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The prognostic role of albumin-bilirubin grade in patients with advanced non-small cell lung cancer treated with immune checkpoint inhibitors

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Abstract. – OBJECTIVE: Our aim was to explore the prognostic role of baseline albumin-bilirubin levels (ALBI) on the efficacy of immunotherapy in patients with advanced non-small cell lung cancer (NSCLC).

PATIENTS AND METHODS: **This retrospective study enrolled 58 cases of advanced NSCLC patients who received immune checkpoint inhibitor therapy from January 2019 to February 2022 in People's Hospital of Macheng. Patients were grouped according to the levels of baseline ALBI. The corresponding cut-off values were determined by receiver operating characteristic (ROC) curves. We also assessed potential predictive models for predicting efficacy of immunotherapy in advanced NSCLC.**

RESULTS: **The median overall survival (OS) was not reached. The median OS of patients with PS ≤ 1 after immunotherapy was significantly longer than that of PS ≥ 2, which was NR vs. 6.67 months (HR=0.14, 95% CI: 0.05-0.46; $p<0.01$). The risk of death for patients with low ALBI (<-2.52) was significantly lower than that of patients with high ALBI (HR=0.28, 95% CI: 0.08-0.94; $p=0.03$). Univariate analysis showed that baseline ALBI and PS were factors significantly affecting OS in patients with advanced NSCLC after immunotherapy ($p<0.05$ for all). The combination of ALBI and PS showed a good predictive value in prognosis of these patients after immunotherapy ($p<0.01$).**

CONCLUSIONS: **The baseline ALBI and PS may serve as prognostic factors for advanced NSCLC patients treated with immunotherapy.**

Key Words:
Immune checkpoint inhibitor, ALBI, ECOG PS, Non-small cell lung cancer, Survival.

Introduction

Non-small cell lung cancer (NSCLC) is one of the most common malignant tumors worldwide, and most patients are diagnosed with advanced diseases with poor prognosis[1]. Although targeted therapy and chemotherapy, as the most common treatment methods, show significant curative effects, patients often face relapse and drug resistance[2,3]. In recent years, treatment strategies involving immune checkpoint inhibitors (ICI) have significantly improved the efficacy and survival of patients with advanced NSCLC; however, not all of these patients could benefit from these regimens[4].

How to predict the efficacy of immunotherapy and screen out the potential population who can benefit from immunotherapy before treatment is the key to achieve better treatment outcomes[5]. At present, a variety of tissue-based biomarkers have been proved[6] to be effective in predicting the efficacy of immunotherapy for advanced NSCLC, such as programmed cell death ligand 1 (PD-L1), and tumor mutation burden (TMB)[7], and these tumor tissue related predictive factors are supported by high-level evidence[7,8]. However, these biomarkers have exerted several limitations during clinical utilization. First, patients with negative PD-L1 or low TMB may also respond to immunotherapy[8]; secondly, biopsy of tumor is difficult, which can limit the detection of the above indicators. Therefore, it is necessary to find new markers and prognostic models, which can cover the aspects of the body's organ function, and have the advantages of being non-invasive, repeatable, and cheap.

Baseline characteristics, such as Eastern Cooperative Oncology Group-Performance Status (ECOG-PS), can reflect the physical status and have shown prognostic effects on efficacy[9,10]. Studies[11] found that NSCLC patients with good PS were associated with better OS after ICI treatment. Systemic liver and nutritional markers derived from blood tests also show potential correla-

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tion with the efficacy of ICI treatment[12]. In recent years, Johnson et al[13] proposed an albumin-bilirubin (ALBI) classification based on serum ALB and TBil to assess liver function and nutrition status. Thereafter, several studies[14-16] have shown that the ALBI score is superior to the Child-Pugh score in the prognosis evaluation of hepatocellular carcinoma patients undergoing sorafenib-targeted therapy or immunotherapy. Whether ALBI can be used in predicting prognosis of advanced NSCLC after immunotherapy is not well determined.

Therefore, in this study, we compared the predictive value of ALBI on the survival outcomes of patients with advanced NSCLC who received ICI, aiming at providing new biomarker for predicting the efficacy of immunotherapy.

Patients and Methods

Patients

The clinical and survival data of 85 patients with advanced non-small cell lung cancer who were treated in People's Hospital of Macheng from January 2019 to February 2022 were retrospectively analyzed. There were 68 males and 17 females; the mean age was 59±12 years. The study had been approved by the Medical Ethics Committee of People's Hospital of Macheng (2022-JY005). Patients' written informed consent was waived as all the data in this retrospective study were anonymous.

Inclusion and Exclusion Criteria

Inclusion criteria: (1) Based on the American Joint Committee on Cancer (AJCC) diagnostic criteria for NSCLC, patients were diagnosed with stage III and IV NSCLC and received ICI. (2) ECOG-PS score of 0-3. (3) Expected survival time > 3 months. (4) Blood routine, liver and kidney function evaluations had been performed within two weeks before treatment, and records were available. (5) Received at least one cycle of ICI therapy.

Exclusion criteria: (1) Stage I and II NSCLC. (2) Not suitable to receive ICI therapy. (3) Insufficient functions of heart, brain, lung, and renal, or accompanied with other malignant tumors. (4) Those with incomplete clinical data and/or lost to follow-up.

Treatments

Patients were treated with ICIs based regimens. ICIs included Pembrolizumab, Camrelizumab, and other agents. Chemotherapy regimens were paclitaxel plus platinum, or pemetrexed plus platinum, or gemcitabine plus platinum, or other strategies. Tumor response assessments were performed every two cycles during active treatments.

Data Collection and Follow-Up

General demographic data (age, gender, etc.), hematological examination results (blood routine, liver and kidney function), imaging examination results (tumor number, tumor size) of the enrolled patients were extracted. Patients were followed up regularly after treatment. The follow-up contents included clinical physical examination, hematological examination (blood routine, liver and kidney function, etc.), and image examination (chest X-ray, abdominal CT, and/or MRI if necessary).

Efficacy Evaluation

The efficacy was determined according to the evaluation criteria for solid tumors (RECIST, version 1.1), which included complete response, partial response, stable disease, and disease progression[17]. The objective response rate is the sum of complete response and partial response, and the disease control rate refers to the combination of complete response, partial response and stable disease. OS was defined as the time from the day when the patient received treatment until the patient's death or last follow-up. The follow-up deadline was on February 28, 2022 or death or loss to follow-up.

Indicators

According to the baseline, data of the enrolled patients, such as ALBI, were extracted and grouped by the metric's mean or optimal cut-off value. ALBI score was calculated according to the baseline serum ALB and Tbil levels: $ALBI=0.66\times\log_{10}[TB(\mu mol/L)]-0.085\times[ALB(g/L)]$[13]. The cut-off value was set according to the receiver operating characteristic (ROC) curve of ALBI. ALBI low group was defined as ≤ ALBI cut-off value; ALBI high group was defined as > ALBI cut-off value.

Statistical Analysis

SPSS 25.0 (IBM Corp., Armonk, NY, USA) statistical software was used for data analysis. Survival curves were drawn using the Kaplan-Meier method, and the log-rank test was used for comparison of survival between groups. Cox regression model was used for univariate and multivariate analysis. In order to avoid the influence of collinearity on the results, albumin, tbil,

and ALBI were entered into different multivariate regression models. The area under the curve (AUC) of the ROC curve was used to evaluate the predictive ability of different scoring models for OS in patients with advanced NSCLC. $p<0.05$ was considered to be statistically significant.

Results

Baseline Characteristics

Among the 85 cases, 58 of them were eligible for final analysis. There were 50 males (86.2%) and 8 females (13.8%). The age ranged from 42 to 80 years, with a median age of 65 years. There were 16 patients with stage III and 42 patients with stage IV. The pathological types were squamous cell carcinoma in 23 cases, adenocarcinoma in 29 cases, and other types in 6 cases. The median number of immunotherapy cycles was 3. 25 patients (43.1%) received radiotherapy (Table I). The follow-up time ranged from 0.5 to 28 months, and the median follow-up time was 5.0 months. According to the ALBI calculation method and the ROC curve, the cut-off value of ALBI was -2.52. The study flow chart is presented in Figure 1.

Overall Efficacy and Survival

At the end of follow-up, 58 patients were included. The overall average survival time was 21.08 (95% CI: 17.78-24.37) months. One patient achieved CR, five were PR, 41 were SD, and 11 were PD, with an overall response rate of 10.3% and disease control rate of 81.0%.

Effect of ECOG PS on Survival of Advanced NSCLC After ICI Treatment

According to the patients' ECOG PS score, these patients were divided into ≤ 1 group and ≥ 2 group. In this section, there were 35 cases in group ≤ 1 and 23 cases in group ≥ 2. The median OS of group ≤ 1 after immunotherapy was significantly longer than that of PS ≥ 2, which was NR *vs.* 6.67 months (HR=0.14, 95% CI: 0.05-0.46; $p<0.01$) (Figure 2A).

Effect of Immunotherapy Cycles on Survival of Advanced NSCLC After ICI Treatment

Patients were divided into ≤ 3 groups and > 3 groups, according to the number of immunotherapy treatment cycles (Figure 2B). There were 25 patients who received > 3 cycles of immunotherapy, and 33 patients who received ≤ 3 cycles of immunotherapy. The risk of death was significantly reduced in patients treated with > 3 cycles of immunotherapy (HR= 0.19, 95% CI: 0.06-0.60; $p=0.02$).

The Survival Outcome Analysis Based on ALBI Classification

The ROC curve of ALBI was constructed based on individual ALBI values, and the optimal cut-off value of ALBI was determined to be -2.52. Among the 58 patients, 38 were classified as low ALBI group, and 20 were grouped into the high ALBI group (Figure 2C). Receiving immunotherapy could result in a significantly reduction in mortality risk in patients with low ALBI group (HR=0.28, 95% CI: 0.08-0.94; $p=0.03$).

Analysis of Prognostic Factors and Comparison of Different Model Prediction Ability

To explore potential prognostic factors associated with survival, we performed the following analyses by including several factors, such as sex, age, ECOG-PS, and ALBI. The univariate analysis showed that ECOG-PS and ALBI were factors correlated with OS in patients with advanced NSCLC who received ICIs (Table II). The multivariate analysis showed that PS and ALBI were independent prognostic factors for OS in these patients. We introduced several clinical factors (such as age and sex) and outcome indicators (such as ECOG-PS, and ALBI) to assess

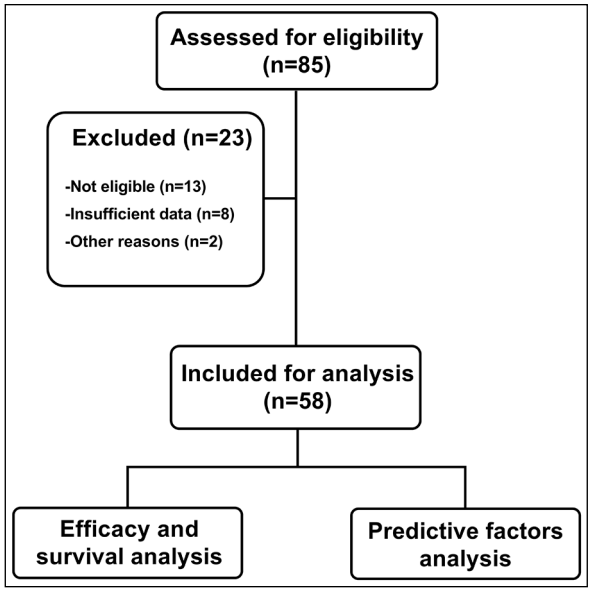

Figure 1. Study flow chart.

Table I. Baseline characteristics of the included patients.

Factors	Number	(%)	Mean or median	Se or IQR	
Sex	58	100.0			
male	50	86.2			
female	8	13.8			
Age at diagnosis	58	100.0			
<60					
≥60		18	31.0		
		40	69.0		
Pathological type		58	100.0		
SC	23	39.7			
AC	29	50.0			
Other	6	10.3			
ECOG PS		58	100.0		
	1	47	81.0		
	2	11	19.0		
Stage		58	100.0		
III	16	27.6			
IV	42	72.4			
Primary treatment		58	100.0		
Yes	34	58.6			
No	24	41.4			
Treatment line		58	100.0		
1st line	32	55.2			
≥2nd line	26	44.8			
Immunotherapy cyclesw	58	100.0	3.0	1.75-5.0	
Cycles of immunotherapy		58	100.0		
	≤3	33	56.9		
	>3	25	43.1		
Radiotherapy		58	100.0		
Yes	25	43.1			
No	33	56.9			
Number of metastatic organs		58	100.0		
	≤3	47	81.0		
	>3	11	19.0		
Complete response		1	1.7		
Partial response		5	8.6		
Stable disease		41	70.7		
Progression		11	19.0		
Overall response rate		6	10.3		
Disease control rate		47	81.0		
Neu	58	100.0	5.1	0.4	
Lym	58	100.0	1.1	0.1	
PLT	58	100.0	241.4	12.5	
NLR	58	100.0	6.3	0.8	
PLR	58	100.0	285.5	26.7	
Hb	58	100.0	116.6	2.8	
ALB	58	100.0	39.6	0.8	
TBIL	58	100.0	10.8	0.7	
ALBI	58	100.0	-2.7	0.1	
Urea	58	100.0	5.9	0.3	
Glu	54	93.1	5.7	0.3	
eGFR	58	100.0	109.5	3.9	
PNI		58	100.0	44.9	0.9

Se, standard error; IQR, interquartile range; SC, squamous carcinoma; AC, adenocarcinoma; ECOG PS, eastern cooperative oncology group performance score; Neu, neutrophils; Lym, lymphocyte; PLT, platelet; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; Hb, Hemoglobin; ALB, albumin; TBIL, total bilirubin; ALBI, albumin-bilirubin grade; Glu, fasting glucose; eGFR, estimated glomerular filtration rate; PNI, prognostic nutritional index.

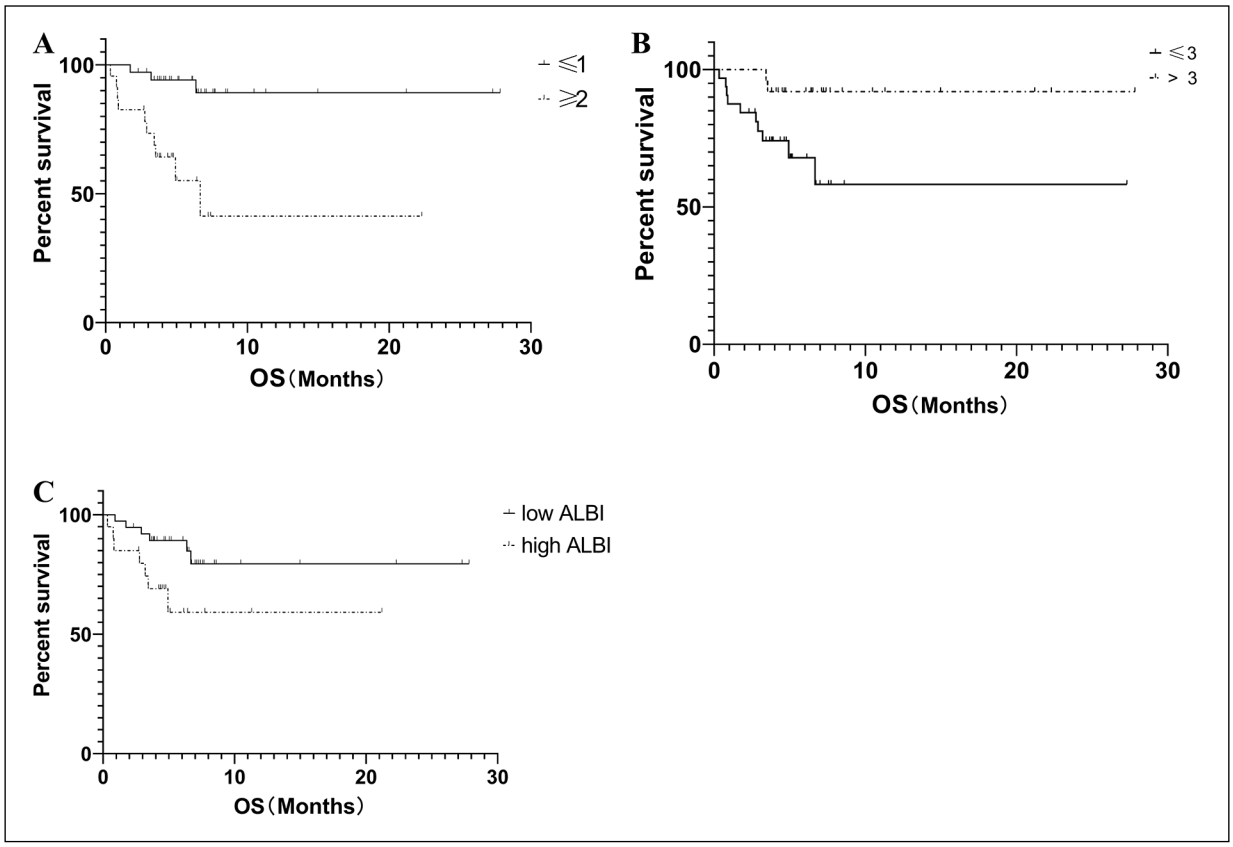

Figure 2. OS analysis based on baseline characteristics and biomarkers. **A**, OS analysis according to the ECOG PS. **B**, OS results based on cycles of immunotherapy. **C**, OS analysis based on baseline ALBI groups.

its predictive value of different models on death. The ROC curve results showed that the combination of ALBI and ECOG-PS was better than that of the ALBI or ECOG-PS in predicting the prognosis of these patients (Figure 3). The sensitivity and specificity of this ALBI and ECOG-PS based model were 0.62 and 0.89, respectively, with an AUC of 0.80 (95% CI: 0.67-0.94; p=0.001).

Discussion

ALBI is an important evaluation index of the liver function status of patients with advanced cancers[12]. Whether ALBI is associated with the survival and prognosis of NSCLC patients during/after treatments is not well determined. Our study investigated the predictive value of ALBI in patients with advanced NSCLC after receiving immunotherapy. The results showed that the level of ALBI was an important factor affecting the

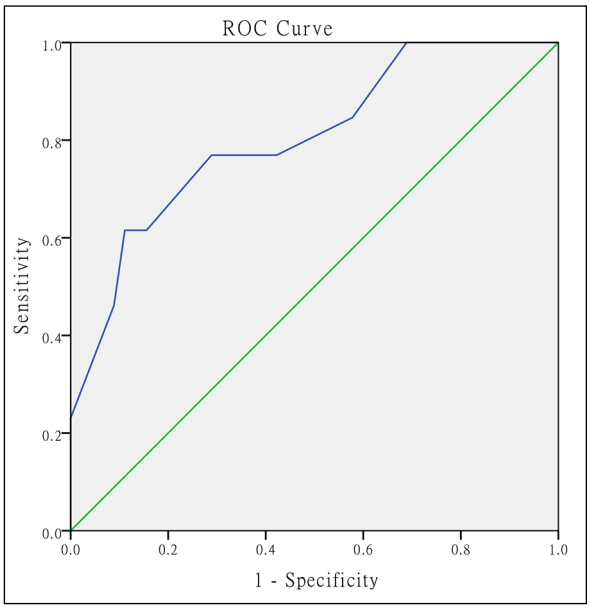

Figure 3. ROC curve for predicting prognosis in advanced NSCLC patients treated with immunotherapy.

Table II. Univariate and multivariate analyses for overall survival.

Features		Univariate Analysis for OS				Multivariate Analysis for OS			
		HR	95% CI		*p*-value	HR	95% CI		*p*-value
Sex	Male/Female	1.74	0.48	6.31	0.33	1.61	0.38	6.81	0.52
Age	≥60/<60	1.34	0.44	4.11	0.78	1.78	0.51	6.19	0.37
PS	2/1	0.14	0.04	0.51	0.003	0.12	0.03	0.47	0.002
Pathology	AC/other	0.67	0.14	3.24	0.39				
Hb	<90/≥90	0.92	0.12	7.07	0.93				
GLU	>6.10/≤6.10	1.29	0.42	3.94	0.66				
PLR	≤196.8/>196.8	0.37	0.10	1.36	0.14				
ALBI	≤-2.52/>-2.52	0.33	0.11	0.99	0.049	0.30	0.09	0.96	0.043
PNI	<44.3/≥44.3	2.25	0.73	6.92	0.16				

HR, hazard ratio; OS, overall survival; CI, confidence interval; PS, performance score; Neu, neutrophils; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; Hb, Hemoglobin; ALBI, albumin-bilirubin grade; GLU, fasting glucose; PNI, prognostic nutritional index.

prognosis of these patients, and the combination of ALBI and PS had a stronger predictive ability. In addition, short-term treatment efficacy, and number of treatment cycles were also associated with survival outcomes of these patients.

The ALBI grade depends on two variables: serum albumin and bilirubin[13]. Albumin, which is produced by the liver, can be used as a biomarker of nutrition status and liverfunction[18]. Bilirubin is another indicator of liver function, and increased bilirubin is usually indicative of hepatic insufficiency[19]. These laboratory values are easily obtained from serum tests and can be measured repeatedly. Therefore, ALBI grade can be indicators of liver function, and predict the prognosis of patients with liver tumors[20-23]. The study of Kelley et al[23] showed that in patients with advanced hepatocellular carcinoma (HCC), patients with ALBI grade 2 had significantly shorter OS and higher mortality[24]. In the current study, we found that ALBI grade was an independent factor influencing the prognosis of advanced NSCLC patients. Although the ALBI classification is more objective and shows better predictive ability, its predictive ability is still unsatisfactory. A more powerful score system can be established by combining with other baseline data of these patients. Several studies[11,25,26] have shown that performance status (PS) is associated with the prognosis of cancer patients. Park et al[25] analyzed the prognosis of 439 NSCLC patients treated with immune checkpoint inhibitors, and the results showed that the OS of patients with PS score ≥ 2 was significantly shorter than that of patients with PS score < 2 (HR=1.75, p=0.02). Another study[11] reached similar conclusions, showing that patients with a PS score ≥ 2 had a worse prognosis than those with a PS score < 2, with significantly shorter OS and PFS (p<0.05 for all). A systematic review[26] of 44 studies with advanced NSCLC found that it is still too early to determine immunotherapy is not the treatment option for PS 2 patients. Therefore, we assessed this factor in the current analysis. The results are in accordance with the previous literature findings. For patients with poor PS, the risk of death is higher than those with good PS.

In the present study, we also assessed whether other factors could be combined with ALBI to improve the ability of predicting prognosis in these patients. In clinical practice, ALBI and ECOG PS are simple, feasible, and easily to obtain, without dramatically increasing the economic burden of advanced NSCLC patients. Therefore, we analyzed the combination of ALBI with PS, which can reflect the liver function, performance status and immune level, in predicting prognosis of these patients, and find that this model is more effective than ALBI or PS alone. However, more studies are needed to determine its actual effectiveness in predicting outcomes.

Limitations

Several limitations should be addressed. First, this is a retrospective study, and the current results

may be affected by selection bias. For example, the relatively small number of patients throughout the analysis may have limited the accuracy of the results. Second, the lack of comprehensive data on liver function and immune indicators limits the discussion of the underlying mechanisms of ALBI grading and prognosis in advanced NSCLC. Third, little is known about the relationship between ALBI grade and the prognosis of advanced NSCLC patients who treated with immunotherapy. The actual relationship between ALBI and prognosis still needs further assessment. Therefore, the findings need to be further validated by multicenter, large-scale, prospective studies.

Conclusions

ALBI could serve as a prognostic factor, and ALBI combined with PS, as a novel model, is more predictive of survival in patients with advanced NSCLC treated with immunotherapy.

Conflicts of Interest

The authors declare there are no conflicts of interests.

Acknowledgments

Not applicable.

Authors' Contributions

X. Shi and X. Xu worked as supervisors and participated in the processes of study design, patient selection, data analysis, and quality evaluation. X. Xu, and G. Zhang evaluated the writing of the manuscript. J. Jiang, X. Xu, and D. Cao performed the study selection, data extraction, and writing. X. Shi, X. Xu, and D. Cao participated in the process of follow-up.

Data Availability Statement

The datasets are available from the corresponding author on reasonable request.

Ethics Approval

The study has been approved by the Medical Ethics Committee of People's Hospital of Macheng.

Informed Consent

The patients' written informed consent was waived since all the data in this retrospective study were anonymous.

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