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RELATIONSHIP BETWEEN PD-L1 EXPRESSION AND SMOKING HISTORY AND THEIR IMPACT ON THE EFFECTIVENESS OF IMMUNOTHERAPY IN NON-SMALL CELL LUNG CANCER

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Non-small cell lung cancer remains one of the leading causes of cancer-related mortality worldwide, and the clinical efficacy of immune checkpoint inhibitors varies considerably among patients. Reliable predictive factors for immunotherapy response are still insufficiently defined, particularly regarding the combined influence of tumor PD-L1 expression and smoking history. This study included 102 patients with metastatic non-small cell lung cancer treated with immune checkpoint inhibitors as monotherapy or in combination with chemotherapy. PD-L1 expression, smoking burden, and clinical outcomes were retrospectively analyzed. Higher smoking intensity was associated with significantly improved progression-free survival and overall survival, with median overall survival increasing from 9.7 to 26.3 months across smoking strata. A significant interaction between high PD-L1 expression and heavy smoking was observed, demonstrating enhanced treatment response only in patients with substantial tobacco exposure. Smoking and PD-L1 expression were identified as independent favorable prognostic factors, suggesting their combined utility for refining immunotherapy stratification strategies in metastatic non-small cell lung cancer.

Key words: non-small cell lung cancer, PD-L1, smoking history, immunotherapy, immune checkpoint inhibitors, survival outcomes.

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ВЗАЄМОЗВ'ЯЗОК ЕКСПРЕСІЇ PD-L1 І ТЮТЮНОВОГО АНАМНЕЗУ ТА ЇХ ВПЛИВ НА ЕФЕКТИВНІСТЬ ІМУНОТЕРАПІЇ ПРИ НЕДРІБНОКЛІТИННОМУ РАКУ ЛЕГЕНІ

Недрібноклітинний рак легені залишається однією з провідних причин онкологічної смертності у світі, а клінічна ефективність інгібіторів імунних контрольних точок істотно варіює між пацієнтами. Надійні предиктори відповіді на імунотерапію досі недостатньо визначені, особливо щодо комбінованого впливу експресії PD-L1 пухлини та тютюнового анамнезу. У дослідження включено 102 пацієнти з метастатичним недрібноклітинним раком легень, які отримували інгібітори імунних контрольних точок у монотерапії або в комбінації з хіміотерапією. Ретроспективно проаналізовано експресію PD-L1, тютюнове навантаження та клінічні результати. Вища інтенсивність куріння асоціювалася зі статистично значущим покращенням виживаності без прогресування та загальної виживаності, при цьому медіана загальної виживаності зростала з 9,7 до 26,3 місяця залежно від стратифікації за курінням. Виявлено значущу взаємодію між високою експресією PD-L1 та інтенсивним курінням, що проявлялася посиленою відповіддю на лікування лише у пацієнтів із значним тютюновим анамнезом. Куріння та експресія PD-L1 визначені як незалежні сприятливі прогностичні фактори, що свідчить про доцільність їх комбінованого використання для удосконалення стратегії стратифікації пацієнтів для імунотерапії при метастатичному недрібноклітинному раку легень.

Ключові слова: недрібноклітинний рак легені, PD-L1, тютюновий анамнез, імунотерапія, інгібітори імунних контрольних точок, виживаність.

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Current treatment approaches for metastatic non-small cell lung cancer (NSCLC) have undergone substantial changes with the introduction of immune checkpoint inhibitors (ICIs), which have demonstrated significant improvements in survival compared with conventional chemotherapy [4]. Despite these advances, the efficacy of ICIs remains highly variable, highlighting the need to identify reliable prognostic and predictive biomarkers. At present, programmed death-ligand 1 (PD-L1) expression is the most widely used clinical marker for selecting patients for immunotherapy; however, its prognostic value is limited, as not all patients with high PD-L1 expression achieve an objective response [12]. Pooled evidence from meta-analyses suggests that the effectiveness of ICIs is determined by a complex interplay of clinical and molecular factors, including both tumor characteristics and patient-related variables [3].

One such factor is smoking history, which plays a key role in lung cancer pathogenesis and in shaping the tumor immune microenvironment. Smoking is associated with an increased tumor mutational burden, which in turn enhances tumor immunogenicity and potentially improves responses to ICIs [6]. Experimental and clinical studies have demonstrated that tobacco carcinogens can directly influence PD-L1 expression through activation of signaling pathways, including the aryl hydrocarbon receptor, thereby promoting tumor immune evasion [9]. Similar mechanisms also support the involvement of smoking in the activation of additional immunoregulatory cascades that contribute to antitumor immune responses.

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Clinical studies indicate that smoking status may affect the efficacy of ICIs in patients with metastatic NSCLC. In particular, patients with a history of smoking have been shown to have a higher likelihood of response to therapy compared with never-smokers [10]. However, these findings remain inconsistent, as some studies suggest a complex and non-linear relationship that depends on smoking intensity, duration of exposure, and other clinical parameters. Moreover, contemporary approaches emphasize that a detailed assessment of smoking history may be crucial for predicting immunotherapy efficacy and optimizing treatment strategies [1].

Despite existing evidence, the relationship between PD-L1 expression, smoking status, and ICI efficacy remains insufficiently explored. Most studies have evaluated these factors in isolation, whereas their combined impact on clinical outcomes may be of substantial importance for treatment personalization.

The purpose of the study was to evaluate the association between PD-L1 expression, smoking status, and treatment response in patients with metastatic non-small cell lung cancer receiving immune checkpoint inhibitors, as well as to identify independent predictors of survival.

Materials and methods. This study was conducted at the clinical base of the Department of Oncology and Radiology of Sumy State University, located at the Sumy Regional Clinical Oncology Center. The study was performed within the framework of the department's scientific and clinical activities and involved the analysis of clinical data obtained from patients treated at this institution. The availability of medical records, pathological reports, and follow-up information enabled the comprehensive assessment of treatment outcomes and prognostic factors in patients with metastatic NSCLC.

The study included 102 patients with metastatic NSCLC. All patients received immunotherapy with immune checkpoint inhibitors either as monotherapy or in combination with chemotherapy. Data collection was performed at the Sumy Regional Clinical Oncology Center between 2016 and 2025. Inclusion criteria were histologically confirmed non-small cell lung cancer, presence of metastatic disease, treatment with atezolizumab or pembrolizumab, age ≥18 years, and availability of PD-L1 expression data. Exclusion criteria included small cell lung cancer or other histological tumor types, absence of metastatic disease, lack of available PD-L1 expression assessment, incomplete clinical or follow-up data, and age <18 years.

Key clinical and pathological variables were prospectively assessed, including age, sex, histological tumor type, smoking status, Eastern Cooperative Oncology Group (ECOG) performance status, treatment regimen, type of ICIs, and line of therapy. Patients were categorized according to smoking status into smokers and non-smokers. Non-smokers were defined as individuals who had smoked fewer than 100 cigarettes during their lifetime. Smokers included both current smokers and former smokers who had quit smoking less than one year prior to study inclusion. Smoking burden (pack-years) was calculated as the number of cigarette packs smoked per day multiplied by the number of years of smoking. The cut-off value for stratification according to smoking burden was determined using the mean value method. Patients were stratified according to PD-L1 expression levels based on clinically established thresholds used for immunotherapy decision-making, with groups defined as 1–49% and ≥50%. PD-L1 expression data were obtained from pathology reports available in the patients' medical records. PD-L1 testing had been performed as part of routine clinical practice prior to initiation of immunotherapy, since PD-L1 status is required for treatment decision-making in patients considered for immune checkpoint inhibitor therapy. The present study had a retrospective design and did not involve additional immunohistochemical analyses. Information on PD-L1 expression was extracted from archived pathological documentation and used for subsequent stratification and statistical analysis.

Ethical approval was granted by the Bioethics Committee of the Educational and Research Medical Institute of Sumy State University (protocol No. 5/12 dated December 17, 2024). All patients included in the study were adults (≥18 years of age), legally competent, and capable of providing informed consent. Written informed consent for participation and use of clinical data for research purposes was obtained from all patients prior to inclusion in the study.

In the studied cohort, treatment response was evaluated according to the immune Response Evaluation Criteria in Solid Tumors (iRECIST) guidelines. A complete response was defined as the disappearance of all signs of tumor involvement. A partial response was defined as at least a 30% reduction in the sum of target lesion diameters or an increase of less than 25% compared with baseline. Stable disease was recorded when neither criteria for partial response nor disease progression were met. Disease progression was defined as at least a 25% increase in the size of existing lesions or the appearance of new tumor lesions. Progression-free survival was calculated as the interval from the first infusion of systemic therapy to documented disease progression. Overall survival was defined as the time from treatment initiation to death from any cause.

Clinicopathological variables were presented as absolute numbers and percentages. Associations between categorical variables were analyzed using Fisher's exact test. Survival outcomes were estimated using the Kaplan-Meier method with corresponding curves and median values. The prognostic role of

smoking history and other clinicopathological factors was assessed using the Cox proportional hazards model. All calculations and graphical visualization were performed using Stata version 19.5 software. The level of statistical significance was set at $p < 0.05$.

Results of the study. The study included 102 patients with metastatic non-small cell lung cancer who received immunotherapy, including 79 patients with moderate PD-L1 expression (1–49%) and 23 patients with high PD-L1 expression (≥50%). No statistically significant differences were observed between groups with different PD-L1 expression levels regarding age, sex, ECOG performance status, treatment regimen, or line of therapy (all P>0.05), indicating their comparability. No significant difference in histological tumor type was found (P=0.051), although a trend toward a higher prevalence of adenocarcinoma was observed in the high PD-L1 expression group.

In contrast, statistically significant differences were identified according to smoking status (P=0.001). In the PD-L1 ≥50% group, patients with a heavy smoking history (≥28 pack-years) predominated. Additionally, differences in the type of immunotherapy were observed (P=0.022), with pembrolizumab being more frequently used in the lower PD-L1 expression group (Table 1).

Table 1

Association between clinicopathological characteristics of patients with metastatic non-small cell lung cancer and PD-L1 expression

Variables	Total, n=102 (100.0%)	PD-L1 expression 1–49%, n=79	PD-L1 expression ≥50%, n=23	P-value
Age, n (%):				
Median	60.7	60.8	60.6	0.547
Range	34–79	35–78	34–79	
< 60	41 (40.2)	33 (41.8)	8 (34.8)	
≥ 60	61 (59.8)	46 (58.2)	15 (65.2)	
Sex, n (%):				
Female	21 (20.6)	15 (19.0)	6 (26.1)	0.459
Male	81 (79.4)	64 (81.0)	17 (73.9)	
Smoking status, n (%):				
Non-smokers	32 (31.4)	26 (32.9)	6 (26.1)	0.001
Smokers <28 pack-years	35 (34.3)	33 (41.8)	2 (8.7)	
Smokers ≥28 pack-years	35 (34.3)	20 (25.3)	15 (65.2)	
ECOG performance status, n (%):				
0–1%	97 (95.1)	76 (96.2)	21 (91.3)	0.315
≥2%	5 (4.9)	3 (3.8)	2 (8.7)	
Immunotherapy regimen, n (%):				
ICI monotherapy	33 (32.4)	28 (35.4)	5 (21.7)	0.216
ICI+chemotherapy	69 (67.6)	51 (64.6)	18 (78.3)	
Type of ICI, n (%):				
Pembrolizumab	68 (66.7)	55 (69.6)	13 (56.5)	0.022
Atezolizumab	34 (33.3)	24 (30.4)	10 (43.5)	
Histology, n (%):				
Adenocarcinoma	57 (55.9)	40 (50.6)	17 (73.9)	0.051
Squamous cell carcinoma	45 (44.1)	39 (49.4)	6 (26.1)	
Line of therapy, n (%):				
First	88 (86.3)	68 (86.1)	20 (87.0)	0.914
Second	14 (13.7)	11 (13.9)	3 (13.0)	

Note: Fisher's exact test was used to calculate p-values.

Thus, the patient groups were generally comparable in terms of the main clinicodemographic characteristics, with the exception of smoking status and the type of administered immunotherapy.

During the follow-up period, disease progression was recorded in 94 patients. The progression rate was 100.0% (32/32) among non-smokers, 94.3% (33/35) among patients with a smoking history of <28 pack-years, and 82.9% (29/35) among patients with ≥28 pack-years.

In the analysis of progression-free survival, statistically significant differences were observed between groups depending on smoking burden (P<0.001). The median progression-free survival was 4.7 months in non-smokers, 5.5 months in patients with <28 pack-years, and 15.9 months in patients with ≥28 pack-years, indicating a substantial prolongation of time to progression with increasing smoking exposure (Fig. 1).

Death was recorded in 97 patients. The incidence of death events was 100.0% (32/32) among non-smokers, 100.0% (35/35) in the group with <28 pack-years, and 85.7% (30/35) in the group with ≥28 pack-years.

The analysis of overall survival also demonstrated statistically significant differences between groups (P<0.001). Median overall survival was 9.7 months in non-smokers, 12.7 months in patients with <28 pack-years, and 26.3 months in patients with ≥28 pack-years (Fig. 2).

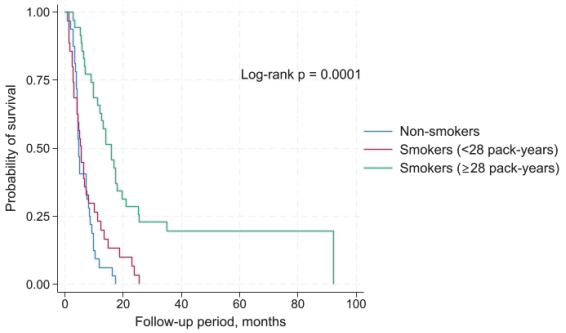

Fig. 1. Progression-free survival in patients with metastatic non-small cell lung cancer stratified by smoking status.

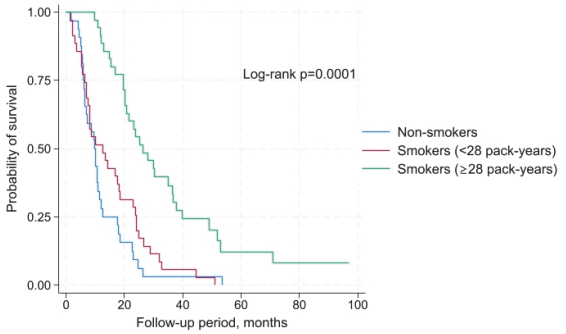

Fig. 2. Overall survival in patients with metastatic non-small cell lung cancer stratified by smoking status.

Thus, for both progression-free survival and overall survival, a statistically significant association was established between smoking intensity and survival outcomes. Greater smoking history was associated with longer survival indicators.

In the non-smoking group (n=32), no statistically significant association between PD-L1 expression level and treatment response was observed (P=0.102). Similarly, among patients with a smoking history of <28 pack-years (n=35), this relationship also did not reach statistical significance (p=0.171).

In contrast, in the group of patients with ≥28 pack-years (n=35), a statistically significant association between PD-L1 expression level and treatment response was demonstrated (P=0.028). In patients with high PD-L1 expression (≥50%), a higher rate of objective response was observed along with an absence of disease progression events (Table 2).

Table 2

Association between treatment response and PD-L1 expression in patients stratified by smoking status

Smoking status and response to treatment, n=102		PD-L1 expression 1–49%	PD-L1 expression ≥50%, n=23
Non-smokers, n=32	Complete response	0 (0.0)	0 (0.0)
	Partial response	11 (42.3)	4 (66.7)
	Stable disease	11 (42.3)	0 (0.0)
	Disease progression	4 (15.4)	2 (33.3)
	Total	26 (100.0)	6 (100.0)
P-value	0.102		
Smokers (<28 pack-years), n=35	Complete response	0 (0.0)	0 (0.0)
	Partial response	10 (30.3)	2 (100.0)
	Stable disease	14 (42.4)	0 (0.0)
	Disease progression	9 (27.3)	0 (0.0)
	Total	33 (100.0)	2 (100.0)
P-value	0.171		
Smokers (≥28 pack-years), n=35	Complete response	1 (5.0)	5 (33.3)
	Partial response	13 (65.0)	10 (66.7)
	Stable disease	5 (25.0)	0 (0.0)
	Disease progression	1 (5.0)	0 (0.0)
	Total	20 (100.0)	15 (100.0)
P-value	0.028		

Note: Fisher's exact test was used to calculate p-values.

Thus, the association between high PD-L1 expression and better treatment response was observed only in patients with a significant smoking history, whereas no statistically significant relationship was found in non-smokers or in patients with a shorter smoking history.

According to the results of multivariate analysis, higher smoking burden and PD-L1 expression were identified as independent favorable prognostic factors for progression-free survival, both being associated with a reduced risk of disease progression (P=0.0001 and P=0.007, respectively). In contrast, second lines of therapy were associated with an increased risk of progression and represented an independent unfavorable predictor (P=0.031). Other clinicopathological characteristics, including age, sex, histological type, type of immune checkpoint inhibitor, and treatment regimen, did not demonstrate a statistically significant impact on progression-free survival, although a trend toward worse prognosis with increasing age was observed (Fig. 3).

The analysis of overall survival showed that higher smoking burden and PD-L1 expression remained independent favorable prognostic factors associated with a reduced risk of death (P=0.0001 and P=0.006, respectively). In contrast, none of the clinical factors, including line of therapy, demonstrated a statistically significant independent effect on overall survival. A trend toward worse prognosis with increasing age persisted, although it did not reach statistical significance. Other variables also showed no independent effect after adjustment for confounding factors (Fig. 4).

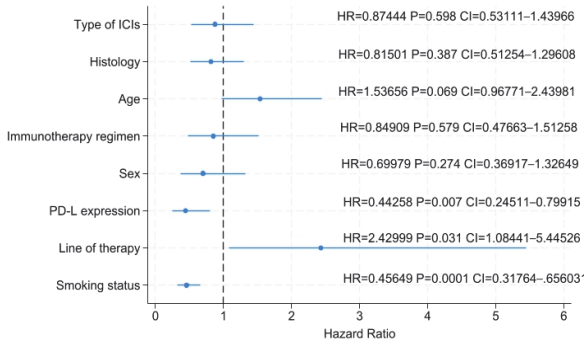

Fig. 3. Forest plot demonstrating independent predictors of progression-free survival in patients with metastatic non-small cell lung cancer receiving immune checkpoint inhibitors.

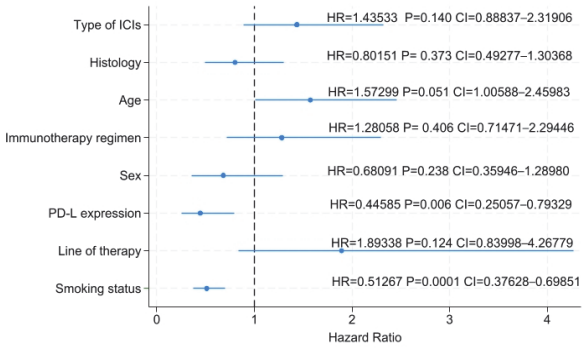

Fig. 4. Forest plot demonstrating independent predictors of overall survival in patients with metastatic non-small cell lung cancer receiving immune checkpoint inhibitors.

In the present study, it was shown that in patients with metastatic non-small cell lung cancer treated with immune checkpoint inhibitors, a higher smoking history was associated with improved progression-free survival and overall survival outcomes. Specifically, median progression-free survival increased from 4.7 months in non-smokers to 15.9 months in patients with ≥28 pack-years, whereas median overall survival increased from 9.7 to 26.3 months, respectively. In addition, high PD-L1 expression (≥50%) was associated with a better treatment response only in patients with a substantial smoking history, suggesting a potential modifying effect of smoking on the predictive value of this biomarker.

Discussion. These findings may be explained by biological mechanisms underlying the interaction between smoking and tumor immune response. It has been demonstrated that tobacco carcinogens can induce PD-L1 expression through activation of the aryl hydrocarbon receptor (AhR). In the study by Wang et al. [9], activation of this receptor by components of tobacco smoke was shown to lead to transcriptional upregulation of PD-L1, thereby promoting tumor immune evasion. At the same time, increased PD-L1 expression may render tumors more sensitive to PD-1/PD-L1 blockades, which partially explains better efficacy of immune checkpoint inhibitors in smokers. Additionally, according to Zhu et al. [15], nicotine-related signaling through the α5 nicotinic acetylcholine receptor activates the STAT3/Jab1 cascade, further contributing to PD-L1 upregulation and immune escape. Thus, smoking simultaneously enhances tumor immune evasion and creates conditions that may increase sensitivity to immunotherapy.

Another important mechanism is the increase in tumor mutational burden in smokers. In a preclinical study, Stabile et al. [8] demonstrated that tobacco carcinogen-induced tumors are characterized by high tumor mutational burden and increased PD-L1 expression. This leads to the generation of a higher number of neoantigens, which can be recognized by the immune system, thereby improving the efficacy of immune checkpoint inhibitors. Consistently, Minervini et al. [6] reported that smoking is associated with a more immunogenic tumor phenotype, which may explain better treatment outcomes in this patient population.

Our results are consistent with clinical evidence from previous studies. Wang et al. [10] demonstrated that patients with a history of smoking had better outcomes with immune checkpoint inhibitor therapy compared with non-smokers, including higher objective response rates and improved survival. In a subsequent analysis by the same group using a multi-omics approach, it was shown that a detailed smoking history allows more precise prediction of immunotherapy efficacy and helps differentiate the benefit of monotherapy versus combination regimens [11]. Similarly, Kim et al. [5] reported that smoking status at diagnosis influences the efficacy of anti-PD-1/PD-L1 therapy, with smokers showing a tendency toward better treatment outcomes.

Meta-analyses also support the relevance of clinical factors, including smoking, in predicting immune checkpoint inhibitor efficacy [14]. According to Xiao et al. [12], smoking status is one of the factors influencing response to immunotherapy, although its role may vary depending on other patient characteristics. A broader analysis further emphasized that the effectiveness of immune checkpoint inhibitors is determined by a combination of factors, and none of them, including PD-L1, should be considered in isolation [3]. This is consistent with our findings, which demonstrate that the predictive value of PD-L1 depends on smoking history.

Notably, in our study, the association between high PD-L1 expression and treatment response was statistically significant only in patients with ≥28 pack-years. This suggests that PD-L1 expression alone may not be a sufficient biomarker without considering the biological context of the tumor [7]. Similar conclusions are supported by Yang et al. [13], who emphasized that the impact of smoking on the efficacy of non-small cell lung cancer therapy is complex and depends on treatment modality and tumor characteristics. Additionally, Bergman et al. [1] showed in a meta-analysis that smoking may modify the effectiveness of various anticancer treatments, including immunotherapy.

It is also important to consider that smoking affects not only PD-L1 but also other components of the tumor immune microenvironment. For example, Guo et al. [2] demonstrated that smoking induces PD-L2 expression and promotes regulatory T-cell recruitment via nuclear factor kappa B-dependent

mechanisms, further modifying the immune response. These findings support the notion that smoking history is a key clinical factor that not only influences survival but also modifies the predictive value of PD-L1 expression. The combined assessment of these parameters may therefore represent a promising approach for patient stratification and personalization of immunotherapy in metastatic NSCLC.

Limitations. Study limitations should also be acknowledged. First, the relatively small sample size and single-center design may limit the generalizability of the findings. Second, heterogeneity of treatment approaches (monotherapy versus combination with chemotherapy) and the lack of assessment of additional biomarkers, such as tumor mutational burden, may have influenced the accuracy of interpretation of immunotherapy efficacy predictors.

Conclusion

In patients with metastatic non-small cell lung cancer treated with immune checkpoint inhibitors, smoking history and PD-L1 expression were identified as independent favorable prognostic factors associated with improved progression-free and overall survival. Patients with a heavy smoking history (≥28 pack-years) demonstrated significantly longer survival outcomes compared with non-smokers and patients with lower smoking exposure. Furthermore, the predictive value of high PD-L1 expression (≥50%) was observed predominantly in patients with substantial tobacco exposure, suggesting a significant interaction between smoking-related biological mechanisms and tumor immune response. These findings indicate that the combined assessment of smoking burden and PD-L1 expression may improve patient stratification and contribute to more individualized selection of immunotherapy strategies in metastatic non-small cell lung cancer.

Prospects for further research. Future studies should include larger multicenter cohorts and incorporate additional biomarkers, particularly tumor mutational burden and molecular profiling parameters, to further refine predictive models of immunotherapy efficacy and validate the clinical applicability of the observed associations.

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