2 (48.6%) and no patient reported high-grade (over grade 3) or drug-resistant rash(online supplemental table 3). There were 10 patients in the PD-1B-/vac +group reporting rash, and all of them reported grade 1 rash.

Impact of vaccination on IrAE of PD-1B treatment

The second matching by propensity scores was carried out in the vaccinated PD-1B group (PD-1B+/vac+) and non-vaccinated PD-1B group (PD-1B+/vac-) to interrogate the impact of vaccination on irAE of PD-1B treatment. The matching yielded a total of 254 patients (127 pairs), with a mean propensity score of 0.49±0.08. The matched variables included age, gender, pathology, chemotherapy status, ECOG-PS, metastatic status, PD-1B treatment duration, and rheumatic comorbidity (table 3). The irAE and potential adverse events for both PD-1B and vaccination were moderate for both groups and no significance was found in these adverse events. Specifically, the rash was found insignificant (p=0.88).

Impact of cancer treatment on vaccination outcome

The third and fourth matching by propensity scores were carried out in the vaccinated PD-1B or non-PD-1B group (PD-1B+/vac+, PD-1B-/vac+) and vaccinated healthy control group to investigate the impact of cancer treatment on adverse events of vaccination (table 4).

The third matching yielded a total of 276 (138 pairs) patients, with a mean propensity score of 0.41±0.06. There were 94 (68.12%) serologically positive cases in the PD-1B+/vac +group, as compared with 111 (80.43%) cases of healthy control (p=0.02). As for vrAE, there were 35 (25.36%) cases of reported rash in the PD-1B+/vac +group, as compared with 12 (8.70%) cases of reported rash in the healthy control group (p<0.01).

The Fourth matching yielded a total of 324 (162 pairs) patients, with a mean propensity score of 0.45±0.05. There were 116 (71.60%) serologically positive cases in the PD-1B-/vac +group, as compared with 135 (83.33%) cases of healthy control (p=0.01). No vrAE were found significant in comparison between the two groups. Details of adverse events have been shown in online supplemental table 3.

Nomogram prediction of seroconversion failure risk

Since there was a significant difference in serological status between patients with cancer and healthy control, multivariate logistic regression was carried out to find independent risk factors in all vaccinated cancer patients (n=302). Variables included gender, age, ECOG-PS, pathology type, chemotherapy status, PD-1B status, metastatic status, comorbidity, and vaccine doses. The model demonstrated an adjusted R^2 of 0.13 and a residual of 53.69 (total of 63.58). Three variables were found significant (online supplemental table 2), including age (p<0.01), pathology types (p=0.01), and chemotherapy status (p<0.01).

A nomogram was shown in figure 1A, which integrated all significant variables in multivariate logistic regression and the doses of vaccination to calibrate the precision of prediction. The calibration curve showing the predicted and actual failure risk of seroconversion was shown in figure 1B (mean absolute error=0.05), which demonstrated moderate agreement between observed and predicted failure risk with a C-index of 0.77±0.05.

Independent nomogram validation

The validation cohort included 195 patients in an independent medical center to evaluate the prediction performance of the nomogram. There were 115 male patients and 80 female patients, with a mean age of 42.90±10.31 years. Sixty-six (33.8%) patients were on PD-1B regimens (35 patients on sintilimab and 31 patients on toripalimab treatment, respectively). Eighty-five (43.6%) patients received one dose of vaccine, and no patients reported vrAE that was over grade 2. The baseline demographics were shown in online supplemental table 4. The validation result of the current nomogram showed that the

Table 3 Propensity score-matched comparison of vaccine in patients with cancer with and without vaccination (N=127 pairs)

		Vaccinated	Non-vaccinated	P value
Age, mean (SD)				
Gender, no (%)	Male	28 (22.0)	33 (26.0)	0.46
	Female	99 (78.0)	94 (74.0)	
PD-1B treatment duration duration, weeks		6.54±2.33	6.56±2.30	0.96
ECOG-PS	0	85 (66.9%)	89 (70.1%)	0.59
	1	42 (33.1%)	38 (29.9%)	
Metastases	Yes	10 (7.9%)	10 (7.9%)	1
	No	117 (92.1%)	117 (92.1%)	
Chemotherapy	Yes	26 (20.5%)	30 (23.6%)	0.55
	No	101 (79.5%)	97 (76.4%)	
Comorbid rheumatic disease	Yes	28 (22.0%)	26 (20.5%)	0.76
	No	99 (78.0%)	101 (79.5%)	
Pathology	NSCLC	42 (33.1%)	46 (36.2%)	0.59
	GI	59 (46.4%)	51 (40.2%)	
	HN	26 (20.5%)	30 (23.6%)	
Diarrhea	Yes	9 (7.1%)	11 (8.7%)	0.64
	No	118 (92.9%)	116 (91.3%)	
Pneumonitis	Yes	7 (5.5%)	8 (6.3%)	0.79
	No	120 (94.5%)	119 (93.7%)	
Rash	Yes	30 (23.6%)	29 (22.8%)	0.88
	No	97 (76.4%)	98 (76.2%)	
Arthralgia	Yes	17 (13.4%)	18 (14.2%)	0.86
	No	110 (86.6%)	109 (85.8%)	
Liver function test	Yes	16 (12.6%)	15 (11.8%)	0.85
	No	111 (87.4%)	112 (88.2%)	

ECOG-PS, Eastern Cooperative Oncology Group-Performance Score; GI, gastrointestinal; HN, head and neck; PD-1B, progression cell death-1 blockers.

C-index of seroconversion was 0.82, with the calibration curve shown in online supplemental figure 3.

DISCUSSION

Our work retrospectively analyzed the serological status and adverse events in patients with cancer receiving PD-1B and/or inactivated COVID-19 vaccines and developed a nomogram to predict failure risk of seroconversion during the 2-month follow-up. The immunogenetic status of both active or inactivated vaccines has been extensively reported in clinical trials of the healthy population, but relevant data concerning patients with cancer receiving ICI have been relatively lacking currently.

All vaccines reviewed in the study belong to the inactivated vaccine, which were manufactured by Sinopharm and Sinovac and are the two main types approved by the health administration in China. Compared with mRNA vaccines, the current types have a relatively lower rate of seroconversion in the general populations as reported in the phase I/II/III trials. In addition, the patients with cancer in this study had an even lower rate of seroconversion than healthy control. Although there have been few reports to date to investigate the reasons behind the poor seroconversion in patients receiving active treatment, several clinical profiles were explored in this work, which was illustrated by multivariate regression analysis, and thus a nomogram was built. We found that age was the most prominent factor in predicting the failure risk. Also, age was found negatively correlated with the titer value in all patients with cancer. Similarly, one previous study of BNT162b2 vaccine found a significant difference in seroconversion rate between the elderly and the young patients with cancer, and the titer value was found also significantly different between the two groups.[20] In the current work, the increase of failure risk was proportional to aging. These findings suggest that aging might be the dominant risk factor in predicting seroconversion failure. Also, we found that among the cancer pathology types included, patients with HN cancers may be the most probable risk population for seroconversion failure, and non-small cell lung cancer pathology predicts better seroconversion outcomes. The clinical course of COVID-19 infection was reported as devastating in lung patients with

Table 4 Propensity score-matched comparison with non-cancer control

Factor		PD-1B+ /vac+	Healthy control	*P* value	PD-1B-/vac+	Healthy control	P value
Age, mean (SD)		51.17 (10.42)	50.08 (11.65)	0.20	49.93 (10.37)	48.04 (11.69)	0.09
Gender	Male	34 (24.6%)	38 (27.5%)	0.58	43 (26.5%)	42 (25.9%)	0.90
	Female	104 (75.4%)	100 (72.5%)		119 (73.5%)	120 (74.1%)	
Dose of vaccine	1	58 (42.0%)	63 (45.7%)	0.54	90 (55.6%)	83 (51.2%)	0.44
	2	80 (58.0%)	75 (54.3%)		72 (44.4%)	79 (48.8%)	
Comorbidity with rheumatic disease	Yes	32 (23.2%)	29 (21.0%)	0.66	38 (23.5%)	36 (22.2%)	0.79
	No	106 (76.8%)	109 (79.0%)		124 (76.5%)	126 (77.8%)	
Fatigue	Yes	20 (14.5%)	17 (12.3%)	0.60	27 (16.7%)	18 (11.1%)	0.15
	No	118 (85.5%)	121 (87.7%)		135 (83.3%)	144 (88.9%)	
Fever	Yes	12 (8.7%)	21 (15.2%)	0.10	12 (7.4%)	22 (13.6%)	0.07
	No	126 (91.3%)	117 (84.8%)		150 (92.6%)	140 (86.4%)	
Lymphadenopathy	Yes	15 (10.9%)	23 (16.7%)	0.16	19 (11.7%)	30 (18.5%)	0.09
	No	123 (89.1%)	115 (83.3%)		143 (88.3%)	132 (81.5%)	
Nausea	Yes	15 (10.9%)	23 (16.7%)	0.16	18 (11.1%)	25 (15.4%)	0.25
	No	123 (89.1%)	115 (83.3%)		144 (88.9%)	137 (84.6%)	
Headache	Yes	13 (9.4%)	8 (5.8%)	0.26	13 (8%)	10 (6.2%)	0.52
	No	125 (90.6%)	130 (94.2%)		149 (92.0%)	152 (93.8%)	
Serocoversion	Positive	94 (68.1%)	111 (80.4%)	0.02	116 (%)	135 (%)	0.01
	Negative	44 (31.9%)	27 (19.6%)		46 (%)	27 (%)	
Rash	Yes	35 (25.4%)	12 (8.7%)	<0.01	10 (6.2%)	14 (8.6%)	0.40
	No	103 (74.6%)	126 (91.3%)		152 (93.8%)	148 (91.4%)	
Arthralgia	Yes	19 (13.8%)	10 (7.2%)	0.08	18 (11.1%)	12 (7.4%)	0.27
	No	119 (86.2%)	128 (92.8%)		144 (88.9%)	150 (92.6%)	

PD-1B, progression cell death blockers; SD, standard deviation.

cancer, and HN cancer were not associated with a worse outcome than other pathological types. Although no data has been reported to associate cancer types with vaccination outcome, the future research in patients with cancer is necessary to investigate how pathology types affect vaccination outcomes.

It was also noted in the nomogram and regression analysis that PD-1 inhibition was not associated with the failure risk of seroconversion in cancer treatment. The finding was also supported by the comparison result in the first propensity score match of vac+/PD-1B+ vs vac+/PD-1B- group. Thakkar *et al*[21] evaluated antispike titers in 200 patients with cancer, including 67% patients with solid cancers and 33% patients with hematological malignancies, and found that patients receiving ICI treatment had surprisingly higher rate of seroconversion than the control group. Indeed, it was expected at the beginning of the current study that PD-1B would probably increase immune response to vaccination based on the prior research that other vaccine types have been already shown to promote better seroconversion when administered concurrently with ICI in preclinical settings.[22] In selected clinical settings, ICI may even enhance the antitumor effect of cancer vaccines.[23] In preclinical models, blocking PD-1 was shown to elevate immune response against RNA virus, and in earlier research of influenza vaccination of patients with cancer, seroconversion was also seen unaffected, or even augmented by ICI.[12] This result may be promising in supporting PD-1B use mixed with COVID-19 vaccination, but the difference may become significant with larger enough samples and therefore future randomized trials or larger-scale research are encouraged to give more conclusive results.

In the vac+/PD-1B+ cohort, the irAEwere sparsely reported during follow-up and all reported cases in the present study were graded less than 2. Compared with previous reports, this study identified some cases of pneumonitis and low-grade colitis in PD-1B treated group, all of which had not been reported in prior research of vaccinated patients with cancer. The discrepancy could be explained by the late onset of these irAEs, as the included patients in this study were followed up for 1–3 months, and most of the symptom onset began late in the course.[24]

Also, matched comparison between vac+/PD-1B+ and vac+/PD-1B- group also showed insignificant difference of both irAE and vrAE. One previous report on influenza vaccines have demonstrated that the vrAE were

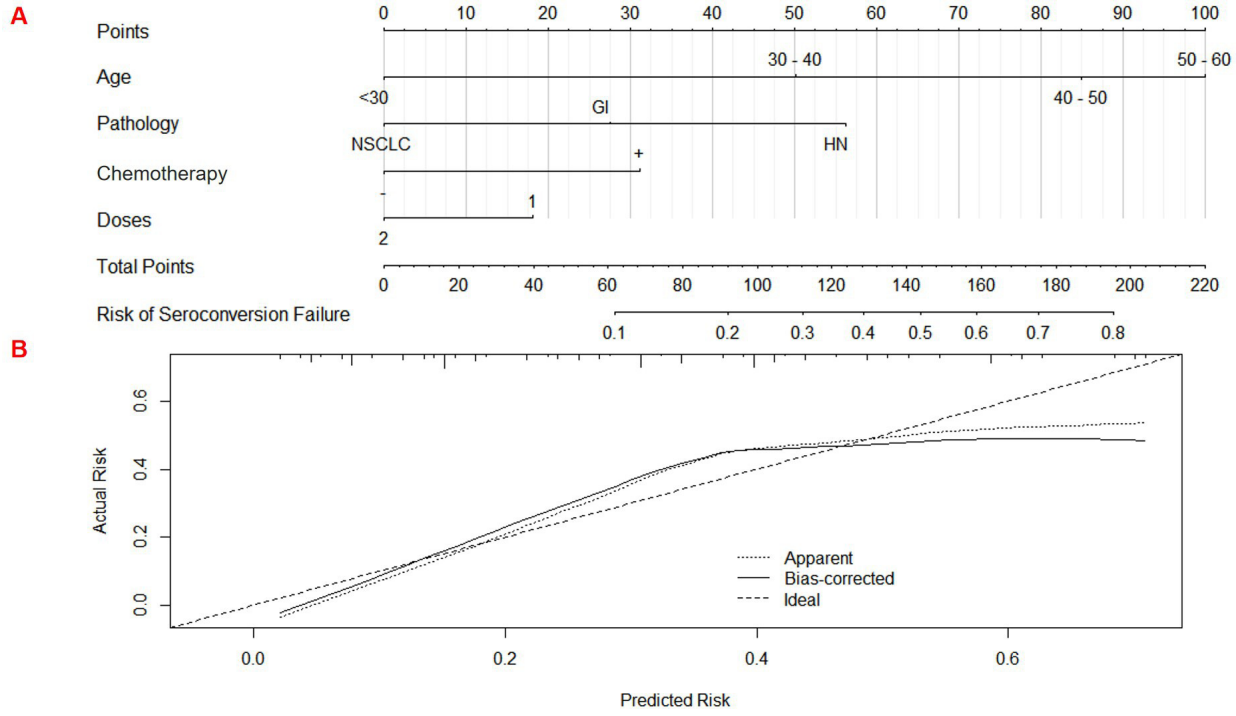

Figure 1 (A) Nomogram predicting the failure risk of serological conversion during 2-month follow-up after vaccination with SinoPharm or SinoVac vaccine; (B) calibration curve showing agreement between predicted and actual failure risk of seroconversion. GI, gastrointestinal; HN, head and neck; NSCLC, non-small cell lung cancer.

potentiated in ICI-treated patients with cancer.[25] In the present study, the dermatological vrAE was seen potentiated in ICI-treated group (26.1% in vac+/PD-1B+group vs 7.5% in vac+/PD-1B- group). However, no other vrAE was different in the propensity score-matched comparison. Because low-grade rash could belong to vrAE, irAE, or an interaction event caused by both vrAE and irAE, we further compared the adverse events between vac+/PD-1B+and vac-/PD-1B+groupand found no significant difference in reported rash cases. These results suggested that the rash was one of irAE instead of vrAE. The result was further validated by the comparison between vaccinated patients with cancer and healthy control, which showed no significant difference between vac+/PD-1B- and healthy control. Prospective, blinded trials or larger-scale studies are encouraged to give more conclusive evidence.

Limitations

This work bears several limitations. The retrospective nature of the study made the recall bias possible during follow-up of adverse events, even though the elapsed period was relatively short since the vaccination initiation. Second, the precise time of seroconversion and the beginning of adverse events related to both vaccination and PD-1B were poorly elucidated during follow-up. This shortcoming could well be overcome in prospective, controlled trials in which different timing of testing could be set to find the impact of PD-1B on the time of seroconversion for patients with cancer. Other limitations lied in the demographic constitution, in which female predominance was found during statistical analysis (493 females), a proportion that could not represent the cancer prevalence or incidence. The reason may probably be multi-factorial, and psychological factors probably played a role. Also, the staging of cancer of the patients involved was relatively in the early phase and the ECOG status was 0 or 1, a fact that prevents massive use of chemotherapy or biological agents. This was probably because of the prudence of attending oncologists who may not recommend patients with the late-stage disease for vaccination.

CONCLUSION

The inactivated vaccine had relatively good immunogenicity and tolerability in patients with cancer with or without PD-1B treatment, and vaccination did not seem to elicit an elevated incidence of irAE/vrAE. Overall, the seroconversion rates in patients with cancer were relatively lower than the healthy population. A nomogram that included age, chemotherapy status, pathology types, and rheumatic comorbidity, was developed to predict the failure risk and was validated with relatively good C-index in an independent cohort.

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