Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Original Research

Predictors of poor serologic response to COVID-19 vaccine in patients with cancer: a systematic review and meta-analysis

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Abstract ***Backgrounds:*** Patients with cancer presented a lower probability to obtain seroconversion after a complete course of COVID-19 vaccination. However, little was known on the factors that predict poor seroconversion in this frail population.
Methods: We searched the PubMed, EMBASE, and China National Knowledge Infrastructure databases for all articles within a range of published years from 2019 to 2022 on the predictors of response to COVID-19 vaccine in patients with cancer (last search was updated on 2st March 2022). The odds ratio corresponding to the 95% confidence interval was used to assess the outcome. The statistical heterogeneity among studies was assessed with the Q-test and I^2 statistics. The review was registered with PROSPERO (CRD42022315687) and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.
Results: Twenty cohort studies met the inclusion criteria for this study, with 5,499 patients with cancer. We found that advanced age, male patients, and metastatic disease increased negative seropositivity to COVID-19 vaccine. Immunoglobulin heavy chain variable mutation status, high concentration of Ig G, Ig M, and Ig A were correlated with seropositivity. Relating to cancer treatment strategy, anti-CD20 therapy within recent 12 months and chemotherapy were negatively correlated with seroconversion. Meta-analysis found no significant difference associated with targeted treatment, immunotherapy, and endocrine treatment.

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Conclusions: Our meta-analysis assessed the factors that predict poor seroconversion in order to plan better prevention strategies in this frail population. The results proposed that enhanced vaccination strategies would be beneficial for the special patients such as advanced male, or patients receiving active chemotherapy, and carefully prevention should be emphasised even after a complete course of vaccination.

1. Introduction

Coronavirus disease-19 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has spread throughout the world, afflicting more than 459.7 million people, resulting in more than 6 million deaths globally as of 16 March 2022, and with a mortality rate about 1.3%. The morbidity and mortality of COVID-19 were found higher in patients with cancer [1,2]. Worldwide, an estimated 19.3 million new cancer cases and almost 10.0 million cancer deaths occurred in 2020, and the global cancer burden is expected to be 28.4 million cases in 2040, a 47% rise from 2020 [3]. It is precisely because that patients with cancer are purported to have poor COVID-19 outcomes [4–7], and recent studies report that hydroxychloroquine and convalescent plasma demonstrate no efficacy against COVID-19 infection [8–10], disease prevention is the most effective way to contain new cases, and major medical societies fostered priority mass vaccination in this high-risk population [11,12].

For this reason, healthcare authorities should prioritise vaccinations for patients with cancer. On the basis of the clinical trials [13], considering the high morbidity and mortality from COVID-19 in patients with cancer, the benefits of vaccination are likely to far outweigh the risks of vaccine-related adverse events. However, researches [14–17] demonstrate a lower probability to obtain seroconversion after a complete course of COVID-19 vaccination, with about 6% of patients with cancer in treatment failed to develop an immune response after mRNA vaccination, as compared to only 0.2% in controls, accounting for a 30-fold higher probability [14].

Patients with cancer have an impaired immune response to COVID-19 vaccination with lower and/or lagged seroconversion rate [18,19]. The vaccination against COVID in cancer (VOICE) study aimed to reveal influences of anti-cancer treatments in response to vaccination [20], and the COVID-19 antiviral response (CAPTURE), a pan-tumour immune monitoring study, suggested a fundamental understanding of the interaction between host immunity, the virus, cancer, and anti-cancer treatments placed in the wider healthcare context in order to minimise harm and optimise cancer outcomes [21]. To propose a tailored approach to COVID-19 vaccination for patients with cancer, a thorough understanding of factors affecting on COVID-19 vaccination efficacy in patients with cancer with poor immune conditions is requisite. We conducted this meta-analysis to assess the factors that predict poor seroconversion comprehensively in order to plan better prevention strategies in this frail population.

2. Methods

We did a systematic review and meta-analysis of studies on factors affecting humoural response to COVID-19 vaccine in patients with cancer. The review was registered with PROSPERO (CRD42022315687) and reported according to PRISMA guidelines [22].

2.1. Publication search and inclusion criteria

We searched the PubMed, EMBASE, and China National Knowledge Infrastructure databases for all articles within a range of published years from 2019 to 2022 on the predictors of response to COVID-19 vaccine in patients with cancer (last search was updated on stMarch 2 2022). The following terms were used in this search: ‘COVID-19 vaccine’ and ‘cancer’ and ‘serologic response or seroconversion’. In order to identify the relevant publications, the references cited in the research papers were also scanned. Combining searches resulted in 51 abstracts (Fig. 1). An additional 17 studies were identified through review articles and meta-analysis, for a total of 68 studies.

We evaluated the eligible studies if all the following conditions were met: (1) evaluation of factors affecting the response to COVID-19 vaccine in patients with cancer; (2) inclusion of sufficient data or the data can be acquired from the manuscript or supplementary materials to calculate odds ratio (ORs) and 95% confidence intervals (CIs); (3) the publication was a cohort study; and (4) the study was published in English.

2.2. Data extraction

Two authors (Wenxing Yang and Dongxue Zhang) independently reviewed and extracted the data needed. Disagreements were resolved through discussion among the authors to achieve a consensus. Publications were read by Wenxing Yang in order to check original data extraction. The following information was recorded for

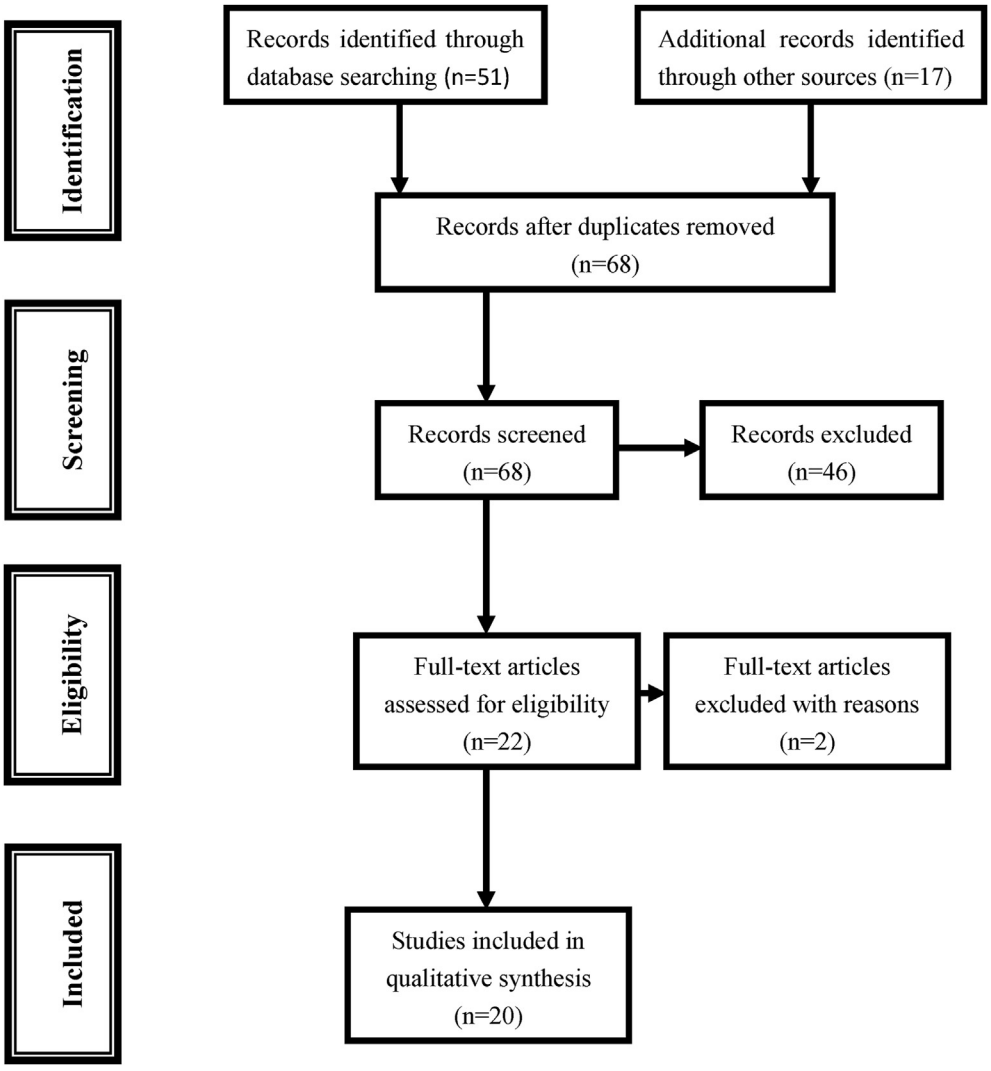

Fig. 1. Flowchart for identification of studies.

each study: first author, year of publication, region, cancer type, vaccine type, vaccine dose, number of cases, and impact factors (all of the data are shown in Table 1).

2.3. Statistical analysis

The OR corresponding to the 95% CI was used to assess the outcome. The potential impact factors include age, gender, metastasis, immunoglobulin heavy chain variable region (IGHV) mutation status, IgG level, IgM level, IgA level, anti-CD20 therapy within recent 12 months, targeted therapy, chemotherapy, endocrine therapy, and immunotherapy.

The statistical heterogeneity among studies was assessed with the Q-test and I^2 statistics [23]. If no obvious heterogeneity, the fixed-effects model (the Mantel–Haenszel method) was used to estimate the summary OR [24]; otherwise, the random-effects model (the DerSimonian and Laird method) was used [25]. Finally, random effects models were used to calculate the OR estimates and 95% CIs of factors which associated with response to COVID-19 vaccine in patients with cancer. To explore sources of heterogeneity across studies, we did logistic meta-regression analyses. We examined the following study characteristics: publication year, region, vaccine dose, and number of cases. Publication bias was evaluated with funnel plot and Begg's rank correlation method [26]. The statistical analyses were performed by STATA 12.0 software (Stata Corp., College Station, TX).

3. Results

3.1. Characteristics of studies

Out of a total of 68 abstracts were screened, 22 were retrieved for more detailed evaluation. The two excluded studies lacked sufficient data (shown in Fig. 1). Finally, 20 cohort studies met the inclusion criteria for this study [14,16,27–44], with 5,499 patients with cancer. All of

Table 1
Characteristics of literatures included in the meta-analysis.

Reference	Year	Region	Cancer type	Vaccine dose	Vaccine type	Cases	Impact factors
Gounant V [39]	2022	France	Lung cancer	Second	BNT162b2	244	Age, gender, metastasis, target therapy, chemotherapy, immunotherapy
Amatu A [14]	2021	Italy	Solid cancer	Second	BNT162b2	171	Age, gender, target therapy, chemotherapy, endocrine therapy, immunotherapy
Cavanna L [31]	2021	Italy	Solid cancer	Second	BNT162b2	257	Age, gender, metastasis, target therapy, chemotherapy, immunotherapy
Yasin AI [44]	2022	Turkey	Cancer	Second	CoronaVac	776	Age, gender, metastasis, target therapy, chemotherapy, endocrine therapy, immunotherapy
Herishanu Y [41]	2022	Israel	CLL	Third	BNT162b2	172	Age, gender, IGHV mutational status, IgG level, IgM level, IgA level, anti-CD20 treatment
Herishanu Y [35]	2021	Italy	CLL	Second	BNT162b2	167	Age, gender, IGHV mutational status, IgG level, IgM level, IgA level, anti-CD20 treatment
Avivi I [28]	2021	Israel	MM	Second	BNT162b2	171	Age, gender
Bagacean C [38]	2022	France	CLL	Second	BNT162b2 or mRNA-1273	530	Age
Di Noia V [33]	2021	Italy	Cancer	Second	BNT162b2	816	Age, gender, target therapy, chemotherapy, immunotherapy
Addeo A [27]	2021	USA	Cancer	Second	BNT162b2 or mRNA-1273	131	Age, gender, target therapy, chemotherapy, endocrine therapy, immunotherapy
Pimpinelli F [36]	2021	Italy	MM and MPM	Second	BNT162b2	92	Age, gender
Haydu JE [40]	2022	USA	CLL	Second	SARS-CoV-2 and PCV13 vaccines	30	Age, IGHV mutational status, IgG level
Buttiron Webber T [30]	2021	Italy	Cancer	Second	BNT162b2	291	Age, gender, target therapy, chemotherapy, endocrine therapy, immunotherapy
Benjamini O [29]	2021	Israel	CLL	Second	BNT162b2	373	Age, gender, IGHV mutational status, IgG level, IgM level, IgA level, anti-CD20 treatment
Grinshpun A [34]	2021	Israel	Cancer	Second	BNT162b2	202	Age, gender, metastasis, target therapy, chemotherapy, endocrine therapy, immunotherapy
Marasco V [42]	2022	Italy	LM	First	BNT162b2	263	Age, IgG level, IgM level, IgA level
Reimann P [43]	2022	Austria	Cancer	Third	BNT162b2	29	Gender
Goshen-Lago T [16]	2021	Israel	Cancer	Second	BNT162b2	218	Gender, metastasis, target therapy, chemotherapy, immunotherapy
Debie Y [32]	2021	Belgium	Cancer	Third	BNT162b2	200	Target therapy, chemotherapy, immunotherapy
Ruggeri EM [37]	2021	Italy	Cancer	Second	BNT162b2	366	Target therapy, chemotherapy, endocrine therapy, immunotherapy

CLL, chronic lymphocytic leukaemia; MM, multiple myeloma; MPM, myeloproliferative malignancies; LM, lymphoid malignancies.

which used a historical cohort design, with seven countries were represented. Of all the studies, one in the United States of America (USA) vaccinated with SARS-CoV-2 and PCV13 vaccines [40], one in Turkey used Corona Vaccine [44], one in USA [27] and one in France [38] underwent BNT162b2 or mRNA-1273, all the others inoculated BNT162b2. The details of the selected studies were listed in Table 1.

3.2. Quantitative synthesis

A summary of the findings from included studies is shown in Table 2, Fig. 2 and Fig. 3. Sixteen studies [14,27–31,33–36,38–42,44] with 4,686 patients with cancer reported on the effect of age. Meta-analysis found increased risk of non-response to COVID-19 vaccine in patients with cancer with advanced age (OR = 1.29, 95% CI = 1.11–1.50, I^2 = 71.1%). On the basis of 16 studies [14,16,27–31,33,34,36,39,41–44] with 4,373 patients with cancer, male patients seem to react negative to COVID-19 vaccine (OR = 1.34, 95% CI = 1.13–1.58, I^2 = 0%). Five studies [16,31,34,39,44] including 1,697 patients with solid tumours reported on the effect of metastatic disease. Meta-analysis found that metastatic disease was negatively correlated with seropositivity (OR = 1.61, 95% CI = 1.04–2.49, I^2 = 53.1%).

IGHV mutational status was reported in four studies [29,35,40,41] including 742 patients with haematologic malignancies, Ig G level in five studies [29,35,40–42] including 1,005 patients with haematologic malignancies, Ig M and Ig A level in four studies [29,35,41,42] including 975 patients with haematologic malignancies. IGHV mutated status, high concentration of Ig G, Ig M, and Ig A were positively correlated with seropositivity (OR = 0.52, 95% CI = 0.28–0.98, I^2 = 37.4% for IGHV mutational status, OR = 0.43, 95% CI = 0.31–0.59, I^2 = 0% for Ig G, OR = 0.42, 95% CI = 0.22–0.81, I^2 = 73.5% for Ig M, OR = 0.40, 95% CI = 0.26–0.61, I^2 = 45.1% for Ig A).

Quantitative synthesis was possible for therapeutic method including targeted treatment, chemotherapy, endocrine treatment, and immunotherapy in patients with solid tumours, and anti-CD20 therapy within recent 12 months in patients with haematologic malignancies. Eleven studies [14,16,27,30–34,37,39,44] were reported on target treatment, 11 studies [14,16,27,30–34,37,39,44] were reported on chemotherapy, six studies [14,27,30,34,37,44] were reported on endocrine treatment, 11 studies [14,16,27,30–34,37,39,44] were reported on immunotherapy, and three studies [29,35,41] were reported on anti-CD20 treatment. Meta-analytical summary of the available studies found that anti-CD20 treatment was positively correlated with seropositivity (OR = 0.37, 95% CI = 0.17–0.78, I^2 = 50.8%). On the contrary, chemotherapy was negatively correlated with seropositivity (OR = 2.79, 95% CI = 1.84–4.23, I^2 = 33.9%). Meta-analysis found no significant difference associated with targeted treatment, immunotherapy, and endocrine treatment.

The influence of a single study on the overall meta-analysis estimate was investigated by omitting one study at a time, and the omission of any study made no significant difference, indicating that our results were statistically reliable. Begg's test was performed to evaluate the publication bias of selected literatures. No evidence of publication bias in our study was observed.

4. Discussion

This systematic review summarises the available global data of the effects of predictors on poor serologic response to COVID-19 vaccine in patients with cancer

Table 2
Analysis for non-serologic response in patients with cancer.

Risk factor	Non-serologic response				Cancer type
	N[a]	Cases	OR (95%CI)	P[b]	
Age	16	4,686	**1.29(1.11–1.50)**	<0.001	All
Gender	16	4,373	**1.34(1.13–1.58)**	0.552	All
Metastasis	5	1,697	**1.61(1.04–2.49)**	0.074	Solid tumours
Anti-CD20 treatment within recent 12 months	3	712	**2.72(1.28–5.78)**	0.131	Haematologic malignancies
IGHV mutational status	4	742	**0.52(0.28–0.98)**	0.188	Haematologic malignancies
IgG	5	1,005	**0.43(0.31–0.59)**	0.410	Haematologic malignancies
IgM	4	975	**0.42(0.22–0.81)**	0.010	Haematologic malignancies
IgA	4	975	**0.40(0.26–0.61)**	0.141	Haematologic malignancies
Target therapy	11	3,672	0.98(0.66–1.45)	0.046	Solid tumours
Chemotherapy	11	3,672	**2.79(1.84–4.23)**	0.128	Solid tumours
Endocrine therapy	6	1,937	1.02(0.98–1.06)	0.439	Solid tumours
Immunotherapy	11	3,672	1.10(0.62–1.98)	0.042	Solid tumours

Boldfaced values indicate a significant difference at the 5% level.
[a] Number of comparisons.
[b] P value of Q-test for heterogeneity test.

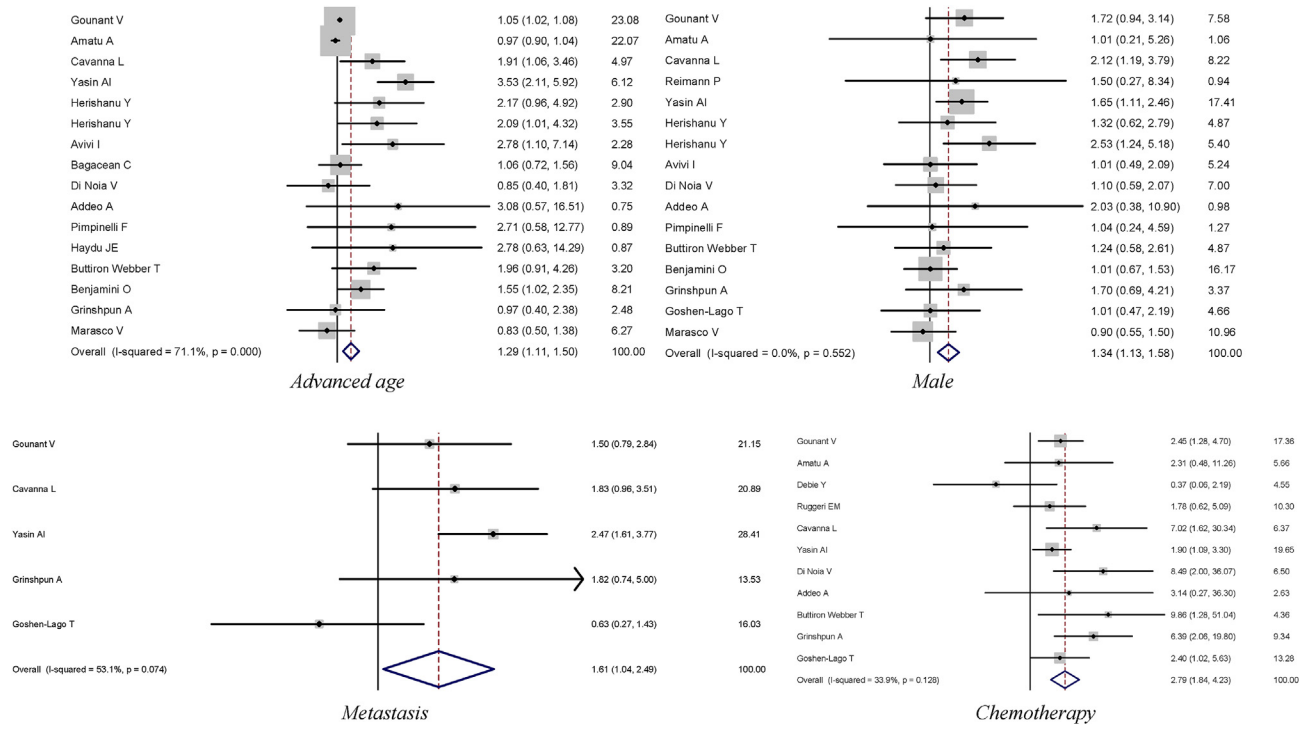

Fig. 2. Forest plot of risk factors associated with non-serologic response in patients with cancer.

during the COVID-19 pandemic. We found that advanced age, male patients, and metastatic disease increased negative seroconversion to COVID-19 vaccine. IGHV mutated status, high concentration of Ig G, Ig M, and Ig A were correlated with seropositivity in patients with haematologic malignancies. Relating to cancer treatment strategy, anti-CD20 therapy within recent 12 months and chemotherapy were negatively correlated with seroconversion. Meta-analysis found no significant difference associated with target treatment, immunotherapy, and endocrine treatment.

There were various technology platforms for the development of COVID-19 vaccines, including whole virus vaccines, nucleic acid vaccines, protein subunit vaccines, and recombinant vaccines [45–51]. In the present meta-analysis, one study in USA vaccinated with SARS-CoV-2 [40], one in Turkey used Corona Vaccine [44], one in USA [27] and one in France [38] underwent BNT162b2 or mRNA-1273; all the others inoculated BNT162b2. Although seroconversion rates after COVID-19 vaccination were significantly lower in patients with cancer [18,19,52], no new immune-related side-effects or exacerbation of existing immune-related side-effects were observed [53]. Thus, COVID-19 vaccine guidance suggested that continued quality oncological care requires patients with cancer to be prioritised for COVID-19 vaccination, where authorised or approved [13].

The immune response to the COVID-19 involves innate immune activation and antigen-specific responses of B and T cells [54]. Serological and immunological tests are primarily applied for population-based seroprevalence studies to evaluate the effectiveness of COVID-19 control measures and increase our understanding of the immunology behind COVID-19 vaccination [55], post vaccination testing of antibody response is an important and feasible tool for following people after vaccination [56].

Patients with cancer may have poor general condition than individuals without cancer because of their systemic immunosuppressive state caused by the malignancy and anticancer treatments [57,58]. Furthermore, vaccination is less effective at old than at young age with a statistically significant relationship between the age and level of anti the receptor-binding domain IgG after first dose of vaccine administration [56]. The present study found advanced age with increased negative seroconversion to COVID-19 vaccine may due to the unresponsiveness of immune system at older age.

Females develop higher antibody responses to vaccines than males [59]. After vaccination, protective antibody responses can be twice as high in adult females than in males [60]. Measures of cell-mediated immunity following vaccination are also higher in females than in males for some vaccines [61,62]. In the patients with cancer, females seem to response positive to COVID-19 vaccine.

Patients with cancer can be immunocompromised of vaccines due to a multitude of factors, such as the patient condition, underlying malignancy itself, coupled with damage to the organs directly or indirectly involved with bone marrow suppressive effects of cytotoxic

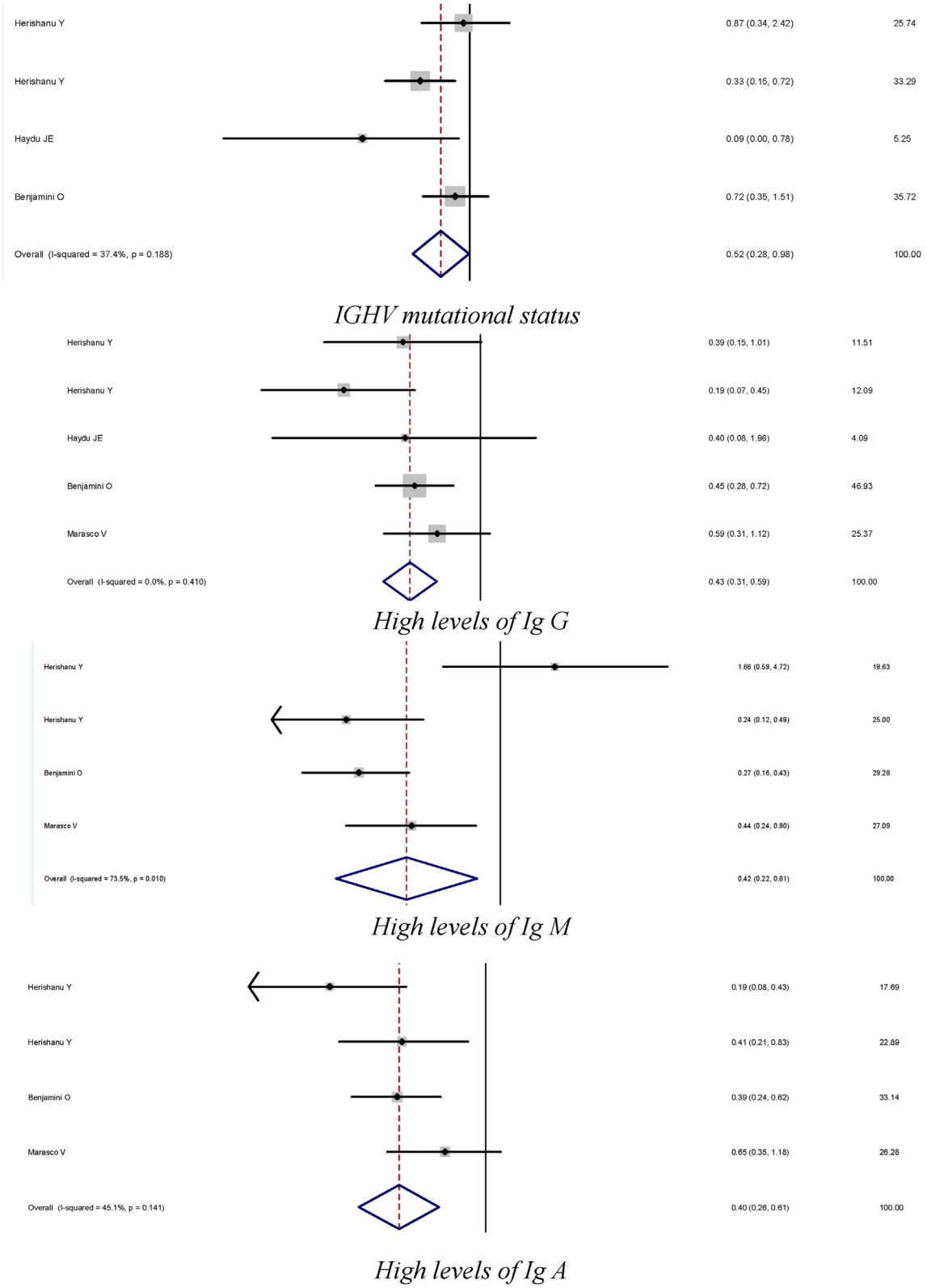

Fig. 3. Forest plot of protecting factors associated with non-serologic response in patients with cancer.

chemotherapy, and prior or ongoing treatments with a high degree of immunosuppressive effects [63]. While patients with cancer clearly represent a highly susceptible group with a strong and immediate need to be protected by available, effective vaccines. It is noteworthy that active cancer therapy modulates the immune response to vaccines depending on the type of treatment [64]. It has not been clearly revealed whether

it would be better to continue or initiate therapy during the COVID-19 pandemic, especially when they receive the vaccine. The present meta-analysis tried to find the optimum seroconversion among patients receiving distinct cancer therapeutics. The results indicated that anti-CD20 therapy within recent 12 months and chemotherapy were negatively correlated with seroconversion. The underlying reason could be that cytotoxic agents may directly or indirectly damage DNA molecules. Furthermore, our results suggested that the targeted treatment, immunotherapy, and endocrine treatment seem not to affect the seroconversion of COVID-19 vaccine.

A few limitations of our study should be considered. Although we did not observe significant publication bias, publication bias is possible in any meta-analysis. Furthermore, although most the studies inoculated BNT162b2, several other studies vaccinated with SARS-CoV-2, Corona Vaccine, or mRNA-1273 may substantially affect the result. Moreover, it remains uncertain how serological and immunological parameters are precisely correlated with the extent of protective immunity [55]; serological diagnostics may ignore the T-cell responses by vaccination. Finally, due to the limited available researches, different cancer types may response differently to COVID-19 vaccine.

In conclusion, our meta-analysis assessed the factors that predict poor seroconversion in order to propose a tailored approach to COVID-19 vaccination in this frail population. The results proposed that enhanced vaccination strategies would be beneficial for the special patients such as advanced male, or patients receiving active chemotherapy, and carefully prevention should be emphasised even after a complete course of vaccination.

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Author contribution

Kui Zhang contributes to the Conceptualisation; Wenxing Yang and Dongxue Zhang contribute to Data curation and Project administration; Zhuo Li contributes to Software and Writing - review and editing; Wenxing Yang and Kui Zhang contribute to Writing - original draft.

Conflict of interest statement

No conflicts of interests to declare.

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