Impact of competition on reimbursement decisions for cancer drugs in China: an observational study

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Summary

Background Annual Chinese National negotiations for including innovative drugs in the National Reimbursement Drug List (NRDL) reveal an increasing number of new drugs with overlapping action mechanisms of action and similar indications. Yet, it is unclear if competition affects reimbursement decisions. Thus, we explored the impact of competition on reimbursement decisions for cancer drugs in China.

Methods We identified the cancer drugs involved in NRDL negotiations from 2017 to 2022 and focused on the initial reimbursement decision for eligible newly negotiated drugs. Drugs were classified as within-class competitors based on their equivalent biological mechanisms of action and approved indications, including identified and potential competitors. Other variables included drug type, clinical benefit and safety, monthly drug cost, and disease incidence rate. We employed traditional univariate and multivariate Firth's penalized logistic regression to assess the association between reimbursement decisions and variables at the indication and drug levels.

Findings Between 2017 and 2022, 102 cancer drugs corresponding to 141 indications were studied, and 66 drugs (64.7%) covering 95 indications (67.4%) were added to the NRDL. The proportion of reimbursements for indications with identified competition was significantly higher than that for indications without identified competition (84.6% vs 52.6%, $p < 0.0001$). However, the difference in reimbursement proportions between groups with and without potential competition was not statistically significant (66.7% vs 68.3%, $p = 0.84$). Firth's penalized logistic regression showed that identified competition was positively correlated with successful NRDL inclusion, whereas potential competition had no significant effect on negotiation outcomes. Improved overall survival or progression-free survival were positively associated with NRDL inclusion, whereas disease incidence negatively impacted reimbursement decisions.

Interpretation Improved clinical benefit and identified competition were positively correlated with NRDL inclusion. In China's value-based negotiation model, clinical benefits served as a crucial foundation of price negotiation for cancer drugs, and market competition helped these drugs enter the NRDL at more reasonable prices. This has important implications for reimbursement decisions and accessibility and affordability improvement for innovative drugs worldwide.

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Keywords: Competition; Reimbursement; Cancer drug; Indication; China

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Research in context

Evidence before this study

We searched PubMed, Web of Science, and China National Knowledge Infrastructure, without language restrictions, for articles from database inception to February 1, 2024, using the terms ("reimbursement" OR "reimburse" OR "coverage") AND ("drug" OR "medicine" OR "medication"). We found that some studies had investigated the potential factors that might influence the reimbursement decision, including clinical benefit, drug cost, disease burden, and cost-effectiveness. However, as the number of innovative drugs with overlapping mechanisms of action and similar approved indications increases, a key question arises: does competition affect reimbursement decisions for innovative drugs? No studies to date have investigated this important issue. From 2017 to 2022, China negotiated over 100 approved cancer drugs into the National Reimbursement Drug List (NRDL), achieving substantial price cuts. However, the potential factors that might influence these negotiations have not been sufficiently explored.

Added value of this study

To our knowledge, this is the first study to systematically explore the impact of competition on reimbursement decisions for cancer drugs. This study identified the cancer drugs involved in NRDL negotiations from 2017 to 2022. Drugs were classified as within-class competitors based on their equivalent biological mechanisms of action and approved indications, including identified and potential competitors. Other factors included drug type, clinical benefit and safety, monthly drug cost, and disease incidence rate. We assessed the association between reimbursement decisions and variables at both the indication and drug levels and focused on the impact of competition. Our results showed that identified competition was positively correlated with successful NRDL inclusion, whereas potential competition had no significant effect on negotiation outcomes. In addition, improved overall survival or progression-free survival were positively associated with NRDL inclusion, whereas disease incidence negatively impacted reimbursement decision.

Implications of all the available evidence

Identified competition and improved clinical benefit were positively correlated with reimbursement decisions, which revealed an improved value-based negotiation model for China. Clinical benefits served as a crucial foundation of price negotiation for cancer drugs, and market competition helped these drugs enter the NRDL at more reasonable prices. China's negotiation model has achieved a balance between promoting innovation guided by clinical value and ensuring the affordability of health insurance funds. This has important implications for reimbursement decisions and accessibility and affordability improvement for innovative drugs worldwide.

Introduction

Innovative drugs usually have high price tags, uncertain long-term effectiveness, and safety profiles.[1] Thus, their financial toxicity challenges drug regulatory and healthcare financing systems. Countries approach drug pricing differently owing to the ongoing debate over the definitions and measurements of value.[2] China uses national value-based price negotiation to fund expensive innovative drugs,[2,3] which may profoundly impact local and global drug pricing and the pharmaceutical industry.

Since 2017, the government tried establishing a dynamic update mechanism of China's National Reimbursement Drug List (NRDL).[4] It implemented an innovative value model based on multiple criteria through negotiation between the payer in the healthcare system and pharmaceutical manufacturers to determine whether innovative drugs should be included.[5] The core task is to scientifically evaluate the comprehensive value of innovative drugs and generate the base price for negotiation. In 2023, 121 new drugs or indications entered the NRDL through negotiations, with an overall success rate of 84.6% and an average price reduction of 61.7%.[6]

Globally, previous studies have described the relationship between drug price and value[1,7–11] and some determinants of reimbursement decisions for cancer drugs.[12–17] However, as the number of marketed innovative drugs on the reimbursement list increases, more competition might impact negotiations and access to new drugs due to overlapping action mechanisms and similar approved indications. Thus, a key question arises: does competition affect reimbursement decisions?

Previous literature on national negotiation of innovative drugs in China focuses on establishing and developing this policy[18] and its impacts on medication price, utilization, accessibility,[19–21] and the financial burden of patients.[22] The evidence for the determinants of price negotiation and reimbursement decisions in China remains limited.[23,24] These existing studies were conducted at the indication level, as most cancer drugs have multiple indications, and the clinical benefits, incidence rates, and dosages might vary among different indications. However, NRDL and drug pricing management are based on the drug level instead of indication level in China. Thus, this study aims to explore comprehensive evidence for innovative drugs that might influence reimbursement decisions at both the indication and drug levels and focuses on the potential impact of competition.

Methods

Sample selection

This study examined cancer drugs participating in the NRDL negotiations between 2017 and 2022. We focused

on cancer agents in the present study because the high prices and increased number of eligible cancer patients led to a global crisis in both the affordability for patients and the sustainable development of healthcare systems. Additionally, cancer drugs outnumbered other therapeutic areas among the new NRDL-covered drugs through negotiation in China.[25]

Considering that the rules and scopes vary annually, we reviewed official documents from 2017 to 2022 and a list of drugs participating in negotiations. The list of negotiated drugs was not disclosed publicly in 2019. Therefore, we assumed this list based on the scope of negotiation in 2019.[26]

The scope of negotiation includes newly negotiated drugs and renewed drugs.[27] Newly negotiated drugs refer to new drugs without reimbursement approved in the past five years, which may be added to the NRDL through negotiation if the negotiations are successful. The negotiated drug contract lasts for two years, after which the contract needs to be renewed, and it is referred to as a renewed drug. If a new indication is approved during the two-year contract period, it is necessary to determine whether it can be reimbursed through renewal rules. This study focused on the first reimbursement decision for eligible newly negotiated drugs and excluded extensions of indications for drugs already listed in the NRDL. The study sample and the negotiation process[5,18] were shown in Fig. 1 and Supplementary Figure S1, respectively. The sample was restricted to on-patent chemical and biological cancer drugs, excluding generic, biosimilar, and diagnostic or prophylactic agents.

This study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines. It did not require institutional review board approval because the data were publicly available and did not include individual-level patient-identifying information.

Drug and indications

We reviewed the latest label and regulatory review documents for each cancer drug and indication in our sample to identify approved indications. Drug labels were obtained from publicly available data from the Center for Drug Evaluation[28] and the manufacturer's websites. Regulatory review documents summarize the evidence supporting indication approvals.

Drugs were categorized according to tumor type, innovation status, drug type, year of NRDL, and company. Furthermore, indications were grouped according to the cancer site and priority review. We extracted the drug mechanism of action from the "Pharmacological Action" section of the product label and categorized the first approved cancer drug in mainland China with the specific mechanism of action as a first-in-class drug.[2,29] We identified the innovation status of a drug based on whether it was first-in-class. Priority review information was obtained from the Center for Drug Evaluation.[30]

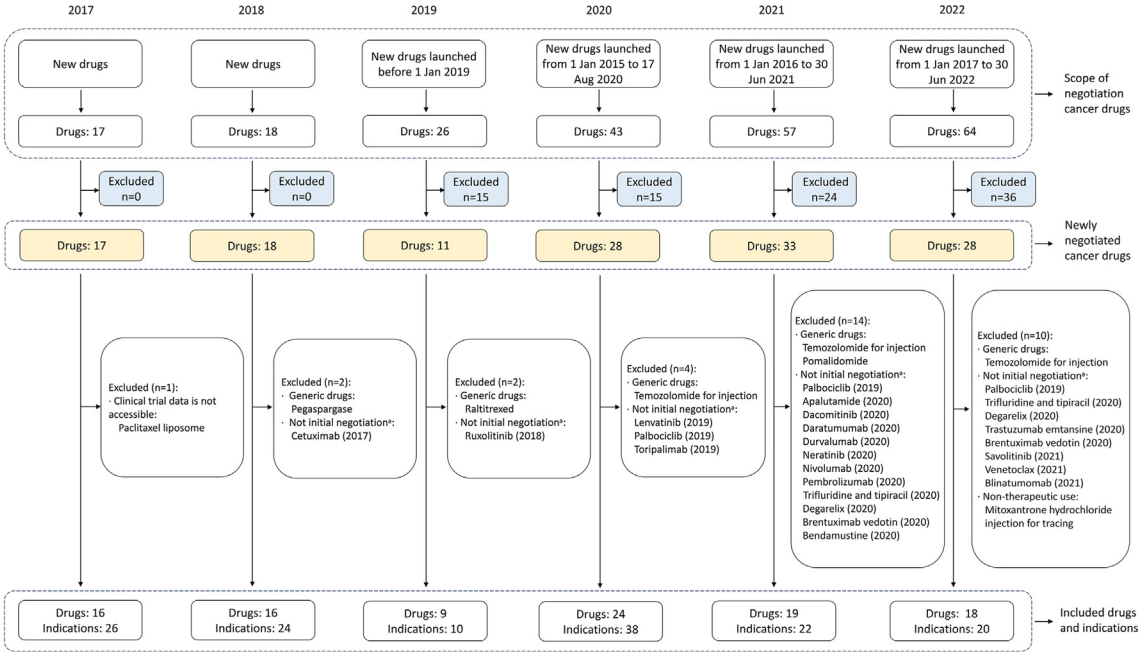

***Fig. 1:* Flowchart of target cancer drugs and indications selection**. The yellow box represents drugs not in the NRDL, and the blue box represents drugs already in the NRDL. [a] Drugs that are not subject to initial negotiations. The year in parentheses indicates the first time the drug participated in negotiations.

Drug competitions

Because the cancer drugs included in this study are exclusive products, we considered within-class competition among different generic name drugs that have a clinical substitution relationship, rather the competition between originator and generic drugs under the same generic name. Consistent with previous studies,[31] we grouped eligible cancer drugs into classes of similar products and considered them within-class competitors if they had equivalent biological mechanisms of action and were approved for the same indication (e.g., EGFR-TKIs in non-small-cell lung cancer).

Considering that current negotiation policies primarily focus on whether innovative drugs have comparative advantages over within-class drugs in the NRDL, we designated these competitors as identified competitors. Additionally, we also wondered whether competitors outside the NRDL might affect the negotiation results. Hence, we designated such competitors as potential competitors. Specifically, identified competitors are drugs listed in the latest version of the NRDL at the time the target drug was negotiated. Potential competitors refer to drugs not included in the NRDL at the time of target drug negotiation, including drugs that have been approved before the negotiation of the target drug, and drugs that will be approved within one year after the negotiation of the target drug. Due to the design of potential competition, cancer drugs participating in the NRDL negotiations between 2017 and 2022 were included in this study, and samples in 2023 were excluded. Because if cancer drugs in 2023 were included, this would mean that potential competitors should encompass all drugs outside the NRDL that were launched before December 31, 2024. However, it is currently not possible to obtain a complete list of drugs launched in 2024 at the time of this study. To make the classification of competition classes clinically meaningful, we categorized different competition classes based on existing literature[31,32] and opinions from qualified oncologists. Two investigators (YS and HJG), who were clinical pharmacists in oncology, independently judged within-class competitors for each indication. Another investigator (SC) resolved disagreements.

Clinical trials and clinical benefits

Pivotal trials supporting regulatory approval for each indication were identified from the latest labels and regulatory review documents. We extracted pivotal trial numbers, phases, designs, masking, and treatment outcomes for each indication. We designated an indication as showing improved overall survival (OS) or progression-free survival (PFS) if a significant difference (the P value reached the prespecified threshold specified in each pivotal trial) was found between the intervention and control groups. We calculated the median gains in OS or PFS only if they were available and statistically significant. For indications supported by multiple clinical trials, we selected the trial with the most favorable result.[33] Additionally we collected black-box information on the label as a proxy for drug safety. Two investigators (MNC and ANS) independently reviewed the clinical trials and clinical benefits, and another investigator (ZGZ) resolved disagreements.

Drug prices and monthly costs

We collected the latest prices of cancer drugs before they were negotiated from the Yaozhi database, which collects updated drug prices nationwide.[34] To ensure comparability with previous studies,[2,7,35] monthly drug costs were calculated for each indication based on an average adult with a body surface area of 1.7 m^2 weighing 70 kg with normal renal and hepatic function. The average monthly drug costs of the indication regimens were calculated based on indication-specific dosage regimens recommended in the latest label.[36] The average dosing schedule was used for indications involving multiple dosing schedules. All prices were converted into and reported in US dollars at an exchange rate of 7.17 from November 10, 2023 (US $1 = CNY ¥7.17).[37]

Epidemiologic burden of disease

Consistent with published literature,[38,39] the incidence rate associated with each indication was retrieved from the Global Burden of Disease (GBD) study for the Chinese population in 2019, if available,[40] otherwise from the latest clinical guidelines of specific cancers or value dossiers submitted by manufacturers for negotiation.[41–45] The reason we used GBD data instead of another important epidemiological data released by the National Cancer Center (NCC) of China[46] was that the classification of cancer type in GBD data is more consistent with that in this study. For example, the incidence of multiple myeloma and mesothelioma, which was required for this study, was available in the GBD data, but was not reported in the NCC data. The incidence rate was obtained for cancer entities, such as breast cancer or melanoma. Therefore, these data did not differentiate between distinct tumor subgroups and therapies.

Statistical analyses

This study was conducted at both the indication and drug levels. At the indication level, we included all indications of eligible cancer drugs at the first reimbursement decision; at the drug level, we selected the information of indications with the largest number of patients to describe the information of multi-indication drugs. Univariate analyses verified the association between reimbursement decisions and variables. For continuous covariates, a between-group comparison of the mean values was conducted using a t-test. For the comparison of categorical variable distributions across different groups, the chi-square test was initially

applied. In cases of small sample sizes, which were indicated by expected cell counts of less than five, the Fisher's exact test was performed to maintain the statistical validity of the results. The results with a two-sided $p < 0.05$ were considered statistically significant.

A multivariate logistic regression analysis using Firth's penalized method[47] was conducted to explore the determinants of reimbursement decisions for various indications and drugs. Firth's penalized logistic regression introduces a correction factor into the likelihood function, reducing bias and providing more accurate results on the relationships between covariates and outcomes.[48] The binary outcome of interest was the reimbursement status, classified as either 'yes' or 'no'. Two primary independent variables included the presence of identified competition and potential competition for each indication or drug. The model was further adjusted for several covariates: the status of PFS or OS improvement ('yes' or 'no'); the year of inclusion in the NRDL; the classification of the pharmaceutical company as either 'international' or 'domestic'; the innovation status of the drug, characterized as 'first-in-class' or otherwise; the provision of priority review ('yes' or 'no'); the monthly cost of the drug; the incidence rate associated with the disease; the drug type, as a multi-categorical variable; the classification of the tumor type as either 'solid tumor' or 'hematologic cancer'; and the presence of a black-box warning, also treated as a binary variable ('yes' or 'no').

Logistic regression analysis was performed using two sensitivity analyses to verify the robustness of the results. First, considering the assumed negotiation list for 2019, regression analyses were repeated at both the indication and drug levels by excluding the samples for 2019. Second, according to the competitor distribution, both identified competition and potential competition were set as multi-categorical variables ('0' or '1–2' or '>2') instead of dummy variables.

All statistical analyses were performed in R (version 4.2.1; R Foundation for Statistical Computing), utilizing the logistf package for Firth's penalized logistic regression.[49]

Role of the funding source

The sponsor of this study had no role in study design, data collection, data analysis, data interpretation, writing of the report, or the decision to submit for publication.

Results

Characteristics of sample and clinical benefit

We included 102 cancer drugs corresponding to 141 indications that met the eligibility criteria (Fig. 1 and Supplementary Table S1). Among these indications, most were for solid tumors (76.6%), and 33 (23.4%) were for hematological malignant neoplasms. The most

	All indication (n = 141)	Reimbursed indication (n = 95)	Non-reimbursed indication (n = 46)	p value
Tumor type				0.60
Solid tumor	108 (76.6%)	74 (77.9%)	34 (73.9%)	–
Hematologic cancer	33 (23.4%)	21 (22.1%)	12 (26.1%)	–
Innovation status				0.25
First-in-class	43 (30.5%)	26 (27.4%)	17 (37.0%)	–
Not first-in-class	98 (69.5%)	69 (72.6%)	29 (63.0%)	–
Cancer site				0.24
Lung cancer	29 (20.6%)	20 (21.1%)	9 (19.6%)	–
Lymphoma	20 (14.2%)	12 (12.6%)	8 (17.4%)	–
Breast cancer	15 (10.6%)	12 (12.6%)	3 (6.5%)	–
Leukemia	8 (5.7%)	6 (6.3%)	2 (4.3%)	–
Prostate cancer	8 (5.7%)	4 (4.2%)	4 (8.7%)	–
Liver cancer	6 (4.3%)	4 (4.2%)	2 (4.3%)	–
Melanoma	6 (4.3%)	5 (5.3%)	1 (2.2%)	–
Colorectal cancer	5 (3.5%)	3 (3.2%)	2 (4.3%)	–
Ovarian cancer	5 (3.5%)	5 (5.3%)	0 (0.0%)	–
Renal cell carcinoma	5 (3.5%)	5 (5.3%)	0	–
Gastric cancer	4 (2.8%)	3 (3.2%)	1 (2.2%)	–
Gastrointestinal stromal tumor	4 (2.8%)	3 (3.2%)	1 (2.2%)	–
Multiple myeloma	4 (2.8%)	3 (3.2%)	1 (2.2%)	–
Pan-tumor	4 (2.8%)	0	4 (8.7%)	–
Esophagus cancer	2 (1.4%)	1 (1.1%)	1 (2.2%)	–
Head and neck cancer	1 (0.7%)	0	1 (2.2%)	–
Nasopharyngeal carcinoma	1 (0.7%)	1 (1.1%)	0	–
Pancreatic cancer	1 (0.7%)	0	1 (2.2%)	–
Thyroid cancer	1 (0.7%)	1 (1.1%)	0	–
Other	12 (8.5%)	7 (7.4%)	5 (10.9%)	–
Drug type				<0.01
Small molecule	79 (56.0%)	66 (69.5%)	13 (28.3%)	–
Immune checkpoint inhibitor	22 (15.6%)	7 (7.4%)	15 (32.6%)	–
Monoclonal antibody	15 (10.6%)	11 (11.6%)	4 (8.7%)	–
Hormonal	10 (7.1%)	6 (6.3%)	4 (8.7%)	–
Cytotoxic	7 (5.0%)	3 (3.2%)	4 (8.7%)	–
Antibody–drug conjugate	5 (3.5%)	1 (1.1%)	4 (8.7%)	–
CAR-T	2 (1.4%)	0	2 (4.3%)	–
Other	1 (0.7%)	1 (1.1%)	0	–
Year of NRDL				<0.01
2017	26 (18.4%)	24 (25.3%)	2 (4.3%)	–
2018	24 (17.0%)	23 (24.2%)	1 (2.2%)	–
2019	10 (7.1%)	7 (7.4%)	3 (6.5%)	–
2020	39 (27.7%)	17 (17.9%)	22 (47.8%)	–
2021	22 (15.6%)	15 (15.8%)	7 (15.2%)	–
2022	20 (14.2%)	9 (9.5%)	11 (23.9%)	–
Company				0.02
International	101 (71.6%)	62 (65.3%)	39 (84.8%)	–
Domestic	40 (28.4%)	33 (34.7%)	7 (15.2%)	–
Priority review				0.02
Yes	92 (65.2%)	56 (58.9%)	36 (78.3%)	–
No	49 (34.8%)	39 (41.1%)	10 (21.7%)	–

Data are n (%). CAR-T, chimeric antigen receptor T-cell; NRDL, the National Reimbursement Drug List.

Table 1: **Characteristics of newly negotiated cancer drugs at the indication level.**

common cancer type was lung (20.6%), followed by lymphoma (14.2%) and breast (10.6%). Small molecules were the most common drug type (56.0%), followed by immune checkpoint inhibitors (15.6%) and monoclonal antibodies (10.6%). No statistically significant differences were observed in the distribution of tumor type, innovation status, and cancer site between the reimbursed and non-reimbursed indications. There were significant differences in the distribution of drug type, year of NRDL, company, and priority review between the two groups (Table 1). Sample characteristics at the drug level were similar to those at the indication level (Supplementary Table S2). The proportion of reimbursed indications and drugs from 2017 to 2022 was also shown (Supplementary Figure S2).

	All indication (n = 141)	Reimbursed indication (n = 95)	Non-reimbursed indication (n = 46)	p value
Phase				0.19
I or II	39 (27.7%)	23 (24.2%)	16 (34.8%)	–
III	102 (72.3%)	72 (75.8%)	30 (65.2)	–
Randomization				0.02
Yes	103 (73.0%)	75 (78.9%)	28 (60.9%)	–
No	38 (27.0%)	20 (21.1%)	18 (39.1%)	–
Masking				0.28
Yes	55 (39.0%)	40 (42.1%)	15 (32.6%)	–
No	86 (61.0%)	55 (57.9%)	31 (67.4)	–
Primary end point[a]				0.04
PFS	46 (32.6%)	37 (38.9%)	9 (19.6%)	–
ORR	38 (27.0%)	21 (22.1%)	17 (37.0%)	–
OS	37 (26.2%)	20 (21.1%)	17 (37.0%)	–
Other	33 (23.4%)	22 (23.2%)	11 (23.9%)	–
OS or PFS improvement				0.08
Yes	82 (58.2%)	60 (63.2%)	22 (47.8%)	–
No/Not Sure	59 (41.8%)	35 (36.8%)	24 (52.2%)	–
OS improvement				0.52
Yes	44 (31.2%)	28 (29.5%)	16 (34.8%)	–
No/Not available	97 (68.8%)	67 (70.5%)	30 (65.2%)	–
OS gain, median (IQR)	2.7 (2.0, 5.0)	2.8 (2.1, 5.0)	2.6 (1.9, 5.1)	0.58
PFS improvement				0.03
Yes	70 (49.6%)	54 (56.8%)	17 (37.0%)	–
No/Not available	71 (50.4%)	41 (43.2%)	29 (63.0%)	–
PFS gain, median (IQR)	4.1 (2.3, 5.8)	4.3 (2.9, 5.8)	2.7 (1.6, 4.7)	0.10
Black-box warning				0.59
Yes	25 (17.7%)	18 (18.9%)	7 (15.2%)	–
No	116 (82.3%)	77 (81.1%)	39 (84.8%)	–

Data are n (%). [a]Due to multiple primary endpoints in clinical trials for certain indications, the numbers of all categories under the "Primary endpoint" item do not sum up to the group totals. ORR, objective response rate; PFS, progression-free survival; OS, overall survival; IQR, interquartile range.

Table 2: **Comparison of clinical benefit and safety of newly negotiated cancer drugs reimbursed vs non-reimbursed at the indication level.**

Most indications (72.3%) were supported by Phase III randomized clinical trials. The most common primary endpoint was PFS (32.6%), followed by ORR (27.0%) and OS (26.2%). Only 82 (58.2%) indications showed a statistically significant improvement in PFS or OS (Table 2 and Supplementary Table S3). The differences between reimbursed and non-reimbursed indications did not reach statistical significance for median (interquartile range) gains in OS (2.8 [2.1–5.0]) vs 2.6 [1.9–5.1]; p = 0.58) and PFS (4.3 [2.9–5.8] vs 2.7 [1.6–4.7]; p = 0.10). No statistically significant difference was observed in the distribution of black-box warnings between the two groups (Table 2). The clinical trials and benefits at the drug level were similar to those at the indication level (Supplementary Table S4).

Characteristics of within-class competition

Our study comprised 77 drug classes (Supplementary Table S5). At the time of the negotiation, 76 indications (53.9%) had no identified competitors, 60 (42.6%) had no potential competitors, and 38 (27.0%) had neither identified nor potential competitors. There were 25 indications (17.7%) with one identified competitor, and four (2.8%) with at least six identified competitors. The distribution of potential competitors was similar to that of identified competitors (Supplementary Table S6).

The proportion of reimbursed indications with identified competition was significantly higher than that without identified competition (84.6% vs 52.6%, p < 0.0001). Meanwhile, there was no statistically significant difference in the proportion of reimbursed indications between the two groups with and without potential competition (66.7% vs 68.3%, p = 0.84) (Fig. 2).

Logistic model

When the regression analysis was performed at the indication level, the identified competition was significantly associated with a greater likelihood of NRDL inclusion. Meanwhile, potential competition was not significantly associated with reimbursement results. Indications for improved OS or PFS and those for domestic companies were significantly associated with a greater likelihood of NRDL inclusion. By contrast, the incidence rate of indications was significantly associated with a lower likelihood of NRDL inclusion (Table 3). When the analysis was performed at the drug level, regression results were consistent with those at the indication level (Supplementary Table S7).

The sensitivity analysis showed the results were robust. When the 2019 sample were removed, the regression result was consistent with the base-case analyses (Supplementary Tables S8 and S9). When competition variables were set as multi-categorical variables instead of dummy variables, the results

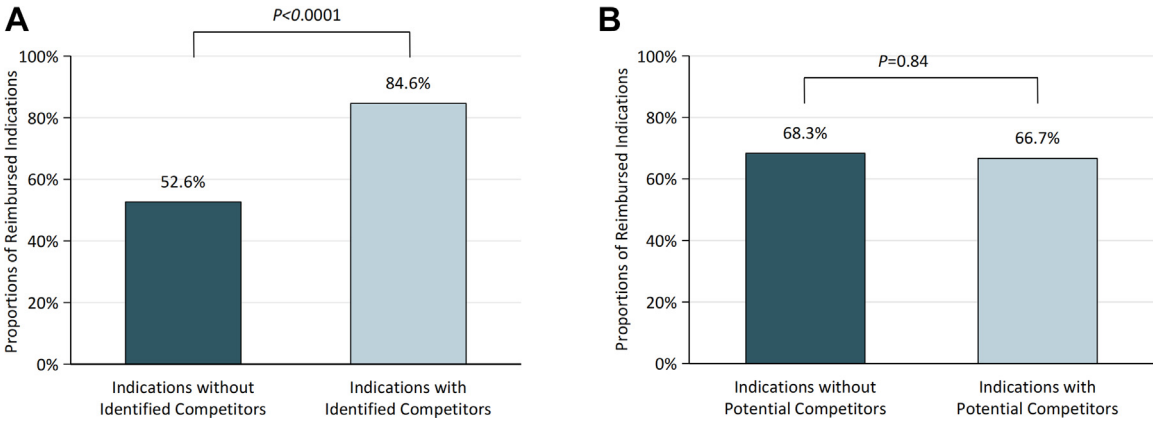

***Fig. 2:* Reimbursement results of indications with or without competition**. (A) Identified competiton, (B) Potential competition.

showed that, regardless of whether the number of competitors was relevantly small or large, the identified competition was significantly associated with a greater likelihood of NRDL inclusion. In contrast, potential competition was not significantly associated with reimbursement results (Supplementary Tables S10 and S11).

Discussion

To the best of our knowledge, this is the first study to systematically explore the impact of competition on reimbursement decisions for innovative drugs worldwide. Our study innovatively included two types of competitors: one was identified competitors for within-class drugs in the NRDL, and the other was potential competitors for within-class drugs outside the NRDL. The principal findings follow. First, identified competition was significantly associated with successful NRDL inclusion. Second, better clinical benefits (improved OS or PFS) significantly influenced the chances of NRDL inclusion. Third, the incidence rate was negatively correlated with reimbursement decisions. Fourth, this study was conducted at both the indication and drug levels, and the logistic regression results were consistent at both levels. The sensitivity analyses also showed the results were robust.

As the number of approved drugs increases, the drug market structure and competition landscape are undergoing rapid and far-reaching changes. The association between competition and drug pricing has been examined in developed countries.[11,31] However, until our study, no research has explored the impact of competition on reimbursement decisions. We found that identified competition was significantly associated with a greater likelihood of NRDL inclusion, while potential competition was not significantly associated with reimbursement results. This indicated that the main influence on the negotiation results of innovative drugs came from within-class competitors in the NRDL, rather than those outside it. The underlying mechanism of such effects might be that identified competition led to more reasonable and consistent expectations for drug pricing between the payer and manufacturers. According to the requirements of price negotiations in China, innovative drugs can only be included in the NRDL and reimbursed if health insurance payer and pharmaceutical manufacturers reach an agreement on the negotiated price. When an exclusively innovative drug lacks competitors in the NRDL, pharmaceutical manufacturers may have much higher expectations of drug price. If the benchmark price calculated by expert groups is much lower than the manufacturers' expectations, the negotiation would fail.

Our study found that the incidence rate was negatively correlated with reimbursement decisions. There were two possible explanations for this. The first explanation was that for cancers with high incidence rates, the large number of patients had a substantial budgetary impact on health insurance funds, which negatively affected the calculation of benchmark price. If the benchmark price was significantly lower than the manufacturers' expectations, the negotiation would fail and the drug would not be reimbursed. The second explanation was likely due to orphan cancer drugs. To encourage the development and reimbursement of drugs for rare diseases, many countries and regions have established special support policies. For example, in cost-effectiveness analyses for reimbursement decision in UK's National Institute for Health and Care Excellence, higher decision thresholds are used to justify higher prices.[38] In China, some scholars also suggested a higher threshold for the cost-effectiveness analysis of drugs for rare diseases.[50] It should be noted that in China's price negotiation, the impact of disease burden on the negotiation outcomes was more likely to attributed to the first explanation, because no indication in

	OR (95% CI)	p value
With identified competitor		
No	Reference	–
Yes	14.44 (2.68–77.86)	<0.01
With potential competitor		
No	Reference	–
Yes	1.62 (0.47–5.59)	0.45
Company		
International	Reference	–
Domestic	26.34 (4.47–155.29)	<0.01
Innovation status		
Not first-in-class	Reference	–
First-in-class	2.74 (0.58–12.95)	0.20
Priority review		
No	Reference	–
Yes	1.10 (0.26–4.59)	0.89
OS or PFS improvement		
No/Not sure	Reference	–
Yes	2.95 (1.03–8.47)	0.04
Black-box warning		
No	Reference	–
Yes	1.16 (0.16–8.46)	0.89
Year of NRDL		
2017	Reference	–
2018	1.20 (0.12–11.73)	0.88
2019	0.04 (0–0.50)	0.01
2020	0.04 (0–0.38)	<0.01
2021	0.08 (0.01–0.68)	0.02
2022	0.05 (0.01–0.44)	<0.01
Tumor type		
Hematologic cancer	Reference	–
Solid tumor	2.13 (0.49–9.28)	0.31
Drug type		
Other	Reference	–
Small molecule	1.71 (0.28–10.34)	0.56
Immune checkpoint inhibitor	0.36 (0.03–4.24)	0.41
Monoclonal antibody	1.88 (0.14–24.44)	0.63
Hormonal	0.23 (0.02–2.25)	0.20
Monthly costs (pre negotiation)	0.90 (0.79–1.03)	0.14
Disease incidence	0.97 (0.94–1.00)	0.04

OS, overall survival; PFS, progression-free survival; NRDL, the National Reimbursement Drug List.

Table 3: **Results of the logistic regression at the indication level.**

this study was identified as rare diseases.[51] Pricing of orphan cancer drugs is probably one of the major challenges for payers in China and abroad, which is a crucial research issue that needs further exploration in the future.

In China's value-based negotiation, whether an innovative drug is reimbursed by health insurance is the result of price negotiations, and price calculation should be based on multi-dimensional value evidence of the drug. Our study found that clinical benefits served as a crucial foundation of price negotiation for cancer drugs, and market competition helped these drugs enter the NRDL at more reasonable prices. This negotiation model has achieved a balance between promoting innovation guided by clinical value and ensuring the affordability of health insurance funds, which has important implications for reimbursement decisions and accessibility and affordability improvement for innovative drugs worldwide.

Our study also provided insights for the potential optimization and improvement of China's negotiation model in the future. Specifically, if an innovative drug prepared for negotiation has no competitors in the NRDL, it indicates a significant unmet clinical need for the disease. At this point, exploring a relatively higher price to facilitate the timely reimbursement of the drug can be considered. This model offers two advantages: firstly, it can improve patient access to the drug and motivate manufacturers to innovate based on clinical needs. Secondly, it can foster competition with subsequent similar drugs. By fully leveraging market competition, a more reasonable pricing of innovative drugs can be achieved. This improved pricing model will not lead to unreasonably high drug prices, as the renewal price adjustment mechanism in China ensures that the drug price does not exceed the initial negotiated price.[52]

Cancer drugs are increasingly approved for multiple indications of varying clinical benefit, and the pricing of such multi-indication cancer drugs is complex. In theory, indication-specific pricing (ISP) could help to better align the clinical benefit. In practice, countries or regions employ different methods, such as weighted-average prices (Germany, France), differential discounts (England, Scotland), as well as financial and outcome based managed entry agreements (Australia, Canada).[16,17] However, China still implements a pharmaceutical policy of one price for one drug.[53] High administrative costs of health insurance payer, fierce opposition of key stakeholders, and legal barriers are the main hurdles to implementing ISP in China. When a multi-indication cancer drug enters negotiations, the expert panel comprehensively considers the value of each indication. In this process, most experts tend to calculate the benchmark price based on the value information of the major indication. This is also the main reason why this study uses the information of the major indication to represent the drug information in the drug-level analysis.

Currently, the factors influencing reimbursement decision for innovative drugs are a topic of great interest worldwide.[12–17] These published have two main characteristics: Firstly, the focus was on cancer drugs. This may be due to the severe disease burden of cancer and the large number of innovative drugs approved globally. The prices of these drugs are usually extremely high, making the value assessment and timely reimbursement of these drugs particularly urgent and important.

Secondly, the influencing factors of reimbursement included clinical trial design, clinical benefits, drug costs, and disease burden. However, there was no study had investigated the potential impact of competition on reimbursement decisions until our study. Theoretically, competition might influence the pricing expectations of manufacturers and thereby affect reimbursement decisions. Nevertheless, systematically elucidating the role of competition is challenging due to potential confounding factors, such as superior clinical benefits of innovative cancer drugs. Therefore, our study conducted both univariate analyses and multivariate regression analyses, which consistently demonstrated a significant positive correlation between identified competition and reimbursement decisions. This study does fill a current gap in the literature and is crucial for a comprehensive understanding of factors influencing reimbursement decisions, including competition.

Price negotiations for innovative drugs in China have profoundly impacted global drug regulations, and currently, the US seeks to curtail excessive drug prices through price negotiations.[54–56] Pharmaceutical companies have long enforced astronomically high prices for prescription drugs in the US, resulting in millions of Americans being unable to access medications. The Inflation Reduction Act revolutionized Medicare drug pricing by authorizing the Health and Human Services Secretary to directly negotiate prices. On August 29, 2023, the Centers for Medicare and Medicaid Services announced the first 10 Medicare Part D drugs subject to the first round of price negotiation will take effect in 2026.[57] When we compare price negotiations between China and the US, some important disparities were observed (Supplementary Table S12). For example, the main objective of negotiations in China is to have drugs listed in the NRDL for reimbursement, whereas in the US, the primary goal of negotiations is to reduce drug prices. The principal finding of this study suggests that the impact of competition should be fully considered in price negotiations in the US to promote more reasonable drug prices. Meanwhile, the main criteria for selecting target drugs in the US negotiation, namely those on the market for many years with the highest drug costs, are also worthy of consideration for China's negotiation.

This study had some limitations. First, some information was not publicly available, such as the list of drugs that participated in the 2019 negotiations; therefore, we could only make assumptions based on the relevant policy. To explore the implications of this hypothesis on the results, we excluded all drugs in 2019 from the sensitivity analyses and found that the results were robust. Second, some OS and PFS data were unavailable when these cancer drugs were approved. Considering that these are the most common indicators of the clinical benefit of cancer drugs in the literature, the use of OS and PFS is conducive to the comparative analysis of our study with results from other countries. Third, value assessment and drug pricing are based on the comprehensive elements of objective evidence and the subjective opinions of experts. However, some possible influencing factors, such as expert characteristics and preferences, are difficult to obtain or measure objectively. Fortunately, this study includes the various variables involved in the existing literature, adds competition as an important independent variable, and explores the impact of competition on reimbursement decisions at both the indication and drug levels. Fourth, In the logistic model, due to small sample sizes in certain covariate groups, we focused on the directional trends of the odds ratios rather than their exact magnitudes. The chi-square test results, comparing the proportion of reimbursed indications among different groups (Fig. 2) were consistent with the findings from the multivariate logistic regression (Table 3). These findings demonstrated consistency in the directional trends, indicating the robustness of the observed associations.

Conclusion

Identified competition and improved clinical benefit were positively correlated with reimbursement decisions, which revealed an improved value-based negotiation model for China. Clinical benefits served as a crucial foundation for price negotiation for cancer drugs, and market competition helped these drugs enter the NRDL at more reasonable prices. This has important implications for reimbursement decisions and accessibility and affordability improvement for innovative drugs worldwide.

Contributors

HJG contributed to study design, data interpretation, and drafted the manuscript. YS contributed to study design, data analysis, figure production and critical revision of the manuscript. JFS contributed to data analysis, data interpretation, and critical revision of the manuscript. MNC, ANS and SL contributed to data collection, and critical revision of the manuscript. SC and ZGZ contributed to the entire project supervision. All authors read and approved the final manuscript. HJG and YS accessed and verified the data of this study. SC and ZGZ were responsible for the decision to submit the manuscript. HJG and YS contributed equally as the co-first authors. SC and ZGZ contributed equally as the co-corresponding authors.

Data sharing statement

All the data used in this study are from publicly accessible databases.

Declaration of interests

HJG has received grants from the National Natural Science Foundation of China (No. 72104151). All other authors declare no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanwpc.2024.101157.

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