Heliyon 9 (2023) e16059

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

A comparison between clinical decision support system and clinicians in breast cancer

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ARTICLE INFO

Keywords:
Clinical support system
Breast cancer
High level conformity
Concordance
Profession

ABSTRACT

Objective: We are building a clinical decision support system (CSCO AI) for breast cancer patients to improve the efficiency of clinical decision-making. We aimed to assess cancer treatment regimens given by CSCO AI and different levels of clinicians.

Methods: 400 breast cancer patients were screened from the CSCO database. Clinicians with similar levels were randomly assigned one of the volumes (200 cases). CSCO AI was asked to assess all cases. Three reviewers were independently asked to evaluate the regimens from clinicians and CSCO AI. Regimens were masked before evaluation. The primary outcome was the proportion of high-level conformity (HLC).

Results: The overall concordance between clinicians and CSCO AI was 73.9% (3621/4900). It was 78.8% (2757/3500) in the early-stage, higher than that in the metastatic stage (61.7% [864/1400], $p < 0.001$). The concordance was 90.7% (635/700) and 56.4% (395/700) in adjuvant radiotherapy and second-line therapy respectively. HLC in CSCO AI was 95.8% (95%CI:94.0%–97.6%), significantly higher than that in clinicians (90.8%, 95%CI:89.8%–91.8%). Considering professions, the HLC of surgeons was 85.9%, lower than that of CSCO AI (OR = 0.25,95%CI: 0.16–0.41). The most significant difference in HLC was in first-line therapy (OR = 0.06, 95% CI:0.01–0.41). When clinicians were divided according to their levels, there was no statistical significance between CSCO AI and higher level clinicians.

Conclusions: Decision from CSCO AI for breast cancer was superior than most clinicians did except in second-line therapy. The improvements in process outcomes suggest that CSCO AI can be widely used in clinical practice.

1. Introduction

Breast cancer has been one of the most commonly diagnosed cancer both in China and worldwide [1,2]. There has been an explosion in the available information related to the properties of drugs and biomedical parameters of patients ascribed to the vast

Abbreviations: CSCO, Chinese Society of Clinical Oncology; HLC, High level conformity; CDSS, Clinical decision support system.

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https://doi.org/10.1016/j.heliyon.2023.e16059
Received 30 March 2023; Received in revised form 28 April 2023; Accepted 4 May 2023
Available online 5 May 2023

population, which also brought substantial challenges to clinicians [3]. In recent years, especially over the last two decades, the approval and regulation processes for pharmaceutical agents have evolved and increased in complexity [4]. Hundreds of target drugs, large data sets related to genetic profiles from next-generation sequencing, and more traditional data from the real world are now easily obtainable. However, the selection of an optimal regimen for every single patient has become a daunting task. The growing data, which are moving beyond the comprehension and capabilities of clinicians, have been a heavy burden to them [5,6]. A novel technology platform to assist clinicians in effective therapy regimens selections with maximum therapeutic efficacy, and minimal adverse events to ensure a good quality of life for breast cancer patients is desperately needed [7,8].

A clinical decision support system (CDSS) is a computer system whose function is to promote clinicians to complete the knowledge acquisition, storage, application, and other projects by reading the expanding scientific literature and collating diverse electronic medical records. As one of the emerging fields, CDSS has played an important role in standardized treatment, chronic disease management, nursing, and other subjects [9–11]. In this respect, we also needed a CDSS for breast cancer patients to improve the efficiency of clinical decision-making.

A qualified CDSS should be set up based on guidelines and an appropriate database [12]. Since 2017, we have started publishing the Chinese society of clinical oncology (CSCO) guidelines for breast cancer [13]. Meanwhile, a database concerning the Chinese breast cancer population was also established in 2017. It has collected more than 90,000 invasive breast cancer cases with detailed information of cancer diagnosis, treatment and survival outcomes by January 2021 [14]. With the CSCO database and guidelines, we developed a novel clinical decision support system based on knowledge mapping and named as CSCO AI system for breast cancer patients in 2018. After inputting key information, this system can provide recommendations of treatment regimens and toxicity management for breast cancer patients. We then completed the phase I/II clinical trials to verify the function and effect of this newly applied system and found a 95% concordance between CSCO AI and CSCO guidelines [15]. Considering the lack of standards for recommending regimens after second line therapy, this system is therefore configured not to provide treatment regimens for this kind of patients. After that, we conducted this phase III study to further assess cancer treatment regimens given by CSCO AI and different clinicians.

2. Materials and methods

2.1. Study design and participants

This study was designed to compare the difference in regimens between clinicians and CSCO AI (research number: CSCO BC-AI 1901). Clinicians were classified into three levels according to their experience and professional titles, resident physicians with less than 5 years of experience as level 1, attending physicians with 5–10 years of experience as level 2 and chief physicians with more than 10 years of experience as level 3. Clinicians at different levels and professions were randomly chosen from different hospitals. Clinicians and CSCO AI were asked to access the chosen cases from the CSCO database independently. Afterward, an evaluation process would be carried out to assess all the regimens given by clinicians and CSCO AI.

Patients age 18–80 years with invasive breast cancer were selected from the CSCO BC database. Data secured included demographic, pathologic, surgical, medical, laboratory, and molecular data. Patients with complex breast cancer were selected because of the higher degree of uncertainty regarding their optimal treatment. Patients with complex breast cancer were defined as: those at high risk of recurrence (age $\leq$ 35 years, tumour $>$ 2 cm, axillary lymph node positive, human epidermal growth factor receptor 2 [HER2] positive, and triple-negative tumour) and those with established metastatic disease requiring first- or second-line therapy. 400 breast cancer patients were screened including 100 cases of newly diagnosis, post-operation, before the first-line, and after first-line therapy respectively. These 400 cases were randomly divided into 2 vol according to the hormone receptor and HER2 status. Two clinicians with comparable levels were randomly assigned one of the volumes (200 cases). CSCO AI was asked to assess all cases.

Both clinicians and CSCO AI should provide an optimal treatment regimen for each case. However, for postoperative cases, both adjuvant chemotherapy and endocrine regimens should be provided. In adjuvant target therapy and radiotherapy, there were only yes or no options for clinicians and CSCO AI to choose from.

There would be two different levels, level I and level II, of recommendations from CSCO AI. The programmer without any medical experience was asked to choose the first regimen in level I recommendations as to the final regimen. This study was approved by the Henan tumour hospital ethic committee (2018019).

2.2. Evaluation process

Two reviewers with more than 10 years of clinical experience were asked to evaluate the regimens from clinicians and CSCO AI separately and independently. Regimens were masked before evaluation. After evaluation, a third reviewer with more than 30 years of clinical experience gave the final score if there were different points between the prior two reviewers. Regimens from clinicians or CSCO AI were blinded to reviewers.

Scoring criteria were subdivided into 4 levels. Exactly conformity (3 points) was defined as the regimens following CSCO guidelines, clinical experience, and drug accessibility in China. Moderate conformity (2 points) was defined as the regimens being in accordance with CSCO guidelines while not by clinical experience or drug accessibility in China. Slight conformity (1 point) was defined as the regimens were not in conformity with CSCO guidelines while following clinical experience or drug accessibility in China. Inconformity (0 points) was defined as the regimens were not in accordance with CSCO guidelines or clinical experience. Both 3 and 2 points were regarded as high-level conformity.

Scores were given for initial therapy after diagnosis, adjuvant chemotherapy, adjuvant endocrine therapy, first-line therapy, and second-line therapy. No scores were given by reviewers in adjuvant target therapy and radiotherapy because there were only yes or no options for clinicians to choose from.

2.3. Outcomes

The primary outcome was the proportion of high-level conformity, which was defined as the proportions of patients with exact conformity (3 points) and moderate conformity (2 points). The second outcome was concordance rate which was defined as the percentage of the regimens with the same level of conformity (points) or the same decisions in radiotherapy and target therapy between clinicians and CSCO AI. Subgroup analyses of high-level conformity were performed in the statistical analysis plan, including clinician professions and different levels. Clinicians were stratified into three levels according to their working years and educational backgrounds. Level 1 was defined as those with less than 5 clinical experience and bachelor's degree, level 2 was defined as those with 5–10 clinical experience and master's degree, and level 3 was defined as those with more than 10 clinical experience and doctoral degree.

2.4. Statistical analysis

Standard descriptive statistics were utilized to characterize concordance and high-level conformity. Associations between variables were evaluated using the $\chi 2$ test (categorical variables). Multivariable analysis to identify clinicians and CSCO AI associated with the high-level conformity according to professions and levels was performed using logistic regression. Odds ratios (OR) and their 95% confidence interval (CI) were estimated with Mantel-Haenszel models. Comparisons between clinicians and the CSCO AI system in Table 2 were tested using the Wilcoxon signed-rank test. All analyses used SPSS 20.0 software, and the forest plot was drawn by GraphPad Prism 6.0. A two-sided α of less than 0.05 was considered statistically significant.

Table 1
Characteristics of chosen patients.

	Volume A N (%)	Volume B N (%)	P
Age			
Median(min-max)	46 (18–79)	48 (21–80)	–
KPS			
≥90	177 (88.5%)	172 (86.0%)	0.454
<90	23 (11.5%)	28 (14.0%)	
Menstruation			
Pre-menopause	123 (61.5%)	111 (55.5%)	0.223
Post-menopause	77 (38.5%)	89 (44.5%)	
Clinical T stage			
T1	88 (44.0%)	97 (48.5%)	0.194
T2	85 (42.5%)	87 (43.5%)	
T3	27 (13.5%)	16 (8.0%)	
Clinical N stage			
negative	86 (43.0%)	93 (46.5%)	0.482
positive	114 (57.0%)	107 (53.5%)	
TNM			
I	42 (21.0%)	52 (26.0%)	0.090
II	74 (37.0%)	85 (42.5%)	
III	84 (42.0%)	63 (31.5%)	
Phenotyping			
HR+/HER2-	108 (54.0%)	107 (53.5%)	0.996
HR+/HER2+	16 (8.0%)	17 (8.5%)	
HR-/HER2+	48 (24.0%)	47 (23.5%)	
HR-/HER2−	28 (14.0%)	29 (14.5%)	
Ki67			
Ki67 ≤ 30	77 (38.5%)	78 (39.0%)	0.918
Ki67 > 30	123 (61.5%)	122 (61.0%)	
G			
G1/2	129 (64.5%)	130 (65.0%)	0.917
G3	71 (35.5%)	70 (35.0%)	
Treatment status			
Initial diagnosis	50 (25.0%)	50 (25.0%)	1.000
Post operation	50 (25.0%)	50 (25.0%)	
After metastasis	50 (25.0%)	50 (25.0%)	
After first line therapy	50 (25.0%)	50 (25.0%)	

Table 2
Scores achieved by clinicians and CSCO AI.

	Professions	Clinician Mean ± SD	CSCO AI Mean ± SD	Difference	%	p
Initial therapy	Physician	2.61 ± 0.73	2.80 ± 0.56	0.19	7.3	<0.001
	Surgeon	2.59 ± 0.74	2.75 ± 0.63	0.16	6.2	0.001
	Overall	2.60 ± 0.73	2.78 ± 0.59	0.18	6.9	<0.001
Adjuvant chemotherapy	Physician	2.69 ± 0.65	2.76 ± 0.48	0.07	2.6	0.069
	Surgeon	2.50 ± 0.74	2.71 ± 0.53	0.21	8.4	<0.001
	Overall	2.61 ± 0.70	2.74 ± 0.50	0.13	5.0	<0.001
Adjuvant endocrine	Physician	2.75 ± 0.59	2.82 ± 0.46	0.07	2.5	0.067
	Surgeon	2.72 ± 0.60	2.80 ± 0.46	0.08	2.9	0.070
	Overall	2.74 ± 0.59	2.81 ± 0.46	0.07	2.6	0.010
First line therapy	Physician	2.85 ± 0.47	2.88 ± 0.33	0.03	1.1	0.359
	Surgeon	2.37 ± 0.81	2.89 ± 0.32	0.52	21.9	<0.001
	Overall	·2.64 ± 0.68	2.88 ± 0.33	0.24	9.1	<0.001
Second line therapy	Physician	2.75 ± 0.61	2.60 ± 0.77	−0.15	5.5	0.006
	Surgeon	2.04 ± 1.03	2.57 ± 0.82	0.53	26.0	<0.001
	Overall	2.44 ± 0.89	2.59 ± 0.79	0.15	6.1	<0.001

3. Results

A total of 14 clinicians from 4 hospitals with distinct professions and levels participated in this trial, 6 surgeons and 8 physicians. Among them, 6 clinicians were classified into level 1, 5 clinicians into level 2, and 3 clinicians into level 3. A total of 4900 regimens and options, 3500 for early-stage and 1400 for metastatic stage, were given by 14 clinicians, and 700 regimens were given by CSCO AI. Among them, 3500 regimens from clinicians and 500 regimens from CSCO AI were evaluated and scored by three independent reviewers. The clinical characteristics were shown in Table 1.

The overall concordance between clinicians and CSCO AI was 73.9% (3621/4900) (Fig. 1). It was 78.8% (2757/3500) in the early stage, higher than that in the metastatic stage (61.7% [864/1400], $p < 0.001$). The concordance was 90.7% (635/700) and 89.4% (626/700) in adjuvant radiotherapy and adjuvant target therapy respectively, yet the proportion was only 56.4% (395/700) in second-line therapy. There are also statistically differences in concordance between CSCO AI and the clinicians in different professions and levels, especially in the metastatic stage (supplemental figure).

High-level conformity in CSCO AI was 95.8% (479/500, 95%CI:94.0%–97.6%), significantly higher than that in clinicians (90.8%, 3178/3500, 95%CI:89.8%–91.8%). No statistical difference was shown in initial therapy (93.0%vs. 90.9%, $p = 0.481$), adjuvant chemotherapy (97.0% vs. 92.4%, $p = 0.139$), and adjuvant endocrine therapy (97.0% vs. 94.7%, $p = 0.462$) when compared with CSCO AI and clinicians. Instead, there was statistical significance in first-line therapy (99.0% vs. 92.1%, $p = 0.006$) and second-line therapy (93.0% vs. 83.9%, $p = 0.017$), which showed higher scores in regimens given by CSCO AI. (Fig. 2).

Considering professions, the high-level conformity of surgeons was 85.9% (Fig. 3A), lower than that of CSCO AI (OR = 0.25,95%CI: 0.16–0.41). In adjuvant chemotherapy, 90.3% of regimens from surgeons were evaluated as 2 or 3 points while it was only 69.0% in second-line therapy. The most significant difference in high-level conformity between surgeons and CSCO AI was in first-line therapy (OR = 0.06, 95%CI:0.01–0.41). There was no significant difference between physicians and CSCO AI even in different treatment stages. In second-line therapy, the high-level conformity of physicians was 95.0%, slightly higher than that of CSCO AI (93.0%), though

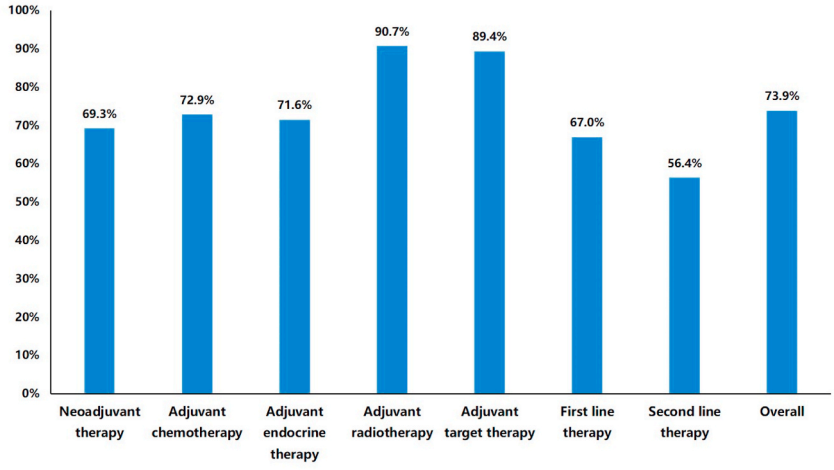


Fig. 1. Concordance between clinicians and CSCO AI.

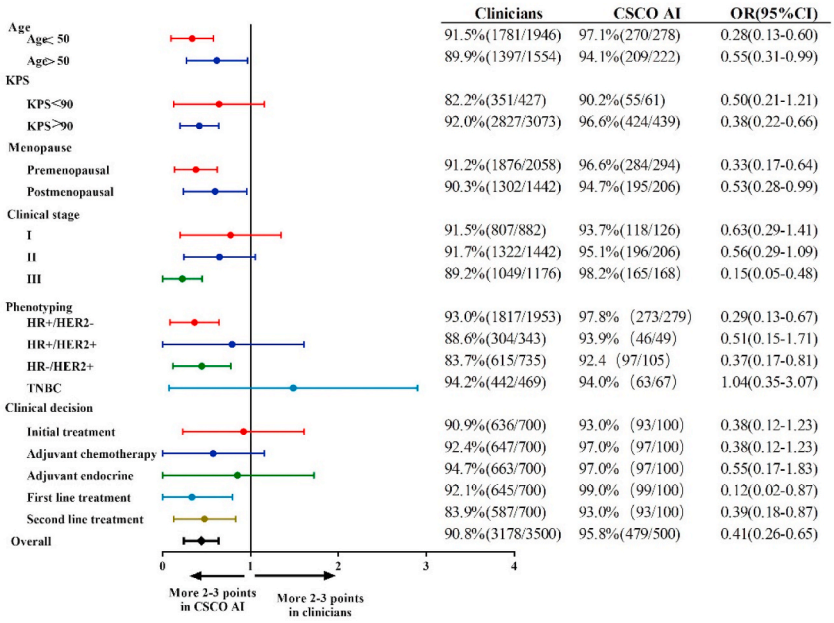


Fig. 2. High-level conformity between clinicians and CSCO AI.

without significant difference (OR = 1.43, 95%CI:0.59–3.48).

When clinicians were divided according to their levels, the high-level conformity of clinicians was significantly lower than that of CSCO AI ($p < 0.05$). However, there was no statistical significance between CSCO AI and level 2 or 3 clinicians (Fig. 3B). In the early stage, there was no significant difference in high-level conformity between level 1 clinicians and CSCO AI in neoadjuvant therapy (OR = 0.48,95%CI:0.20–1.12) and adjuvant endocrine therapy (OR = 0.74,95%CI:0.20–2.76). The most significant difference was shown in first-line therapy (OR = 0.06,95%CI:0.01–0.48).

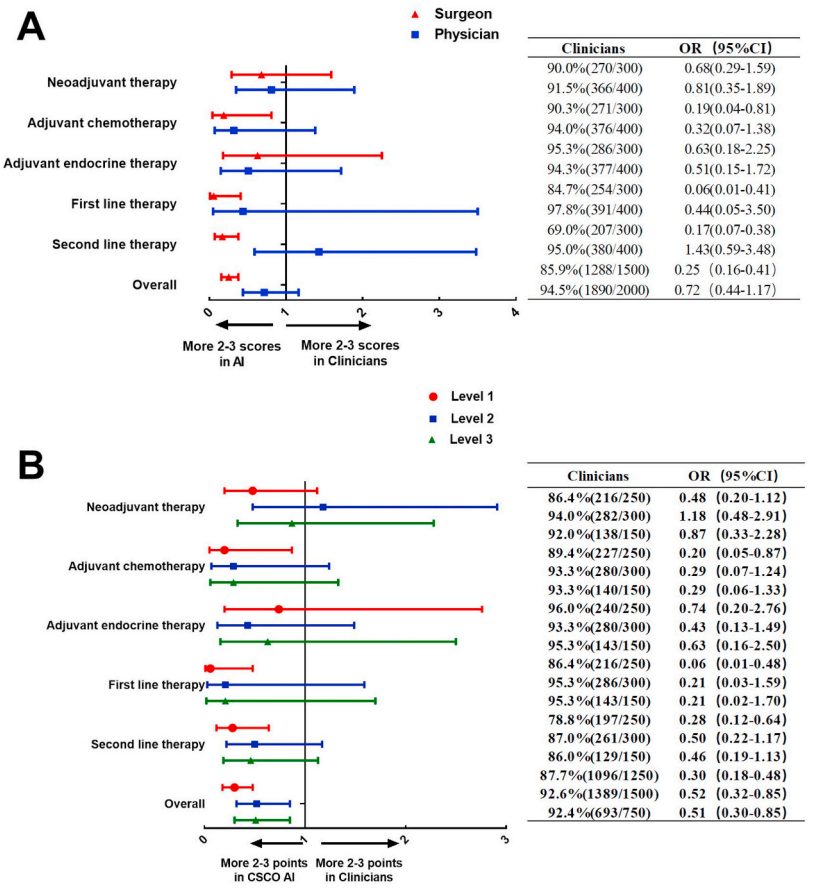
The Wilcoxon signed-rank test was used to compare the difference between clinicians and CSCO AI. Scores from CSCO AI were significantly higher than that from clinicians in each treatment stage, especially in first-line therapy ($\Delta = 0.24$, $p < 0.001$) (Table 2). The difference varies depending on different professions. 300 regimens from 6 surgeons received an average of 2.72 ± 0.60 score in adjuvant endocrine therapy, with no significant difference when compared with that from CSCO AI (2.80 ± 0.46, $p = 0.070$). Regimens from 8 physicians in adjuvant chemotherapy ($p = 0.069$), adjuvant endocrine therapy ($p = 0.067$), and first-line therapy ($p = 0.359$) showed no significance when compared with that from CSCO AI. Physicians got a 2.75 ± 0.61 score in second-line therapy, significantly higher than that CSCO AI did (2.60 ± 0.77, $p = 0.006$).

4. Discussion

As the first CDSS concerning breast cancer in China, we used a double-blind evaluation process to verify this system. From this study, we found the concordance between clinicians and CSCO AI had reached 73.9%. Higher concordance was seen in the early stage when compared with that in the metastatic stage. Considering the conformity, CSCO AI achieved 95.8% high-level conformity, much higher than clinicians did. Besides, the high-level conformity of CSCO AI was similar to that of physicians, while superior to that of surgeons or junior clinicians, especially in metastatic stages. In second-line therapy, CSCO AI makes inferior decisions when compared with physicians, suggesting the possible limitations in promoting CSCO AI application.

There has been a long history of the development of CDSS in cancer [16]. Watson for Oncology (WFO) system, established by memorial Sloan Kettering cancer centre breast cancer training cases, is one of the most popular CDSS in cancer ever since. In 2018, Indian oncologists conducted a study [17]assessing the level of agreement regarding cancer treatment between WFO and the multidisciplinary tumour board. The study showed a 93% concordance between clinicians and WFO. However, the concordance in this trial was defined as the clinicians' recommendation corresponding to the 'recommended' or 'for consideration' categories of WFO. It would be 62% if only the 'recommended' option was included. To further the application of WFO in China, we also started a phase III trial to compare the concordance between clinicians' decisions and their decisions with WFO [18–20]. The adherence of clinicians' decision to National Comprehensive Cancer Network guidelines was 82%, however, it was only 56% when compared with CSCO guidelines. The special situation and guidelines in China have become an important factor limiting the use of WFO in this country. Under this circumstance, a novel qualified CDSS consistent with native guidelines and clinicians' decisions are needed.

In this study, we used a double-blind method to score the decisions from clinicians and CSCO AI systems at the same time, and then compared the scores between clinicians' regimens and level I recommendations in the CSCO AI system, whose definition is similar to the 'recommended' option in WFO. We found an overall 73.9% concordance between CSCO AI and clinicians. This is significantly



A, high-level conformity according to professions;

B, high-level conformity according to different levels of clinicians

Fig. 3. High-level conformity according to clinicians professions and levels A, high-level conformity according to professions; B, high-level conformity according to different levels of clinicians.

higher than that between WFO and clinicians, especially in adjuvant target therapy. Treatment decisions in these cases are challenging because disagreement may occur even among experts due to the different local practice patterns. Meanwhile, socioeconomic status, and variability in available therapeutic modalities results from regulatory approval and economic factors may also have impact on the decisions from clinicians. Remarkably, only 21.4% of clinicians selected in this study were level III clinicians, and the clinicians gave the regimens without any training before. These factors may contribute to an underestimated concordance compared with the real world. In the next step, CSCO AI and the same clinicians, with the help of CSCO guidelines, would assess again the same cases. The comparison between the two groups would show the actual concordance between CSCO AI and clinicians.

The increasing reasonable regimens contributed to the less reliability of concordance [21]. For example, both TC and AC-T are options for a moderate-risk patient to receive adjuvant chemotherapy. However, according to the scoring criteria, it could be 3 points for TC while 2 points for AC-T. The endpoint of concordance can hardly show the real efficacy if clinicians chose AC-T while CSCO AI chose another. The mayhem caused by concordance has brought about substantial changes in choosing another indicator. In our study, high-level conformity from an independent, double-blind scoring process was used to classify all the regimens from clinicians and CSCO AI [22]. Although the concordance was only 73.9%, the high-level conformity was as high as 90% in clinicians and CSCO AI, showing that high-level conformity is a more reasonable endpoint than concordance. As high as 95.8% of high-level conformity also suggests the significant advantages of decision-making by CSCO AI over that by a clinician alone, especially in first line and second line therapy. In addition, for hormone receptor positive and HER2 negative patients, high level conformity from CSCO AI was 97.8%, significantly higher than that from clinicians. The low odd ratios suggest the complexity of decision-making in this type of patient.

To further explore the efficacy of CSCO AI, clinicians were classified according to their professions and levels. When compared with surgeons or low-level clinicians, CSCO AI had a higher proportion of high-level conformity, especially in the metastatic stage. The difference in this conformity was no longer significant when compared with physicians. Two reasons may bring about this diversity.

For one thing, the CSCO AI system is designed to help clinicians choose the optimal therapy for breast cancer patients. The internal logic program is more akin to the multidisciplinary tumour boards' pattern. For another, the further division of the professions and controversies over surgery in advanced breast cancer [23] leads the surgeons to pay less attention to the metastatic stage. The above two reasons determine the low conformity of surgeons or low-level clinicians in the metastatic stage. The disparities in decision-making from different professions and levels also showed the necessity of CDSS promotion to pursue high-quality decision-making.

Notably, in second-line therapy, CSCO AI got a lower score when compared with physicians. Decisions on cancer therapy are a complicated process [24] and would be determined by clinicians' experience, the patients' willingness, previous treatments, and physical conditions [25]. The complex disease and limited data decreased the accuracy of conformity from CSCO AI in second-line and subsequent therapy lines in breast cancer [26]. Comparatively, it is easier for clinicians to take all the factors into account, especially for physicians and high-level clinicians. The decision in the second line may become the watershed between clinicians and CSCO AI.

There were also some limitations in this study. For instance, the clinician selection bias may directly determine the result of this study [27]. Besides, increases in the experience of treating physicians over time and improvements in decision support technology may produce different results in subsequent time periods. To complete a large number of cases within a limited time can also affect the accuracy of the decision from clinicians. Several actions were taken to reduce the possible bias. First, clinicians with CSCO guidelines will assess the same cases and will be compared with CSCO AI afterward. Second, to minimize possible errors from clinicians due to their fatigue or other reasons [28], we add some options such as neoadjuvant therapy or not, target therapy or not. Third, in addition to the double-blind scoring process, we also required the designer of this study to avoid participating in the process of this study from choosing clinicians to scoring [29].

In conclusion, there are differences in decision-making when compared with the CSCO AI system and clinicians according to different professions and levels, which also suggest that CSCO AI can be widely used in clinical practice.

Author contribution statement

Jianbin Li: performed the experiments; analyzed and interpreted the data; wrote the paper. Li Bian, Yuan Yang, Qiang Lin, Hua Yang, Li Ma, Ling Xin, Feng Li, Shaohua Zhang, Tao Wang, Yinhua Liu: contributed reagents, materials, analysis tools or data. Zefei Jiang: Conceived and designed the experiments; wrote the paper.

Written informed consent

All the participants gave 'written informed consent' to take part.

Data sharing

Access to the dataset supporting the conclusion of this article can only legally be accessed on acceptance from the Chinese Society of Clinical Oncology breast cancer database collaborative group. Interested parties can contact the corresponding author for further information. We confirm that others would be able to access these data in the same manner as the authors. We also confirm that the authors do not have any special access privileges that others would not have.

Funding statement

This work was supported by the Beijing Science and Technology Planning Project (Grant numberZ181100001718215) and the innovative projects of PLA general hospital (Grant number CX19011)

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e16059.

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