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RESEARCH ARTICLE

Estimating the number of Chinese cancer patients eligible for and benefit from immune checkpoint inhibitors

Kaili Yang*, Jiarui Li*, Lin Zhao, Zhao Sun, Chunmei Bai (✉)

Department of Medical Oncology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100032, China

Abstract **The total number of cancer patients who are eligible for and will benefit from immune checkpoint inhibitors (ICIs) in China has not been quantified. This cross-sectional study was conducted to estimate the number of Chinese cancer patients with eligibility and response to ICIs based on the 2015 Chinese cancer statistics and the immune checkpoint inhibitor clinical practice guideline of the Chinese Society of Clinical Oncology. A total of 11 ICIs were recommended for 17 cancer types. The estimated number of eligible patients annually was 1 290 156 (55.18%), which included 888 738 males (60.05%) and 400 468 females (46.67%). The estimated number of responders annually was 448 972 (19.20%), which included 309 023 males (20.88%) and 139 764 females (16.29%). Gastric cancer (*n*=291 000, 12.45%), non-small-cell lung cancer (*n*=289 629, 12.39%), and hepatocellular carcinoma (*n*=277 100, 11.85%) were the top three cancer types with the highest number of eligible patients. Non-small-cell lung cancer (*n*=180 022, 7.70%), hepatocellular carcinoma (*n*=75 648, 3.24%), and small-cell lung cancer (*n*=64 362, 2.75%) were the top three cancer types with the highest number of responders. In conclusion, ICIs provide considerable benefit in Chinese cancer patients under optimal estimation.**

Keywords benefit; China; eligibility; immune checkpoint inhibitor; public health

Introduction

The application of immune checkpoint inhibitors (ICIs) is one of the major clinical cancer research advances over the last decade. By the end of 2020, the US Food and Drug Administration (FDA) has passed more than 50 approvals of 7 ICIs [1]. China is the most populous country in the world with distinct cancer patterns and different responses to ICIs from other countries, and the survival for many major cancer types in China remains lower than developed countries [2–4]. Therefore, the integration of effective cancer treatment strategies, such as ICIs, into clinical practice is important. Current studies mostly focus on the efficacy of ICIs in certain cancer types, whereas the overall eligibility and response pattern of ICIs remains unknown. A quantitative estimation of the potential use and benefit of ICIs in Chinese population can illustrate the current application status of ICIs and provide further insights into their rational applications in China. Therefore, we conducted this cross-sectional study to estimate the number of Chinese cancer patients with eligibility and response to ICIs.

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Correspondence: Chunmei Bai, baichunmei1964@163.com

*These authors have contributed equally to this work.

Materials and methods

Overview

This cross-sectional study was conducted according to the Strengthening the Reporting of Observational Studies in Epidemiology reporting guideline from December 2020 to April 2021 [5]. The primary outcome was the estimated number of Chinese cancer patients who were eligible for and responded to ICIs. This study was exempt from formal institutional board review because of its retrospective design and deidentified data.

Data set

The number of annual cancer deaths from the 2015 Chinese cancer statistics of the National Cancer Center

was used to estimate the number of Chinese patients with advanced or metastatic cancers, which were the major target population for ICI treatment [6]. The 2015 Chinese cancer statistics was selected because it was the latest available cancer statistics data of China with high quality and national representativeness. We used grade 1 and 2 recommendations in the immune checkpoint inhibitor clinical practice guideline of Chinese Society of Clinical Oncology (CSCO) (version 2020) to identify eligible patients for ICI treatment [7]. This guideline was established by a panel of senior experts specializing in immunotherapy based on evidence-based medicine, and the 2020 version was the latest version during the completion of this study. Recommendations in the guideline were based on different levels of evidence (Supplementary material 1) [8]. In brief, grade 1 recommendations were based on high-level evidence with suitable applicability for Chinese cancer patients; grade 2 recommendations were based on high-level evidence with limited applicability for Chinese cancer patients, and grade 3 recommendations lacked strong evidence-based data. We opted for the grade 1 and 2 recommendations from the CSCO guideline to best represent the ICI application status in China because of the relatively lagging drug approval process of the National Medical Products Administration. The objective response rates (ORRs) of ICIs were estimated using the ORRs reported in pivotal clinical trials stated in the CSCO guideline.

Estimation

We included all ICI-containing regimens for the systemic treatment in advanced or metastatic cancers. The adjuvant and neoadjuvant treatments were not investigated in this study. Eligible patients were defined as patients with certain types of cancer that were recommended for ICIs in the guideline. If a specific histologic subtype or biomarker status was required in the recommendation, we searched relevant publications to estimate the proportion, including well-designed meta-analyses, clinical guidelines, and epidemiological studies with large sample sizes. The median number was used for calculation if the proportion of a certain biomarker was in a range according to available studies. Patients who responded to ICIs were defined as eligible patients who could obtain objective response (complete response or partial response) to ICIs. The number of patients who responded to ICI treatment was calculated by multiplying the ORR and the number of eligible patients. If multiple treatment regimens were available for the same cancer type, we selected the regimen with the highest ORR to provide an optimal estimation. For instance, we calculated the eligibility and benefit of ICIs for colorectal cancer patients in China. According to the CSCO guideline, only patients with microsatellite instability-high (MSI-H) colorectal cancer were recommended for ICI treatment [7]. A total of 187 000 Chinese patients dies from colorectal cancer annually, and MSI-H colorectal cancer accounted for 5% of the total metastatic colorectal cancer cases according to the latest National Comprehensive Cancer Network guideline [9]. Therefore, approximately 9350 colorectal cancer patients were eligible for ICI treatment. Based on the results from two phase 2 trials, the use of nivolumab and pembrolizumab were recommended in the guideline, and their ORRs were 34% and 52% [10,11]. We selected the highest ORR to calculate the response. Thus, we estimated that 4862 colorectal cancer patients could respond to ICIs in China annually. The total number of eligible and responsive patients was calculated by adding the number of corresponding patients with certain cancer types. The percentage of patients with eligibility and response was calculated using the population divided by the total number of cancer deaths. For sex-specific eligibility and response, the population was calculated using the sex-specific cancer death data, and the percentage was calculated using the population divided by the total number of sex-specific cancer deaths.

Statistical analysis

The investigators performed a descriptive analysis using Microsoft Excel. The 95% confidential intervals for the percentage of eligible and responsive cancer patients were calculated using R version 4.0.3.

Results

Overview

A total of 106 recommendations were identified in the CSCO guideline based on the data from 79 pivotal clinical trials (Table 1). Out of the 79 clinical trials, 35 studies (44.3%) were randomized controlled trials, and 41 studies (51.9%) were single-arm clinical trials. The median number of enrolled participants was 305 (interquartile range (IQR) 91−763), and the median percentage of female participants was 33.6% (IQR 22.8%−40.9%). Chinese participants were enrolled in 42 studies (53.2%). A total of 11 ICIs were recommended for 17 cancer types, including 4 Chinese domestic ICIs (camrelizumab, toripalimab, sintilimab, and tislelizumab). A total of 56 studies (70.9%) supported ICI monotherapy, and 25 studies (31.6%) supported combination therapies. In 14 studies, biomarkers, including certain programmed cell death ligand-1 (PD-L1) expression status in tumor biopsies (n = 11, 13.9%) and microsatellite instability-high (MSI-H) status (n = 3, 3.8%), were required as prerequisites for ICI treatment. The characteristics of clinical trials and relevant publications used to estimate

Table 1 Characteristics of pivotal clinical trials[a]

	Total	Grade 1 and 2 recommendations (eligible)
Total clinical trials, *n* (%)	79 (100)	52 (100)
Study design		
Randomized controlled trial	35 (44.3)	29 (55.8)
Single-arm clinical trial	41 (51.9)	22 (42.3)
Other	3 (3.8)	1 (1.9)
Clinical trial phase		
Phase 1	12 (15.2)	5 (9.6)
Phase 2	29 (36.7)	18 (34.6)
Phase 3	34 (43.0)	28 (53.8)
Not specified	4 (5.1)	1 (1.9)
Participants, median (IQR)	305 (91−763)	412 (99−827.5)
Female participants (%), median (IQR)	33.6 (22.8−40.9)	30.4 (22.8−41.2)
Chinese patient participation[b]		
Major	17 (21.5)	11 (21.2)
Minor	25 (31.6)	19 (36.5)
None	37 (46.8)	22 (42.3)
Cancer types[c]		
HNSCC (except nasopharyngeal carcinoma)	3 (3.8)	3 (5.8)
Nasopharyngeal carcinoma	5 (6.3)	0
Esophageal squamous cell carcinoma	3 (3.8)	3 (5.8)
Non-small-cell lung cancer	10 (12.7)	10 (19.2)
Small-cell lung cancer	5 (6.3)	2 (3.8)
Breast cancer	1 (1.3)	0
Gastric cancer	3 (3.8)	2 (3.8)
Hepatocellular carcinoma	9 (11.4)	5 (9.6)
Colorectal cancer	2 (2.5)	2 (3.8)
Renal cell carcinoma	7 (8.9)	6 (11.5)
Urothelial carcinoma	8 (10.1)	1 (1.9)
Cervical cancer	2 (2.5)	2 (3.8)
Endometrial cancer	2 (2.5)	1 (1.9)
Ovary cancer	1 (1.3)	1 (1.9)
Melanoma	10 (12.7)	7 (13.5)
Skin cancer (except melanoma)	6 (7.6)	4 (7.7)
Hematological malignancy	7 (8.9)	6 (11.5)
ICI type[c]		
CTLA-4 inhibitors	4 (5.1)	3 (5.8)
Ipilimumab	4 (5.1)	3 (5.8)
PD-1 inhibitors	64 (81.0)	44 (84.6)
Pembrolizumab	28 (35.4)	22 (42.3)
Nivolumab	21 (26.6)	13 (25.0)
Camrelizumab	9 (11.4)	4 (7.7)
Toripalimab	3 (3.8)	2 (3.8)
Sintilimab	1 (1.3)	1 (1.9)
Tislelizumab	1 (1.3)	1 (1.9)

(*Continued*)

	Total	Grade 1 and 2 recommendations (eligible)
Cemiplimab	1 (1.3)	1 (1.9)
PD-L1 inhibitors	15 (19.0)	8 (15.4)
Atezolizumab	10 (12.7)	6 (11.5)
Avelumab	3 (3.8)	1 (1.9)
Durvalumab	2 (2.5)	1 (1.9)
Treatment regimen[c]		
ICI monotherapy	56 (70.9)	38 (73.1)
ICI + chemotherapy	11 (13.9)	7 (13.5)
ICI + targeted therapy	9 (11.4)	4 (7.7)
ICI + chemotherapy + targeted therapy	1 (1.3)	1 (1.9)
ICI + ICI	4 (5.1)	3 (5.8)
Biomarker requirement[c]		
PD-L1 CPS ⩾ 1	6 (7.6)	3 (5.8)
PD-L1 TPS ⩾ 50%	1 (1.3)	1 (1.9)
PD-L1 TPS ⩾ 1%	2 (2.5)	2 (3.8)
PD-L1 IPS ⩾ 1%	2 (2.5)	1 (1.9)
MSI-H status	3 (3.8)	3 (5.8)

[a]Pivotal clinical trials were defined as clinical trials that were described as pivotal for making recommendations in the CSCO guideline.
[b]Major participation was defined as the condition that participants of a clinical trial were exclusively Chinese; minor participation was defined as the presence of Chinese participants in a clinical trial; none participation was defined as the absence of Chinese participants in a clinical trial.
[c]The types of cancer, ICI, treatment regimen, and biomarker requirement were identified based on the recommendations in the CSCO guideline.
Abbreviations: CPS, combined positive score; CTLA-4, cytotoxic T lymphocyte-associated antigen-4; HNSCC, head and neck squamous cell carcinoma; ICI, immune checkpoint inhibitor; IPS, immune positive score; IQR, interquartile range; MSI-H, microsatellite instability-high; PD-1, programmed cell death-1; PD-L1, programmed cell death-ligand 1; TPS, tumor proportion score.

the eligibility and response were listed in Supplementary material 2.

Eligibility

In 2015, approximately 2 338 000 cancer deaths were reported in China. A total of 17 cancer types, which included 1 896 820 cancer deaths (81.13%) (Supplementary material 3), were evaluated in the CSCO guideline. Among the evaluated cancer types, 1 290 156 patients (55.18%), including 888 738 male patients (60.05%) and 400 468 female patients (46.67%), were eligible for ICI treatment. Gastric cancer (n = 291 000, 12.45%), non-small-cell lung cancer (NSCLC) (n = 289 629, 12.39%), and hepatocellular carcinoma (n = 277 100, 11.85%) were the top three cancer types with the highest number of eligible patients (Figs. 1 and 2). This result was consistent in males (hepatocellular carcinoma, n = 205 700, 13.90%; gastric cancer, n = 201 000, 13.58%; NSCLC, n = 198 977, 13.44%) and females (NSCLC, n = 90 653, 10.57%; gastric cancer, n = 90 000, 10.49%; hepatocellular carcinoma, n = 71 400, 8.32%) (Fig. 3). Gynecological cancers (cervical cancer, endometrial cancer, and ovary cancer) contributed 34 411 female patients (4.01%) eligible to ICI treatment. Patients with nasopharyngeal cancer or breast cancer were not eligible because only grade 3 recommendations were available for these two cancer types.

Response

A total of 448 972 Chinese patients (19.20%), including 309 023 male patients (20.88%) and 139 764 female patients (16.29%), which accounted for 34.80% of the eligible patients, could respond to ICI treatment by estimation. Among the evaluated cancer types, NSCLC (n = 180 022, 7.70%), hepatocellular carcinoma (n = 75 648, 3.24%), and small-cell lung cancer (SCLC) (n = 64 362, 2.75%) were the top three cancer types with the highest number of responders (Figs. 1 and 4). This result was consistent in males (NSCLC, n = 123 676, 8.36%; hepatocellular carcinoma, n = 56 156, 3.79%; SCLC, n = 44 217, 2.99%) and females (NSCLC, n = 56 346, 6.57%; SCLC, n = 20 145, 2.35%; hepatocellular carcinoma, n = 19 492, 2.27%) (Fig. 3). Gynecological cancers contributed 7329 female responders (0.85%) to ICIs treatment.

Discussion

China is the most populous country in the world. Although a substantial increase in cancer survival has been achieved over the last decade, cancer is still the leading cause of death in China with over 3.9 million of newly diagnosed cases and 2.3 million of deaths annually [3,6]. The integration of effective cancer treatment

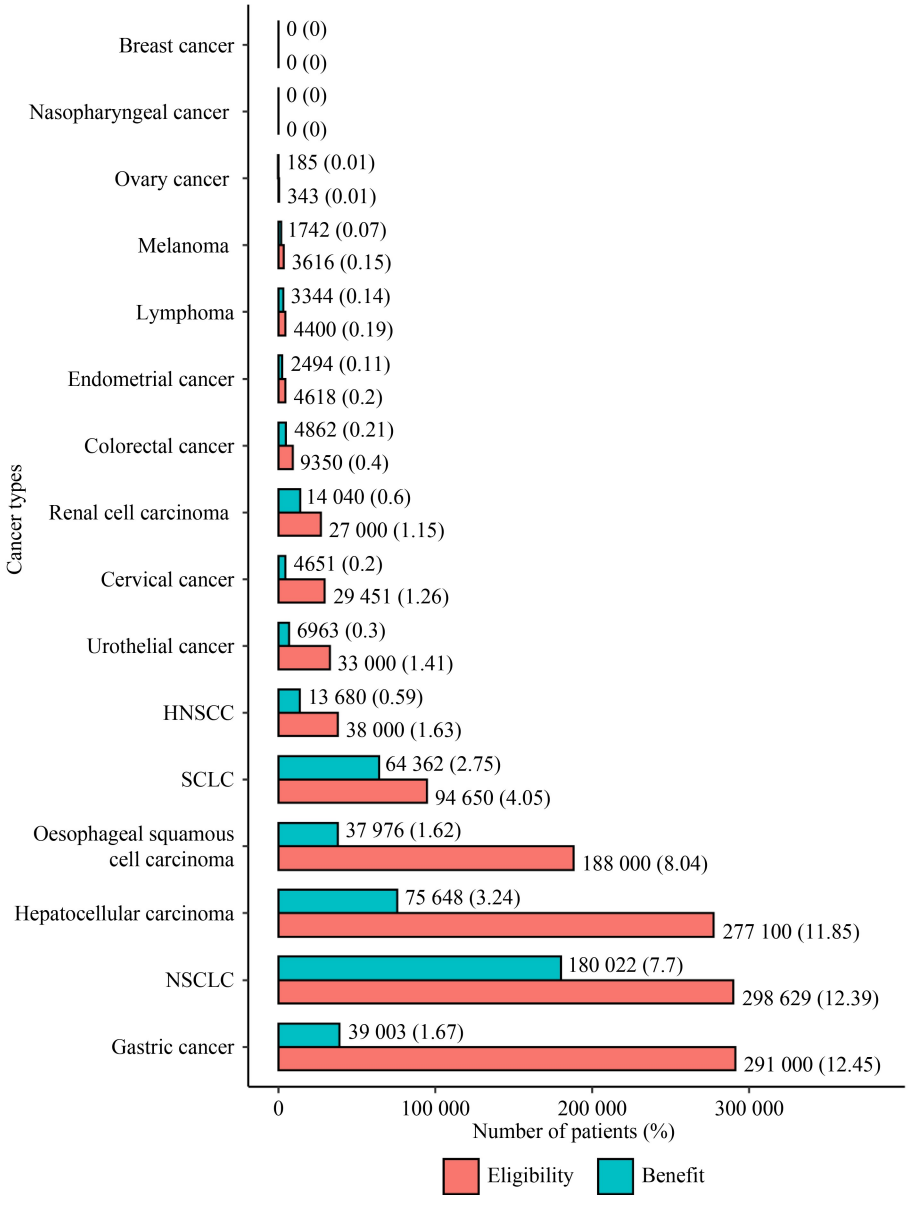

Fig. 1 Eligibility and benefit of ICIs for different cancer types. Non-melanoma skin cancers were not estimated for eligibility and response in Chinese patients because no cancer death statistics was available. HNSCC, head and neck squamous cell carcinoma; NSCLC, non-small-cell lung cancer; SCLC, small-cell lung cancer.

strategies, such as ICIs, into clinical practice and the evaluation of their clinical significance are important. To the best of our knowledge, this study is the first to quantitatively estimate the number of Chinese cancer patients who had eligibility and response to ICIs. A total of 17 cancer types were evaluated for diverse ICI-containing treatments, including 4 Chinese domestic ICIs. Our study found that about 1 290 156 patients (55.18%) were eligible for and 448 972 patients (19.20%) responded to ICIs annually in China. Considering the heavy disease burden in China, ICIs provide considerable benefit in Chinese cancer patients under optimal estimation.

A previous study suggested that about 44% of the US cancer patients were eligible for ICI treatment, and 13% of them could benefit from ICIs [12]. Our study demonstrated a higher percentage of eligibility and response in Chinese patients. Several factors could account for the difference. First, the US study was based on the FDA approvals while we used the CSCO guideline to represent the real-world setting, which might expand the scope of ICIs application. Second, China and the US exhibited different cancer patterns. For example, cancer of stomach, liver, and esophagus accounted for 34% of total cancer deaths in China but only accounted for less than 5% of cancer deaths in the US [4,6,13]. The use of ICIs was strongly recommended for these cancer types in

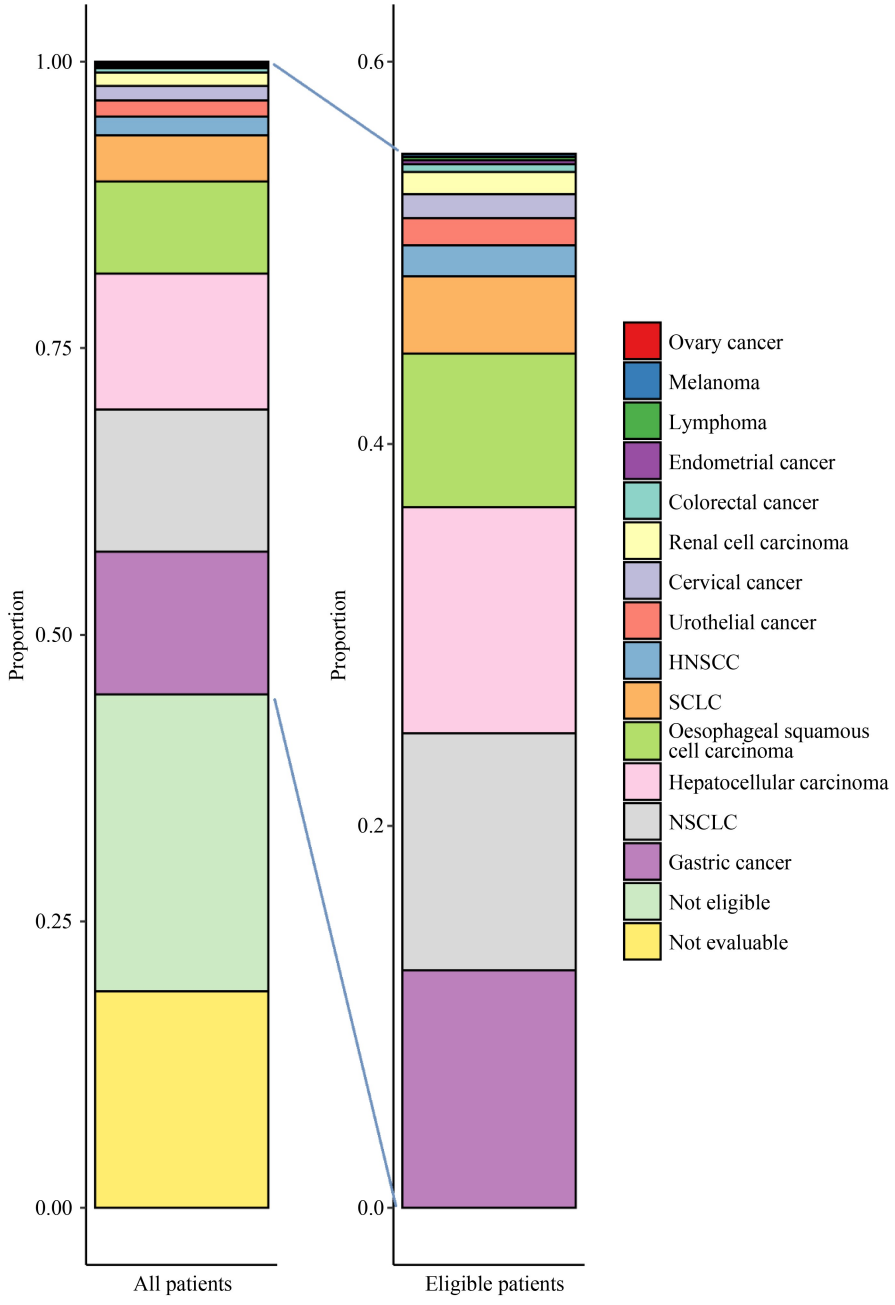

Fig. 2 Percentage of Chinese cancer patients who receive ICIs with eligibility. HNSCC, head and neck squamous cell carcinoma; NSCLC, non-small-cell lung cancer; SCLC, small-cell lung cancer.

the CSCO guideline, which contributed to the higher percentage of eligibility and benefited Chinese patients. Besides, previous studies have reported that Asian patients could obtain a higher survival benefit from ICI treatment compared with non-Asian patients [2].

When focusing on cancer-specific eligibility and response, a concordance was observed in our estimation and the cancer epidemiology in China. Lung cancer, liver cancer, and gastric cancer were the most common causes of cancer deaths in China, and most of the eligibility and response to ICIs was derived from these cancer types by estimation, indicating that developing effective ICI treatment strategies for common cancer types could generate maximum benefit [6]. Notably, the eligibility and response remained limited in some common cancer types in China. Breast cancer has been the most common cancer type in Chinese females with a trend of ascending incidence and mortality. Nearly two thirds of Chinese breast cancer patients were diagnosed with advanced disease, thereby suggesting the importance of systemic treatment strategies [14]. Although the combination of atezolizumab with nab-paclitaxel was approved by FDA

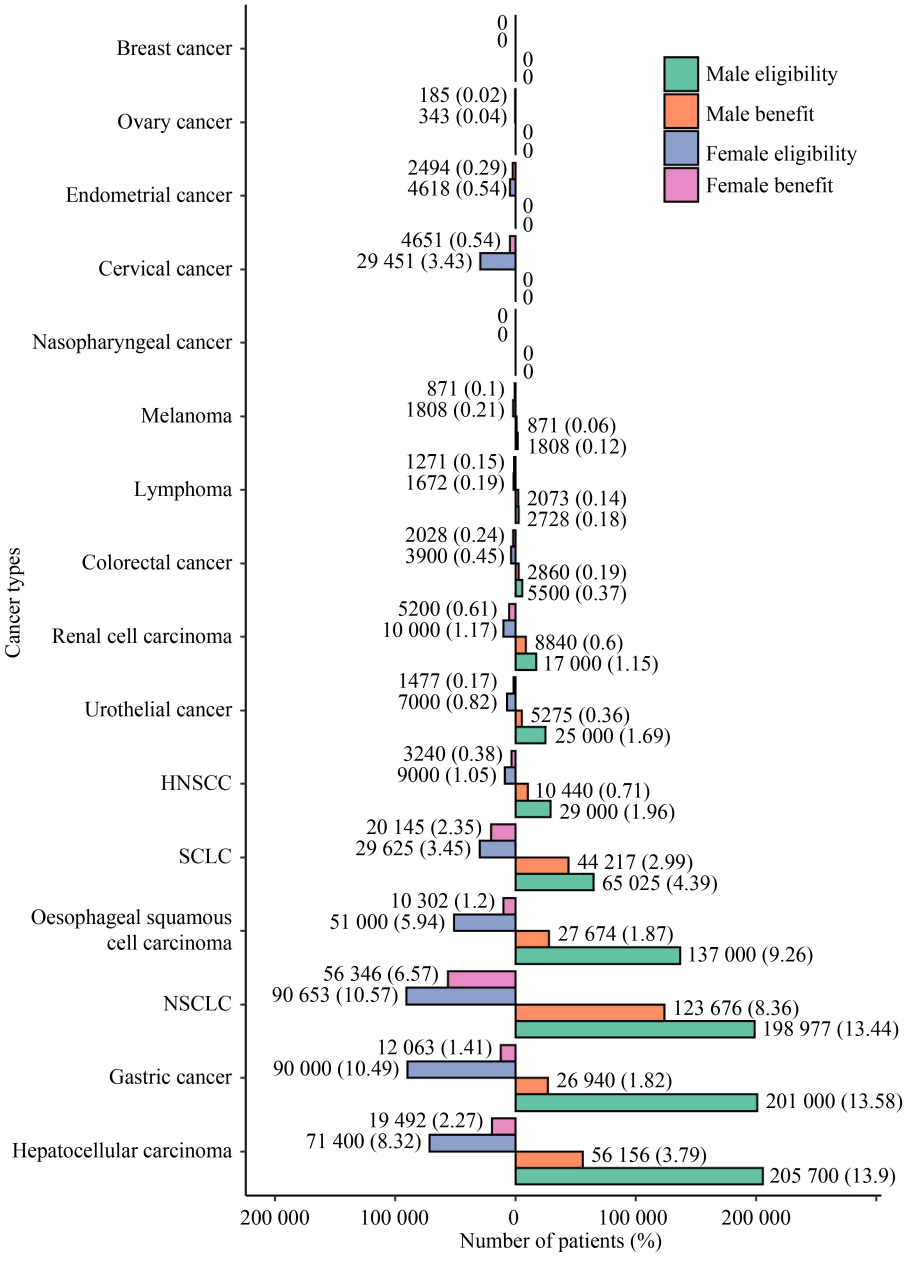

Fig. 3 Sex-specific eligibility and benefit of ICIs for different cancer types. Non-melanoma skin cancers were not estimated for eligibility and response in Chinese patients because no cancer death statistics was available. HNSCC, head and neck squamous cell carcinoma; NSCLC, non-small-cell lung cancer; SCLC, small-cell lung cancer.

in triple-negative breast cancer (TNBC) patients with positive PD-L1 expression, it was not listed as grade 1 or 2 recommendations in the CSCO guideline due to the lack of evidence in Chinese patients [15]. Moreover, considering that TNBC only accounted for about 15% of the total invasive breast cancer cases and the percentage of patients with positive PD-L1 expression ranged from 13% to 40%, the benefit was still limited even taking the FDA approval into account [16,17]. Similarly, colorectal cancer was the third most common cancer in China with an annual death of 388 000 patients. Patients eventually progressed after standard chemotherapy plus targeted therapy, and few later-line treatment options were available with limited benefit. In contrast with the pervasive need of effective treatment, ICIs only showed efficacy in MSI-H colorectal cancer, which accounted for 5% of all metastatic colorectal cancer cases [9]. Thus, the need to develop effective ICI treatment strategies for common cancer types is still unmet.

This study demonstrated a higher number and percentage of eligibility and response to ICIs in males than females. Although the overall cancer incidence and mortality were higher in males than females, the difference in eligibility and response could not be fully

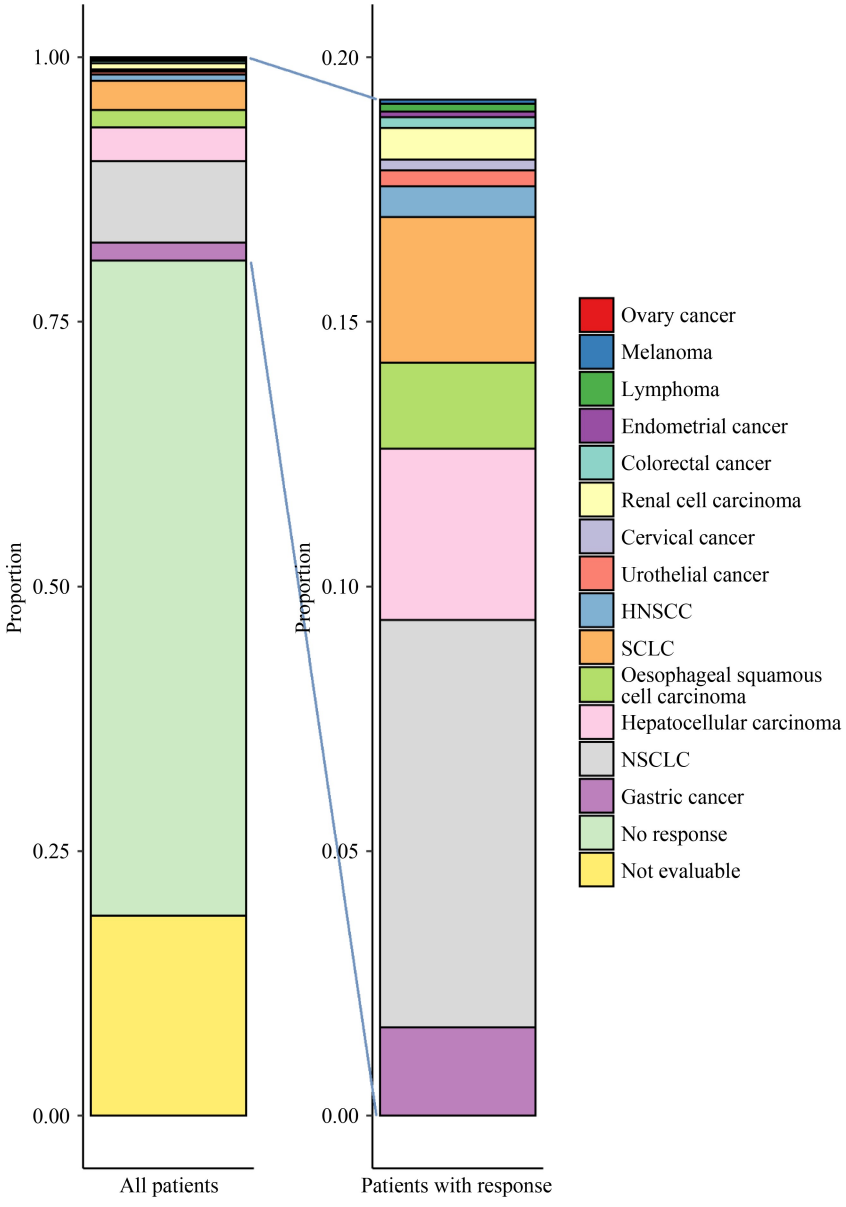

Fig. 4 Percentage of Chinese cancer patients who receive ICIs with response. HNSCC, head and neck squamous cell carcinoma; NSCLC, non-small-cell lung cancer; SCLC, small-cell lung cancer.

explained [3,6]. Notably, Chinese females exhibited distinct cancer patterns from males. Breast cancer, together with other gynecological cancers, accounted for 30% of annual cancer cases in Chinese female patients with ascending incidence and mortality over the last two decades. The burden of advanced disease was high, and the survival rate was generally unsatisfactory because of delayed diagnosis and inadequate treatment options, addressing the importance of effective systemic treatment for these female patients [14,18]. Nevertheless, by our estimation, only a small subset of these patients could benefit from ICIs, mostly for those with MSI-H cancers. More efforts should be paid on the development of effective ICIs treatment strategies for female cancer patients.

Although more than half of Chinese cancer patients were eligible for ICIs by estimation, only 19.20% of them could respond to ICIs. Because of the high cost and potential risk of immune-related adverse events, the population who can respond to ICIs treatment must be carefully selected [19,20]. Multiple predictive biomarkers, including indicators of tumor immunogenicity, such as MSI and tumor mutation burden, and indicators of patient immune milieu, such as circulating immune cell subsets, have been explored in current studies [21]. Integrative multivariable predictive models were also developed and had demonstrated predictive capacities superior to single biomarkers [22–24]. However, these strategies were

restricted in preliminary studies of small cohorts without a uniform methodological standard. Current FDA approvals and CSCO recommendations only required PD-L1 expression status, MSI-H or tumor mutation burden status in certain cancer types, whereas ICIs were still applied in a non-selected population for most cases [25]. Future studies should focus on the exploration and confirmation of integrative biomarkers in prospective large cohorts to optimize patient selection and maximize the clinical benefit of ICIs.

Approximately 441 180 patients (18.87%) had cancer types that were not evaluated in the guideline, including cancer types that were considered with limited systemic treatment options and poor prognosis, such as glioblastoma and pancreatic cancer (Supplementary material 3). Preliminary studies have suggested the potential efficacy of ICIs in these cancer types [26–29]. Novel ICI treatment strategies for these patients may also expand the quantitative benefit of ICIs.

This study has several limitations. First, we used the highest ORRs ever reported in clinical trials to provide an estimation regardless of clinical factors, including previous treatment lines and patient general conditions. However, the ORRs of ICIs vary among different treatment lines, and the expenses of drugs limit their availability [30]. Thus, our analysis only provides an optimal estimation that may deviate from real-world applications and exaggerate the benefit of ICIs. Second, we used ORRs to calculate the number of patients who have response to ICIs and represent the benefit of ICIs. However, the response pattern of ICIs is complicated and it remains a challenge to select the most suitable endpoint to evaluate the benefit of ICIs in clinical trials [31,32]. The long-term survival benefit of ICIs remains to be elucidated in future studies. Third, although we used the most updated cancer statistics and guideline to give the estimation, some recent advances were not included in this analysis [33]. Fourth, we did not investigate off-label use of ICIs beyond the guideline, which may exist in the real-world setting and is difficult to estimate. Fifth, bias may exist in the ORRs reported in the clinical trials, because nearly half of the included studies in the guideline did not involve Chinese participants. Future clinical trials should be conducted in Chinese populations to further validate the efficacy.

In conclusion, 1 290 156 patients (55.18%) were eligible for and 448 972 patients (19.20%) responded to ICIs annually in China under an optimal estimation, which suggested that ICIs could provide considerable benefit for Chinese cancer patients. To generate the maximum benefit of ICIs, future studies should focus on developing effective ICI treatment strategies for common cancer types (e.g., breast cancer, colorectal cancer) and implementing integrative biomarkers to optimize patient selection.

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Compliance with ethics guidelines

Kaili Yang, Jiarui Li, Lin Zhao, Zhao Sun, and Chunmei Bai declare no competing interests. This study was exempt from formal institutional board review because of its retrospective design and deidentified data.

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