Cognitive adverse events in patients with lung cancer treated with checkpoint inhibitor monotherapy: a propensity score-matched analysis

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Summary

Background Cancer-related cognitive decline is a serious problem in long-term survival but no pivotal study has investigated whether checkpoint inhibitors (ICI) may be associated with cognitive adverse events.

Methods This propensity score-matched analysis recruited non-small cell lung cancer (NSCLC) patients prescribed with or without ICI monotherapy from three Chinese tertiary hospitals. Patients were excluded from study who developed brain metastasis or had disorders severely affecting cognitive abilities. Primary outcomes were changes in neuropsychological battery test (NBT) at baseline, 6- and 12-month sessions, and any NBT score changes that exceeded 3*SD of baseline scores would be marked as objective cognitive adverse events (CoAE). Secondary endpoint was the 20-item Perceived Cognitive Impairment (PCI) sub-scale score change in Functional Assessment of Cancer Therapy-Cognitive Function questionnaire, administered at baseline, 3-, 6-, 9-, 12-, and 15-month follow-up session. Per-protocol ICI and control arms were matched with propensity scores that incorporated baseline variables to compare both NBT and PCI assessment results. Patients participating in PCI assessments were analysed in intention-to-treat analysis. Kaplan–Meier survival curves with log-rank tests were adopted to analyse incidence of perceived cognitive decline events (PCDE).

Findings Between March 12, 2020, and March 28, 2021, 908 participants were enrolled. Compared to control, 3 of 4 subtest of NBT scores in ICI arm showed significant cognitive decline in 6- and 12-month sessions, in which Trail Making Test score change (13.56 ± 11.73) reached threshold of cognitive deficit diagnosis in the 12-month session. In 1:1 matched 292 pairs from 908 patients, PCI score changes in ICI arms were −4.26 ± 8.54 (3rd month), −4.72 ± 11.83 (6th month), −6.16 ± 15.41 (9th month), −6.07 ± 15.71 (12th month), and −7.96 ± 13.97 (15th month). The scores were significantly lower than control arm in 3-, 6-, and 12-session follow-up. The result was validated after adjusting quality

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of life scores and in intention-to-treat analysis. Mean PCI change exceeded 1/2 SD of baseline PCI score (5.81) in 9-, 12-, and 15-month sessions in ICI arm, but not in control arm. PCDE incidence/prevalence was significantly higher in ICI arm (incidence 26.4% vs. 5.1%, and prevalence 16.2% vs. 1.7%). Immune-related adverse events related to incidence of PCDE after adjusting for baseline variables.

Interpretation ICI monotherapy seemed to relate to higher cognitive decline represented by score changes and incidence/prevalence rates. The decline deteriorated as treatment progressed, and immune-related adverse events seemed to be associated with higher cognitive adverse events incidence in the ICI treatment.

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Keywords: Checkpoint inhibitor; Cognitive adverse events; Minimal clinically important difference; Propensity score matching; Immune-related adverse events

Research in context

Evidence before this study

Long-term immunotherapy treatment may cause adverse immune events related to cognitive impairment. Small reports of cognitive decline associated with immune checkpoint inhibitors have not been able to provide conclusive evidence, and larger cohorts are currently lacking to investigate independent effects in patients at the beginning of treatment.

Added value of this study

Therefore, we followed cancer patients enrolled in real-world settings who receive or did not receive ICI monotherapy for 15 months and compared changes in cognitive adverse events (CoAE) incidence/prevalence with propensity score matching (PSM). The results showed that ICI monotherapy was significantly associated with cognitive decline severity, and CoAE occurrence. They were more severe in later follow-up than in earlier follow-up, and immune-related adverse events in ICI treatment appeared to be associated with a higher incidence of CoAE.

Implications of all the available evidence

This study is the first longitudinal study to investigate effect of ICI monotherapy on mid-term cognitive changes in cancer patients in a relatively large-sample study. Immunotherapy may affect cognitive performance both in objective tests and in subjective reports.

Introduction

Cancer-related cognitive decline (CRCD) is prolonged and subtle changes in cognitive function in cancer patients receiving active treatment. Subjective changes range from 16% to 60%.[1] Inciting agents are generally attributed to chemotherapy and for this reason, CRCD is referred to as "chemobrain".[1] Recent studies found constitutional changes during cancer therapy in elderly patients.[2] Studies of lung cancer suggested that when comorbid with autoantibodies, patients suffered from a greater level of cognitive decline.[3] More recently neurobiological mechanisms behind CRCD were found that involve tumor biology, diagnosis-related stress, and treatment-associated neuropathy.[3,4] In non-small cell lung cancers (NSCLC), one of the most prevalent mechanisms of cognitive impairment is inflammation or immune-related central neurological damage.[3] Studies found strong associations between self-immunity and cognitive decline in patients with neuronal auto-antibodies.[3] Also, links between T- and B-cell activity and cognition have been observed.[5]

Immunotherapy in recent years has revolutionised the management and survival outcome in NSCLC. Immune checkpoint inhibitors (ICI) that blocked T cell inertia during immune attack against cancer cells may sometimes activate off-target T cells into action systemically. Growing evidence of immune-related adverse events (irAE) in the context of long-term treatment leads to concerns of sub-clinical neuro-inflammation or autoimmunity that may ensue in cognitive impairments.[1] Preclinical non-cancer models found protective effects of ICIs on tau-related neuropathy, but in human patients with melanoma, immune-related changes in autoantibodies were found to result in cognitive decline.[6–9] Small-scale ICI-related cognitive decline reports did not give conclusive evidence,[10] and there are lack of larger-scale cohorts to investigate independent effects in chemotherapy-naive patients. Moreover, confounding bias of cancer biology or paraneoplastic syndromes should be considered as well because of possible effects on CRCD.[11] Thus, we did a propensity score-matched (PSM) comparison in cancer patients

with or without ICI monotherapy in real-world settings to identify independent effects on cognitive functions.

Methods

Research setting

The prospective, consecutively-recruiting study was approved by institutional review boards of the Second Affiliated Hospital of the Shantou University Medical College, and procedure was performed according to Helsinki Declaration. Included patients gave written informed consent to the study. We recruited treatment-naive patients with NSCLC scheduled to receive ICI monotherapy from following research sites: Department of Medical Oncology in First Affiliated of Zhengzhou University, Department of Thoracic Surgery of Hainan Hospital of People's Liberation Army General Hospital, and Cancer Registry Database of Sun Yat-Sen Cancer Centre, from March 12, 2020, to March 28, 2021. In the same research setting, control group included lung cancer patients without medical treatment after surgical resection. Primary aim was to compare treatment-associated cognitive function changes with or without ICI monotherapy.

Patient recruitment

Based on the inpatient record and oncologist prescription data on whether to initiate ICI therapy, patients were recruited to participate in full-length follow-ups if inclusion and exclusion criteria were met. The inclusion criteria were as follows: 1) patients were diagnosed with NSCLC, treatment-naive, scheduled to have ICI monotherapy (ICI arm) or medical checkups only (control arm); 2) over the age of 35 (NSCLC incidence is low in individuals younger than 35 years) and speak Chinese; 3) Eastern Cooperative Oncology Group Performance Scores (ECOG-PS) < 5; 4) treatment window period less than 3 months from prescription started. Key exclusion criteria were: 1) brain tumors, brain injury, or brain stroke either at baseline or during follow-up; 2) history of stroke or disorders with a high risk of future dementia or recurrence; 3) active psychiatric diseases or active narcotic usage, including daily to >4 times per week of alcohol usage; 4) neurocognitive diseases, e.g., Parkinson or Alzheimer's disease, that affected cognitive function; 5) history of drug-related encephalopathy or brain infections (control); 6) patients who changed treatment protocols to chemotherapy; 7) patients currently taking or have taken antidepressant drugs.[12]

Follow-up and assessment

Patients were asked to complete patient-reported questionnaires on paper or online form before ICI treatment initiation and at recruitment for control (baseline). Functional Assessment of Cancer Therapy–Cognitive Function (FACT-Cog, version 3) was applied in assessment of cognitive function for included patients.[13,14] Scale included 4 domains that assessed perceived cognitive impairment (PCI, 20 items), perceived cognitive abilities (9 items), comments from others (4 items), and impact on quality of life (4 items). Lower scores indicate greater cognitive function decline. A 1/2 of standard deviation (SD) of baseline PCI scores was defined as minimal clinically important difference (MCID), based upon distribution method.[15] Distribution-based measures are based on distribution properties of baseline scores which were usually treated as comparable norms in prospective cohorts. A 1/2 of SD was generally regarded as moderate level of cut-off value.[15]

Neuropsychological battery tests (NBT, Table 1) were performed to evaluate for objective cognitive performance: Trail Making Test (TMT), Hopkins Verbal Learning Test-Revised (HVLT-R), and Stockings of Cambridge from CANTAB battery (www.cambridgecognition.com/cantab). According to published recommendations[16,17] of the International Cognition and Cancer Task Force (ICCTF), we adopted the following criteria to determine objective cognitive impairment: two test score changes ≥1.5* SD from baseline scores, or one test score ≥2* SD from baseline scores.

Included patients were followed up in outpatient setting during routine medical check-ups every 3 months at cancer check-up clinics of research site. Follow-up sessions were baseline (time 0), 3, 6, 9, 12, and 15 months after treatment initiation (ICI arm) or recruitment (control arm). Follow-up rationale was designed to co-occur with medical check-ups. Patients were given 1 hundred yuan as compensation if completing all sessions. During each session, FACT-Cog was administered in addition to general condition evaluation. NBT was performed in the baseline, 6-, and 12-month follow-up sessions. In addition, considering the confounding effects of quality of life on subjective questionnaire results during ICI treatment, the Functional Assessment of Cancer Therapy–General (FACT-G) questionnaires were given in the 6 and 15-month sessions as adjusting variables (Supplementary Materials). Other patient-reported events would also be recorded, which would be reported otherwise. Primary data was analysed in August 2022 as per-protocol and intention-to-treat analysis.

Study endpoint and analytic variables

Primary study endpoint was changes in NBT scores, and any NBT score changes at each session that exceeded 3*SD of baseline scores would be marked as CoAE. We calculated prevalence of CoAE in per-protocol matched arms. In this analysis a more conservative threshold was adopted to delineate cases of CoAE (cutoff = 3*SD of baseline NBT) to decrease classified proportion worsened because of assessment-level variability.[18] As patients with baseline cognitive deficits may perform differently, we did baseline assessment analysis in both arms. Patients with baseline deficits were here defined

Test name	Cognitive function assessed	Test strategies	Scoring strategy	Indication of Higher score
Trail Making Test A (TMT)	Psychomotor speed and executive function	Connecting randomly positioned numbered circles (1–25) in ascending order as quickly as possible	Completing time	slower processing speed
Immediate Hopkins Verbal Learning Test-Revised (HVLTi)	Verbal memory and delayed recall	Participants were shown a list of 12 Chinese nouns with a 2-s interval from 3 categories (4 nouns from each category). Then participants were asked to recall them. The test was then repeated twice to get a total score.	Words number (0–36).	Greater immediate verbal memory
Delayed Hopkins Verbal Learning Test-Revised (HVLTd)		A second HVLT-R test (HVLTd) was done after 30–40 min, during which time other cognitive tests were done to mimic memory delay.	Words number (0–12).	Greater delayed recall of verbal memory
Cambridge Stockings (SOC)	Spatial and planning memory	Participants were given two monitors, each with colored balls. Participants must move the ball in the lower display to replicate the pattern displayed on the upper display. Participants were asked to move as little as possible to match the two patterns.	Number of perfect solutions	Better spatial and planning function

Table 1: **Neuropsychological battery test and explanation.**

as any baseline NBT score less than 2*SD from mean score value.

Secondary endpoint was changes of PCI scores at each follow-up session. PCI score changes at each session that exceeded MCID would be marked as perceived cognitive decline events (PCDE). The only exposure was ICI treatment in two comparable groups. Other variables of comparison groups were treated as confounding variables during analysis to determine independent association between ICI and PCI changes or PCDE risks. The demographic variables included age, sex, socioeconomic status, smoking status, body mass index, and diabetes co-morbidity. Socioeconomic status (SES) was evaluated by Chinese version of subjective socioeconomic status scale (CSSS), a 2-item self-rating scale with 10 points per item. The first item assesses self-position in the entire social environment, and the second item assesses self-position in community.[19] During follow-up, we also monitored patients who developed irAEs, which in this study involved colitis, hepatitis, neuropain, rash, and arthritis. These events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (V.4.03).[18]

Statistic analysis

PSM analysis of per-protocol cohorts was thus carried out between ICI group and control group by means of a greedy nearest matching algorithm. Propensity scores were calculated with multiple logistic regression using potentially confounding baseline variables. Variables included the following for NBT analysis: age, sex, socioeconomic status, smoking status, body mass index, diabetes co-morbidity, baseline PCI scores, baseline NBT scores, and FACT-G scores. Variables included the following for PCI analysis: age, sex, socioeconomic status, smoking status, body mass index, diabetes co-morbidity, baseline PCI scores, and FACT-G scores. Calculated scores of 2 comparable groups were 1:1 paired with a pre-specified caliper width of 0.2. Matching quality was evaluated with standardised mean difference (SMD), calculated for each matched variable according to Austin PC et al.[20,21] Any variable match with SMD over $(\sqrt{((n1+n2)/n1*n2)})*1.96$ is regarded as imbalanced matching (n1 and n2 stood for pre-matched sample sizes).[20]

To calculate incidence rate, or new case rate, of PCDE during follow-up, Kaplan–Meier survival analysis was adopted to estimate mean event-free survival (EFS) time. Log-rank test was adopted to compare differences in EFS rate as univariate analysis. Power remains over 90% to calculate difference of EFS rate of over 10% difference in log-rank test, assuming a two-sided, 5% type I error. Factors significant in univariate analysis would be subject to multivariate EFS analysis that adopted proportional hazards model. The model enabled assessment of hazard ratio (95% confidence interval, CI) of irAE that adjusted for other confounding variables.

Statistical tests of difference in matched samples were evaluated with McNemar tests for categorical variables and Wilcoxon signed-rank tests for continuous variables because all comparable variables were tested to have skewed distribution.[20] There was no randomisation or blinding in patient recruitment, and we did not recruit patients from other randomised trials in the current observational study. Sensitivity analysis was done in matched samples of patients who participated in PCI and NBT studies, which included analysis adjusting for the following variables: cancer stage (I and above), age

over 65, research sites, and testing sites (online or offline), and baseline cognitive performance. To gauge sample size required for statistical significance, it was calculated to be at least 139 patient pairs to detect a difference of 4 points for a pre-determined statistical power of 90% and type I error of 0.05.[13,22] Sample size and power were calculated in the PASS (version 15.0), and all statistical analysis was performed in R (version 4.0.5) software.

Role of the funding source

All the funders had no role in study design, data collection, data analyses, interpretation, or writing of the report.

Results

Baseline characteristics and propensity score matching

Between March 12, 2020, and March 28, 2021, 1298 patients were screened and 908 eligible participants were enrolled who consented to participate, with detailed workflow and demographic information of patients participating in NBT and PCI tests shown in Fig. 1, Table 2, and Supplementary Table S1. A total of 49 patients died in the 15-month session, 31 died of disease and 18 died of other causes. Exclusion or dropout analysis was shown in Supplementary materials.

Baseline variables were relatively balanced for participants of NBT before matching ($p > 0.05$ for all variables). As for participants of PCI test, there was a significant difference in BMI ($p < 0.05$) between ICI and control arm, and SES (CSSS scores, $p = 0.07$) and PCI scores ($p = 0.09$) were borderline different. All patients were in the post-operative state at recruitment.

Propensity scores were calculated in per-protocol cohorts to yield 240 pairs of participants of NBT and 292 matched pairs of PCI from ICI and control arms. Matching results were evaluated by SMD calculation and paired non-parametric tests, which showed well-balanced results (Table 2, Supplementary Table S2). The entire age range was 35–86 years (35–86 in ICI arm, and 40 to 82 in control arm). The quartile range was 52–68 (53–68 in ICI arm, and 51 to 69 in control arm) years. Our a priori MCID for PCI was 5.81 (0.5*11.62 = 5.81) in ICI arm and 4.61 (0.5 * 9.21 = 4.61) in control arm.

NBT score changes and cognitive adverse events

Overall, NBT score changes in 2 arms in 6th and 12th month, controlling for baseline scores, were shown in Fig. 2. Mean TMT score changes with 95% confidence interval of ICI arm reached 2* SD (10.00) of baseline scores of TMT in 12th-month session (Fig. 2A). Scores of other tests of either ICI or control arm did not reach this threshold. The result was not seen in intention-to-treat analysis (Fig. 2E), where TMT test score change did not reach 2*SD in the 12th-month session. None of other NBT reached 1.5*SD or 2*SD of baseline scores. Based upon ICCTF recommendations, objective deficits were observed in the 12th month in matched per-

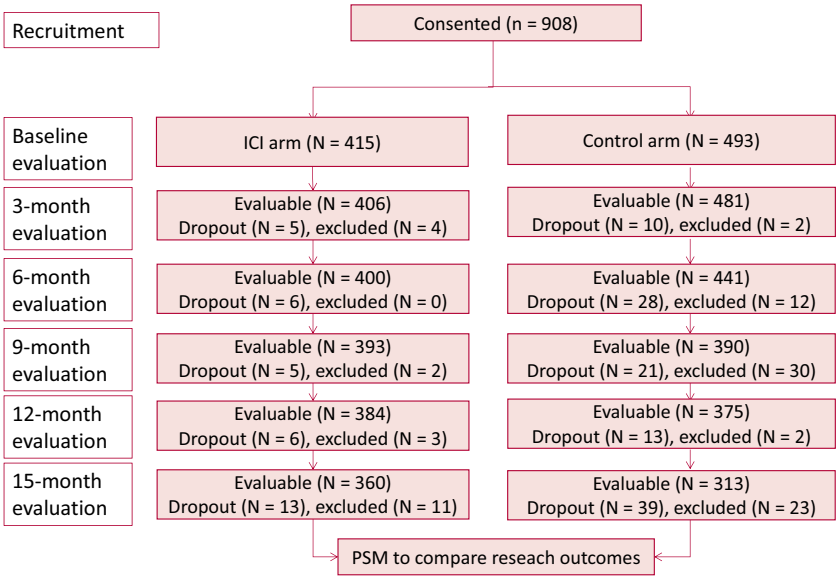

Fig. 1: **Study profile.** All patients in ICI arm received ICI therapy without interruption. Control arm was relatively over-sampled as compared to ICI arm to accommodate maximum matching. The final follow-up destination ended as per protocol and a total of 55 patients were excluded or dropped out from ICI arm, accounting for 13.3% of ICI arm. 180 patients in control arm were excluded or dropped out, accounting for 36.5% of control arm. Total dropout rates were 27.4%. See dropout analysis in Supplementary materials.

Variables	Before matching		p	After matching		|SMD|	p
	ICI (N = 289)	Control (N = 260)		ICI (N = 240)	Control (N = 240)		
Age	60.81 (10.73)	60.42 (10.62)	0.68	61.08 (10.63)	60.42 (10.43)	0.06	0.49
Body mass index	22.77 (2.88)	22.97 (2.99)	0.43	23.01 (2.85)	22.84 (2.95)	0.06	0.51
Male sex	186 (64.4)	173 (66.5)	0.59	154 (64.2)	157 (65.4)	0.03	0.77
Positive smoking history	172 (59.5)	160 (61.5)	0.63	146 (60.8)	145 (60.4)	0.01	0.93
Co-morbid diabetes	57 (19.7)	53 (20.4)	0.85	47 (19.6)	47 (19.6)	<0.01	1.00
Socio-economic status[a]	12.13 (4.16)	11.75 (4.14)	0.28	12.12 (4.27)	11.97 (4.10)	0.04	0.70
Time to diagnosis (weeks)	9.34 (2.14)	9.33 (2.17)	0.95	9.40 (2.07)	9.32 (2.30)	0.03	0.69
ICI types							
Durvalumab	42 (14.5)	–	–	37 (15.4)	–	–	–
Nivolumab	141 (48.8)	–	–	113 (47.1)	–	–	–
Pembrolizumab	106 (36.7)	–	–	90 (37.5)	–	–	–
Cancer stage = I	118 (40.8)	260 (100.0)	–	97 (40.4)	240 (100.0)	–	–
Baseline PCI scores	66.09 (11.16)	64.98 (9.86)	0.22	65.54 (11.49)	65.60 (9.34)	0.01	0.95
Baseline FACT-G scores	70.09 (18.38)	68.38 (18.02)	0.27	68.70 (18.65)	69.27 (17.52)	0.03	0.73
Baseline TMT scores	21.68 (5.07)	22.02 (7.21)	0.52	21.75 (5.00)	21.78 (6.97)	<0.01	0.97
Baseline HVLTi scores	24.32 (9.33)	23.98 (9.70)	0.68	23.99 (9.60)	23.95 (9.82)	<0.01	0.97
Baseline HVLTd scores	8.34 (3.48)	8.16 (3.86)	0.57	8.21 (3.46)	8.19 (3.88)	0.01	0.94
Baseline SOC scores	9.07 (3.72)	9.16 (3.32)	0.78	9.11 (3.75)	9.08 (3.25)	0.01	0.92

The variables were shown in numbers (percentage) or mean (standard deviations). PCI, perceived cognitive impairment; ICI, immune checkpoint inhibitor; FACT-G, Functional Assessment of Cancer Therapy–General. SMD, standardized mean difference to show imbalance levels of variables after matching. Variable with |SMD| > 0.25 is considered poorly unmatched. [a]Socioeconomic status is represented by Chinese version of socioeconomic status scale.

Table 2: **Baseline variables before and after propensity score matching for patients participating in neurocognitive battery tests.**

protocol TMT test studies. Overall, prevalence of CoAE in ICI arm was 34.2% (82 patients) in 6-month session and 42.5% (102 patients) in 12-month session, which significantly higher than that of control arm in both 6-month (6.7%) and 12-month (23.3%) session.

In ICI arm, 28 patients (11.6%) had baseline cognitive deficits as a prior defined, in whom 11 patients (39.3%) developed CoAE at 6-month and 15 patients (53.6%) at 12-month session. These proportions were not significantly different from patients without baseline cognitive deficits in ICI arm in either 6-month ($p = 0.54$) or 12-month ($p = 0.21$) session. In control arm, 36 patients had baseline deficits, in whom 3 (8.3%) patients developed CoAE in 6-month, and 6 (16.7%) patients in 12-month session. These proportions were also not significantly different from those of patients without baseline deficits in either 6-month ($p = 0.66$) or 12-month ($p = 0.31$) session.

We then analysed whether patients with higher age or cancer stage would perform differently during follow-up sessions (Table 3). Besides, mean age of patients developing CoAE at 6-month session was 60.4 ± 10.5 years, compared to 61.4 ± 10.7 years in patients who did not develop CoAE ($p = 0.47$). Mean age of patients developing CoAE at 12-month session was 62.4 ± 10.2 years, compared to 60.1 ± 10.9 years in patients who did not develop CoAE ($p = 0.10$). Overall, 46 patients developed irAEs during follow-up, including 6 patients with neuropain, 2 patients with meningitis, 19 patients with colitis, 8 patients with colitis + dermatological rash, 6 patients with arthritis, and 5 patients with arthritis + colitis. Patients who developed any irAE would be more likely to develop CoAE in the 12-month checkpoint. Patients with neurological irAEs would be more likely to develop CoAEs in 6-month and 12-month checkpoint (Table 3). In ICI arm, it was shown no significant difference divided by age in NBT score changes, other sensitivity test results were also shown in Supplementary Fig. S1.

Changes in PCI scores and adjusted analysis

PCI score changes in matched 2 arms from 3rd to 15th month, controlling for baseline scores, were shown in Fig. 3A. In control arm, no session reached MCID although significant difference was observed in 6th and 9th-month sessions. Score changes in ICI arms were –4.26 ± 8.54 (3rd month), –4.72 ± 11.83 (6th month), –6.16 ± 15.41 (9th month), –6.07 ± 15.71 (12th month), and –7.96 ± 13.97 (15th month). The 9th, 12th, and 15th-month sessions of ICI arm reached MCID. A similar pattern of results was observed in intention-to-treat analysis (Supplementary Fig. S2). Considering possible interactions with quality of life, analysis of co-variance was performed that adjusted changes in quality-of-life scores in mid-term (6-month) and final (15-month) sessions, and found similar results (Supplementary Fig. S3). Simple-effect analysis was done as a second method of adjusting analysis (Supplementary Table S4). PCI scores were compared in all patients after adjusting for research sites, and there was no significant difference between 2 arms

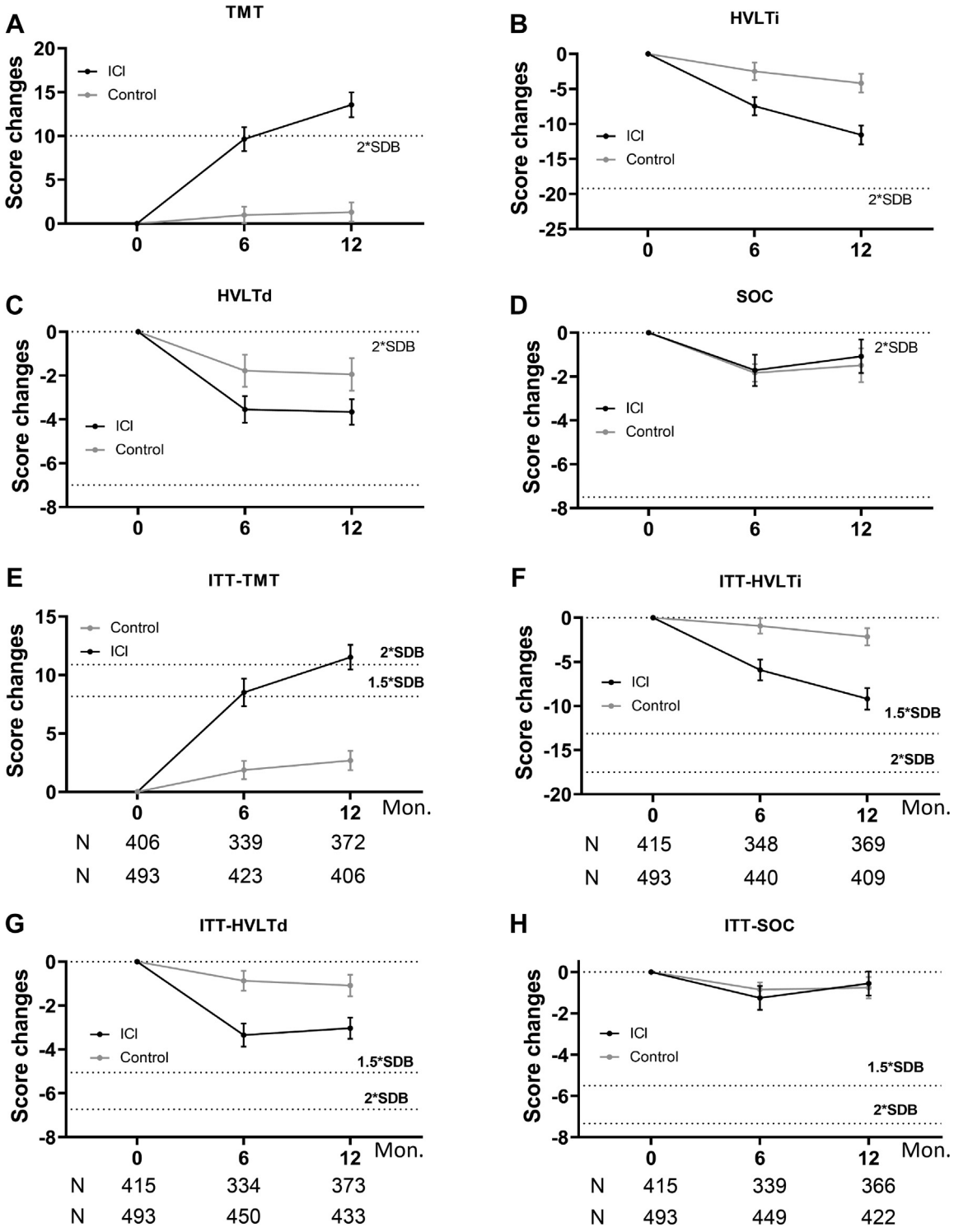

Fig. 2: **Neuropsychological battery test (NBT) score changes in comparable arms over follow-up sessions.** Data are plotted as the mean ± 95% CI (dot and error bar). Recommended threshold for cognitive impairment was shown by dot line. Results of NBT score changes after propensity score matching in per-protocol cohorts (n = 240 pairs): Trail Making Test (TMT, A), Immediate Hopkins Verbal Learning Test-Revised (HVLTi, B), Delayed Hopkins Verbal Learning Test-Revised (HVLTd, C), and Cambridge Stocking (SOC, D). Wilcoxon signed rank test showed significant difference between 2 arms in TMT, HVLTi, and HVLTd tests in both 6th and 12th session ($p < 0.01$). No difference was seen

CoAE in ICI arm			CoAE in Control arm		
Variables	6-month (n = 82)	12-month (n = 102)	**Variables**	6-month (n = 16)	12-month (n = 56)
Baseline cognitive deficits (n = 28)	11 (39.3%)	15 (53.6%)	**Baseline cognitive deficits (n = 36)**	3 (8.3%)	6 (16.7%)
Age > 65 (n = 89)	32 (36.0%)	41 (46.1%)	**Age > 65 (n = 79)**	5 (6.3%)	20 (25.3%)
Stage > I (n = 143)	51 (35.7%)	69 (48.3%)[a]	**Stage > I (n = 240)**	NA	NA
IrAE (n = 46)	20 (43.5%)	26 (56.5%)[a]	NA	NA	NA
Neurological irAE (n = 8)	2 (25%)[a]	2 (25%)[a]	NA	NA	NA

CoAE, cognitive adverse event; irAE, immune-related adverse events. [a]Stands for $p < 0.05$ in Wilcoxon signed rank test (continuous variables) or McNemar test (categorical variables).

Table 3: **Sensitivity analysis in patients participating in neurocognitive battery tests (n = 240 pairs).**

(Supplementary Fig. S5). As cancer stage may affect cognitive performance, we compared PCI score changes in both arms only in stage I patients, and the difference also was significant (Supplementary Fig. S6). Whether patients were tested online had no effect on PCI score changes (Supplementary Fig. S7).

Within ICI arm, patients aged >65 years had significantly higher PCI score changes than patients aged ≤65 years ($p < 0.01$ for all sessions, Supplementary Fig. S8). There were significant differences in score changes between the 3rd- and 6th-month session ($p < 0.001$), and 12th and 15th-month session ($p < 0.001$, Fig. 3B), suggesting an increased level of cognitive decline as treatment progressed. The score change difference between 9th and 12th-month sessions was not significant ($p = 0.06$). There was a poor correlation between the outcomes of perceived cognitive impairment and objective neurocognitive test (Supplementary Table S5).

To rule out primary or secondary dementia regardless of ICI therapy, all patients were assessed with PET/CT for exclusion/diagnosis of cancer metastasis at baseline and during follow-up. Those with baseline PCI score <50 points, suspected brain metastasis and other neurological diseases were assessed by neurologists and with brain MRI, and patients would be excluded if pathological dementia was diagnosed.

Prevalence and incidence of PCDE

Individual score changes of two arms were compared with their corresponding MCID. Patients were categorised as having a PCDE (a score reduction of >5.81), and no PCDE. Overall PCDE prevalence was 237 over 1460 patient-sessions (16.2%) in ICI arm, and 25 over 1460 patient-sessions (1.7%) in control arm ($p < 0.001$ by McNemar non-parametric test). Session-specific prevalence of PCDE in ICI arm was significantly higher ($p < 0.001$ for all sessions, Fig. 4A–E).

The estimated mean PCDE EFS time was 14.76 (95% CI 14.61–14.94) months and 13.23 (95% CI 12.81–13.68) months for control arm and ICI arm, respectively. Incidence rate of PCDE was 26.4% in ICI arm and 5.1% in control arm. By log-rank test, there was significant difference in EFS rate in ICI arm and control arm ($p < 0.001$, Fig. 4F).

We then compared the change of PCI scores in ICI arm after grouping by different onsets of PCDE (Supplementary Fig. S9). It was found that the trend of score changes did not change much in the early-onset subgroup (e.g., 3-month subgroup), but in the later-onset subgroups, the trend of scores was that they tend to decrease more rapidly as the follow-up session went forward.

The association between immune-related adverse events (irAE) and PCDE in ICI arm: an exploratory outcome

We gauged the relationship between irAE and PCDE as post hoc analysis, in which type I error (α) was specified at 0.025. During follow-up, 31 (10.6%) of ICI arm had irAE, including 19 patients with colitis, 5 patients with hepatitis + neuro-pain, 2 patients with rash + colitis, 2 patients with arthritis, and 3 patients with arthritis + colitis.[23] We first made a univariate survival analysis of PCDE by means of Kaplan–Meier methods. Besides incident irAE, we found 4 variables that significantly affected PCDE risk in the log-rank tests: age, smoking history, baseline PCI scores, and BMI values. They were then subject to multivariate analysis in proportional hazards model. Two variables were independently associated with PCDE incidence: incident irAE (HR = 3.16, 95% CI 1.83–5.46, Supplementary Table S3) and age (HR = 0.36, 95% CI 0.21–0.61).

Discussion

The 15-month, 5-session follow-up study of ICI arm versus control arm without chemotherapy or target therapy interactions found significant CoAE and PCDE during treatment courses in patients receiving active ICI

in SOC test. Results of unmatched, intention-to-treat (ITT) analysis: TMT (E), HVLTi (F), HVLTd (G), and SOC (H). N stands for evaluable sample number. Independent t test showed significant difference between 2 arms in TMT, HVLTi, and HVLTd tests in both 6th and 12th session ($p < 0.01$). No difference was seen in SOC test.

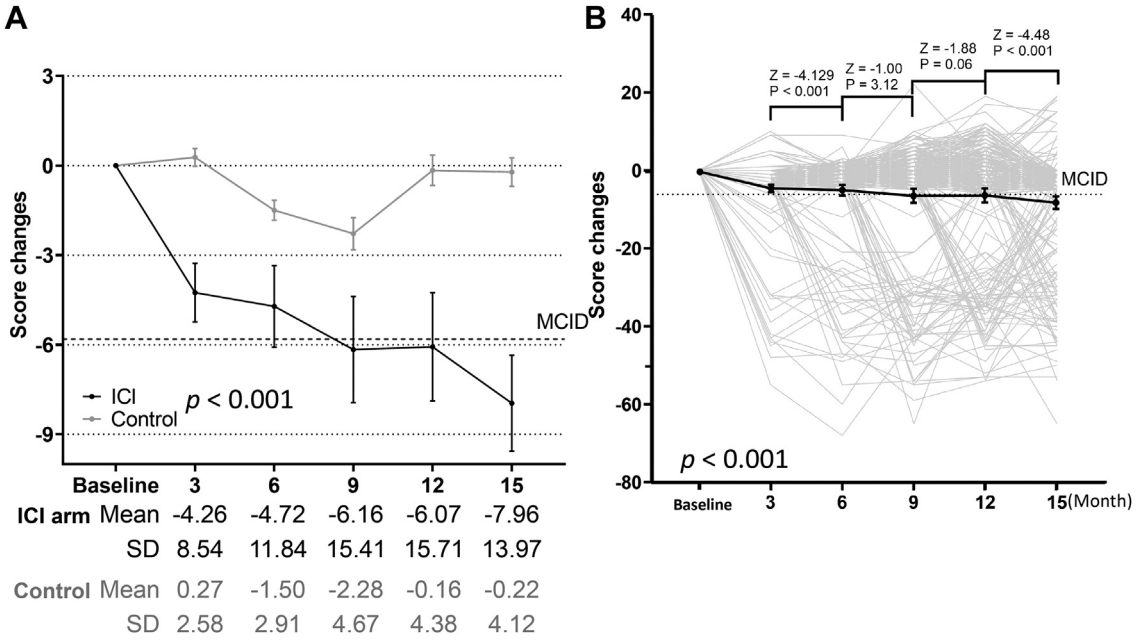

Fig. 3: **PCI score changes in comparable arms over follow-up sessions**. (A) Change of PCI scores during follow-up in the ICI arm (black) and control arm (gray) after 1:1 propensity score matching (n = 292 pairs) in per-protocol cohorts, plotted as the mean ± 95% CI (dot and error bar). A minimal clinically important difference (MCID) of 5.81 is represented by the dot line. By Wilcoxon signed-rank test, there was significant difference of changes of PCI scores between ICI and control arm in the 3rd month (Z = −11.27), 6th month (Z = −11.24), 9th month (Z = −7.25), 12th month (Z = −5.70), and 15th month (Z = −10.57) follow-up session (all based on negative ranks, $p < 0.001$ for all sessions). Of all 1460 sessions (292 patients * 5 sessions), The overall mean score changes were −5.83 ± 13.41 in ICI arm, and −0.78 ± 2.19 in control arm ($p < 0.001$ by Wilcoxon signed-rank test). Overall mean score changes of ICI arm reached 5.81 (MCID), although by a small margin (0.02), and score changes of control arm did not reach MCID. (B) Individual PCI score change comparison in ICI arm, and the 95% CI of score changes in each session (plotted as mean ± 95% CI). The change of scores over time was compared with the non-parametric Wilcoxon signed rank test, and the statistical value (Z value) was shown between score changes in 6th month and 3rd month, in 9th month and 6th month, in 12th month and 9th month, in 15th month and 12th month, respectively. The results showed that the PCI scores were decreasing over time in ICI arm.

treatment alone, tested by the well-validated objective and self-reported measures of cognition in cancer patients. The overall prevalence (16.2%), incidence (26.4%), and PCI score decrease (–5.83 ± 13.41) in ICI arm suggested an important issue during ICI treatment, although it should be noted differences remain relatively small in Kaplan–Meier estimated survival time ($p < 0.001$). Since most contemporary research focused on the pervasive effects of chemotherapy on cognitive function, the current one was the first longitudinal study to investigate the role of ICI monotherapy in mid-term cognitive changes of cancer patients.[24,25]

In a preclinical mouse model with tau-related diseases, Y Lin et al. reported minimal effects of ICI on cognitive functions.[7] However, Neuronal autoantibodies causing cognitive decline were found in melanoma patients treated with ICI.[9] Patients treated with ipilimumab had a significantly higher prevalence of neuronal autoantibodies compared to patients without ICI treatment. In our follow-up trajectory, serum autoantibodies were not reported, which was a limitation of our study and this could be an important follow-up analysis. It may be hypothesised potentially that ICI could induce the production of neuronal autoantibodies or increase titers of existing antibodies which in turn leads to cognitive impairment. Mechanisms of ICI-related cognitive decline have been inconclusive and research into molecular underpinnings is to be encouraged. Recent studies have found activated microglia, which is one of the main effector immune cells inside the brain, may play a key role in disrupting numerous neuroplasticity and thus cognitive deficits may ensue.[17] Also, inflammation was suggested as potential mechanism for long-term cognitive decline, indicating that immunomodulation would be mediating mechanism.[26]

Overall, our follow-up results indicated global worsening of objective cognitive performances in a relatively short time (6 and 12 months) in ICI or control arm. Usually, cognitive decline would be seen in a longer period.[24] This result is likely to be related to the very difficult period of Covid-19 pandemic and related restrictions. Also, it could be noted TMT score changes were the only NBT that reached threshold for diagnosis in ICI arm, indicating that immunotherapy may affect

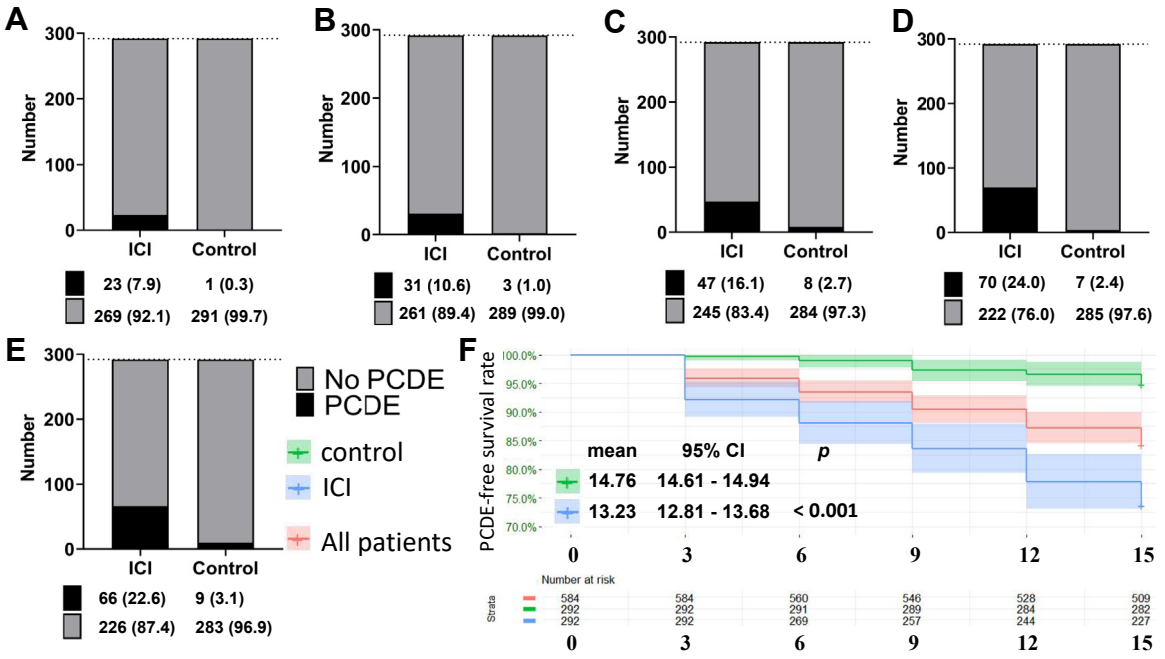

Fig. 4: **Prevalence and incidence of cognitive adverse event (PCDE) in ICI and control arm**. (A–E) Absolute patient number and prevalence (%) of PCDE in ICI arm and control arm after 1:1 propensity score matching (n = 292 pairs) in the 3rd month (A), 6th month (B), 9th month (C), 12th month (D), 15th month (E) follow-up session. By McNemar non-parametric test, there was significant difference of PCDE prevalence between ICI arm and control arm in each follow-up session ($p < 0.001$ for all sessions). (F) Kaplan–Meier survival curve of new-onset PCDE at each follow-up session of ICI arm (blue), control arm (green), and all patients, plotted as mean ± 95% CI (shaded areas). The estimated mean PCDE event-free survival (EFS) time was 13.23 (95% CI 12.81–13.68) for control arm and ICI arm, respectively. Incidence rate of PCDE was 26.4% in ICI arm and 5.1% in control arm. By log-rank test, there was significant difference of EFS rate in ICI arm and control arm ($p < 0.001$).

information processing in the specific brain regions. TMT assesses the cognitive domains of psychomotor speed and executive function.[17] More study, especially regional radiological study, is encouraged to find role of immunotherapy in affecting regional metabolism associated with information processing.

More direct evidence of 15 cancer patients with ICI plus chemotherapy found inconclusive evidence due to the small sample size.[10] Thus, to find the independent effects of ICI, more strict criteria are necessary to exclude potential interaction effects. In this study, the relatively strict criteria of ICI monotherapy versus no medical therapy at all provided a good opportunity to analyse the independent effects of ICI on cognitive functions. Should there be simultaneous chemotherapy or targeted therapy, there may exist interaction effects between treatment protocols and the effects of immunomodulators on higher-level neurological functions could be complicated.[1]

FACT-cog questionnaires included four sub-scales that measure multiple aspects of cognition-related problems during cancer treatment, and we did not apply the whole questionnaires to study. On the other hand. PCI subs-scale was the measure of self-reported deficits, which would more likely to reflect treatment-related adverse outcomes.[13] Therefore, one limitation of the study did not comprehensively record patient feelings and functions associated with the deficits. In the literature, the negative control group usually included the age-matched healthy control in prior studies of chemotherapy-associated cognitive impairments. Research suggested the pathology of cancer itself could independently induce cognitive decline and the decline may result from traumatic stress from diagnosis,[11] and we recruited cancer patients without medical therapies as control. To minimise potential bias in associations with baseline variables, we adopted PSM approach. This post hoc randomisation approach may allow for balanced confounding factors, such as comorbid conditions. The binary classification of cognitive impairment in this study may be interpreted with caution as prior studies found that multiple subgroups of cognitive function deficits exist,[27,28] and a binary classification may have low validity in detecting cognitive impairments.[29,30]

As an exploratory outcome, we found the association between irAE and PCDE incidence during post hoc analysis. The relationship between ICI and neurological irAE has been reported previously, ranging from 4% to 6% with less than grade II severity, but some

researchers suggested that this irAE was underestimated due to sub-clinical or transient clinical course and no specialist consultation was required.[4,31,32] In the current study, no patient was diagnosed with neurological irAE. However, the occult existence or incidental symptoms may cause deteriorated cognitive functions over a prolonged period.

The current research bears several limitations. Subjective method of self-reported scales was reported with fewer associations with neuropsychological assessments, although researchers found greater sensitivities in assessment of cancer therapy-related cognitive decline[31] and associations with brain imaging.[33] All diagnostic scans were performed before the tests and the scanning results were reported to patients, and only patients with verified pathological and radiological cancer diagnoses were included. The per-protocol design of data cleansing may introduce bias in ICI or control arm due to potential dropout effects and unadjusted baseline and overall dropout rates were satisfactory (27.4%). The dropout rates in control arm were relatively high due to lost follow-up (36.5%). To combat these potential biases, we did intention-to-treat analysis, and validate findings in per-protocol analysis. In addition, 1/2 of a standard deviation is a very liberal criterion compared to the prior cognition and cancer literature and therefore likely overestimated the incidence and prevalence of cognitive adverse events.[34–36]

The current sample was selected in real-world settings without random assignment. There is a risk of bias that patient groups systematically differ in demographic and treatment. For instance, the therapeutic regimen of ICI alone was decided by treating oncologists with non-randomised preference. Therefore, trajectory of cognitive performance might be different in ICI compared to control, even if patients start from the same level. Patients recruited in control arm were all stage I cancer patients, and thus the limitation was that we cannot include cancer stage as baseline PSM variables. However, in real-world settings, all patients with ≥ II cancers will receive postoperative anti-cancer therapies. Also, multivariate survival analysis did not find significance in association between cancer stages and risks, but we encourage future research reports from randomised trials that may solve this bias.

The primary outcome of ICI monotherapy versus control showed a greater objective and self-reported cognitive decline in patients receiving ICI therapy in PSM analysis. Single-arm analysis showed that cognitive decline deteriorated as the ICI monotherapy periods prolonged. The exploratory outcome showed that irAE was independently associated with PCDE risks.

Contributors

Yifei Ma was responsible for data curation, formal analysis, funding acquisition, writing-original draft, and writing-review & editing. Nianqi Liu was responsible for data curation, formal analysis, writing-original draft, and writing-review & editing. Yanqi Wang was responsible for project administration and investigation. Ao Zhang was responsible for conceptualisation, funding acquisition, supervision, and writing-review & editing. Yiming Li, Guangmin Jian, Zirui Zhu, Guangzhen Fu, and Pengfei Zhu were responsible for Project administration. Zhiying Zhang, Mingming Dong, Guoxing Zheng, Shenrui Bai, Xiaolong Wei, and Shuqin Chen were responsible for investigation. Guanqing Zhong was responsible for project administration and investigation. Jifan Tan was responsible for conceptualisation and supervision. Xinjia Wang was responsible for conceptualisation, supervision, and writing-review & editing. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work. The work reported in the paper has been performed by the authors, unless clearly specified in the text. Yifei Ma and Xinjia Wang accessed and verified the underlying data. Xinjia Wang was responsible for the decision to submit the manuscript.

Data sharing statement

Data are available upon reasonable request to the corresponding authors. The personal information of the study participants is kept strictly confidential as mandated by the request of the study participants.

Declaration of interests

We 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.eclinm.2023.101987.

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