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Hyperprogressive disease in patients receiving immune checkpoint inhibitors

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A B S T R A C T

Hyperprogressive disease (HPD) is an unexpected response pattern observed in immune checkpoint therapy and associated with poor prognosis in several cancers. Such patients can't benefit from immunotherapy and even experience a rapid disease progression. At present, many researchers have explored the HPD phenomenon, but there is no consensual definition of HPD in different studies. The incidence of HPD is about 4%-29% in various tumors. Many studies demonstrated that HPD was associated with worse prognosis, but the mechanism of HPD has not yet been fully clarified. Predictive factors in patients with HPD before treatment is one of the keys to managing patients receiving immune checkpoint inhibitors. Some factors, such as *MDM2/4* amplification, *EGFR* mutations, and old age may be risk factors for HPD, but the results are discordant in different studies. Performing imaging evaluation and biopsy as early as possible is the main method to avoid the iatrogenic injury of immunotherapy at present.

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Introduction

Immune checkpoint inhibitors (ICI) have been approved for the treatment of various cancers such as melanoma,[1,2] non-small-cell lung cancer (NSCLC),[3] head and neck squamous cell carcinoma (HNSCC),[4] and showed improvement in patients' survival rate. Different from chemotherapy or targeted therapy, ICI are mainly targeting cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), programmed cell death protein 1 (PD-1), and its ligand PD-L1, which can inhibit tumor immune escape and promote a tumor-specific immune response. Therefore, ICI can induce a durable immune response. With the wider clinical application of ICI, pseudoprogression and hyperprogressive disease (HPD) have been observed as 2 novel response patterns. Pseudoprogression after immunotherapy was reported in patients with melanoma.[5] The tumor size increased at first because of inflammatory cell infiltration and then decreased. HPD was first reported as paradoxical progression induced by ICI in 2016.[6] The tumor size also increased during the early assessment. However, different from pseudoprogression, the tumor still grows fast after imaging evaluation and leads to poor prognosis. 20 cases of progressive disease (PD) were observed in 89 NSCLC patients receiving anti-PD-1/PD-L1 therapy, and 9 of them experienced rapid disease progression at the first assessment. The tumor growth rate (TGR) of these patients increased by more than 50% after treatment. Champiat et al.[7] made a systematic exposition of HPD in 2017, and about 9% of patients treated with anti-PD-1/PD-L1 showed rapid growth in tumors. Meanwhile, the overall survival (OS) of these patients was worse. These studies remind us that immunotherapy, which is one of the most revolutionary therapies in the field of oncology, could worsen the condition of some patients. It is controversial whether HPD is specifically caused by ICI as an immune-related adverse event.[8,9] Nevertheless, the HPD phenomenon has already brought challenges for the clinical use of ICI.

This review focused on the HPD phenomenon, including the definition, incidence, potential mechanisms, and predictors of HPD, in order to provide a reference for the solutions of HPD.

Definitions of HPD

At present, several studies have reported abnormal growth of tumors after initiation of ICI in many cancers, including melanoma,[10] NSCLC,[11,12] HNSCC,[13] and other tumor types.[14,15] However, there is no agreed definition of HPD, and the assessment approaches of HPD in different studies are not identical (Table 1). Champiat et al.[7] defined HPD as a disease progression consistent with the Response Evaluation Criteria in Solid Tumors (RECIST) and TGR that was more than 2-fold greater than before treatment. While another study of NSCLC defined HPD as a more than 50% increase in TGR. TGR was calculated based on tumor volume, which was equivalent to the change of tumor volume per unit time. The tumor was considered as sphere approximately and R is the radius of the sphere, so the volume of tumor (V) is equal to $V = 4\ \pi\ R^3\ /\ 3$. The TGR can be calculated by $TGR = (V_t - V_0)\ /\ t$, where V_t is the tumor volume at time t and V_0 is the volume at baseline.[16,17] In another study, tumor growth kinetics (TGK) increasing more than 2 times was regarded as a criterion of HPD. TGK was calculated by the sum of the largest diameters of the target lesions (Σ), and TGK was equal to $TGK = (\Sigma_t - \Sigma_0)\ /\ t$, where Σ_t is the sum of the largest diameters of the target lesions at time t and Σ_0 is the sum of the largest diameters at baseline.[13] That means when TGK is doubled, TGR increases by 8-fold. Therefore, although both TGR and TGK consider the acceleration of tumor growth, there are considerable

Table 1
Definition, incidence, predictors, and prognosis of HPD.

Tumor Histology	Drugs	HPD Criteria	Incidence	Predictor	Prognosis	References
HNSCC	Anti-PD-1/PD-L1 monotherapy	$TGK_R \geq 2$	29.4% (10/34)	Regional recurrence	(1) PFS HPD vs non-HPD (2.9 vs 5.1 months, P = 0.02) (2) OS HPD vs non-HPD (6.1 vs 8.1 months, P = 0.77)	[13]
NSCLC	ICI	At least 3 of: (1) TTF < 2 months (2) ≥50% increase in the sum of target lesions major diameters (3) ≥2 new lesions in the organ already involved (4) Spread to a new organ (5) ECOG ≥ 2	25.7% (39/152)	No association between *MDM2/4* and HPD		[11]
NSCLC	PD-1/PD-L1 inhibitors	>50% increase in TGR	13.8% (56/406)	>2 metastatic sites	OS HPD vs non-HPD (3.4 vs 6.2 months, P = 0.003)	[16]
NSCLC	PD-1/PD-L1 inhibitors	(1) >2-fold increase in TGR (2) >2-fold increase in TGK (3) TTF < 2 months	(1) 20.5% (54/263) (2) 20.9% (55/263) (3) 37.3% (98/263)*	(1) Lower frequencies of $CCR7^{-}CD45RA^{-}CD8^{+}$ T cells (2) Elevated frequencies of $TIGIT^{+}PD\text{-}1^{+}CD8^{+}$ T cells (3) No association between advanced age, *EGFR* mutations and HPD	(1) OS HPD vs non-HPD (50 vs 205 days, P < 0.001) (2) PFS HPD vs non-HPD (19 vs 48 days, P < 0.001) (3) More metastatic sites, liver metastasis and high level of LDH in HPD patients (4) RMH, GRIM and LIPI scores are higher in HPD patients	[12]
GC	Anti-PD-1 monotherapy	(1) TTF < 2 months (2) >50% increase in tumor burden (3) Progression pace > 2x	11.1% (4/36)			[14]

(*continued on next page*)

Table 1 (*continued*)

Tumor Histology	Drugs	HPD Criteria	Incidence	Predictor	Prognosis	References
Melanoma (45), lung (13), renal (9), colorectal (8), others (56)	Anti-PD-1/PD-L1 monotherapy	(1) RECIST progression (2) >2-fold increase in TGR	9.2% (12/131)	>65 years old	(1) OS HPD vs non-HPD (4.6 vs 7.6 months, P = 0.19) (2) Incidence of new lesions HPD vs non-HPD (33% vs 84%, P = 0.0019)	[7]
Melanoma (51), NSCLC (38), HNSCC (11), Cutaneous squamous cell carcinoma (9), renal cell carcinoma (6), colorectal cancer (5)	CTLA-4, PD-1/PD-L1 inhibitors or other agents	(1) TTF < 2 months (2) >50% increase in tumor burden (3) Progression pace > 2x	3.9% (6/155)	(1) *MDM2/4* amplification (2) *EGFR* mutations		[18]
Melanoma (12), pancreatic (9), renal (7), colon (7), breast (7), lung (5), others (9)	IL-2, PD-1 inhibitors and/or CTLA-4 inhibitors		10.7% (6/56)	CNI score		[24]

Abbreviations: CNI, chromosome number instability; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; ECOG, Eastern Cooperative Oncology Group; HPD, hyperprogressive disease; HNSCC, head and neck squamous cell carcinoma; ICI, immune checkpoint inhibitors; NSCLC, non-small-cell lung cancer; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed cell death protein ligand 1; PFS, progression-free survival; TGK, tumor growth kinetics; TGK_R, tumor growth kinetics ratio; TGR, tumor growth rate; TTF, time-to-treatment failure.

* The incidence of HPD was calculated by TGR, TGK and TTF respectively.

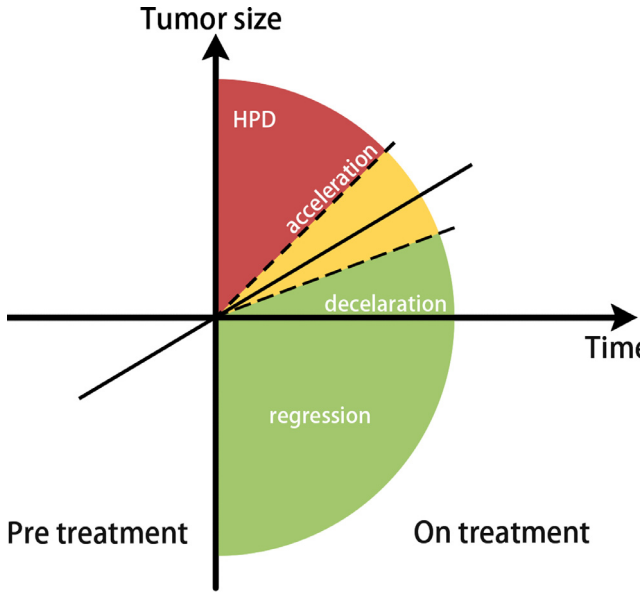

Fig. 1. Response patterns after the initiation of immunotherapy are elevated by the change of tumor growth speed in most studies. Abbreviations: HPD, hyperprogressive disease.

differences between them in clinical practice. Moreover, some patients discontinued due to the early disease progression in treatment, which may result in an underestimation of the incidence of HPD in these studies. Kato et al.[18] proposed a more complex HPD criterion, including time-to-treatment failure (TTF) of less than 2 months, a >50% increase in tumor burden, and a more than 2-fold increase in progression pace. This criterion took into account the clinical characteristics of the patient after treatment, but as in previous studies, the pretreatment imaging data was required for comparison. As a result, it didn't apply to patients who lack pretreatment data. And it involved only the target lesion but not the occurrence of new lesions. Lo Russo et al.[11] used 5 clinical and imaging data as criteria in the study to identify HPD in patients treated with ICI as first-line treatment. Patients who discontinued early or whose tumors had metastasized can be identified when HPD occurred (Table 1).

Differences in HPD criteria may lead to large differences in the incidence of HPD in different studies. Kim et al.[12] analyzed the incidence of HPD by 3 criteria in the same patients. The results calculated by TGR and TGK were about 20%. However, nearly 40% of patients were identified as HPD patients by TTF criteria. In addition, most studies have used the change of growth rate as the main criterion for HPD (Fig 1). This standard has a premise that the rate of tumor progression is constant without immunotherapy, but the control group was not set in most studies. Therefore, whether the tumor will experience accelerated growth without immunotherapy requires further verification.

Incidence of HPD

There was a difference in the incidence of HPD observed in different solid tumors. The incidence of HPD in HNSCC patients receiving anti-PD-1/PD-L1 monotherapies was up to 29.4%,[13] and in the 2 studies of NSCLC, respectively. HPD occurred in 25.7% and 13.8% of patients.[11,16] The incidence of HPD in other multitumor studies was about 4%-11%, and HPD was also found to be independent of tumor type. In most studies, HPD was mainly seen in patients treated with anti-PD-1/PD-L1 monotherapy, and there was no significant difference between these 2 drugs.[18] In

addition, the incidence of HPD was not associated with tumor histology, hematology at baseline, treatment line, T stage, or M stage.[7,13] It is noted that the data is limited by the retrospective nature of the studies, such as the underestimation of incidence caused by death or termination of treatment before the TGR assessment, and the association between specific tumor type and HPD needs to be further studied.

Potential mechanisms of HPD

Champiat et al.[19] proposed 5 hypotheses about the occurrence of HPD, including the expansion of regulatory T (Treg) cells, exhaustion of T cells, modulation of tumor-promoting cells, aberrant inflammation, and activation of an oncogenic pathway. Although these hypotheses are different in the mechanisms of HPD, it is agreed that the blockade of PD-1 may induce a complicated cascade of reactions, which eventually leads to cancer immune escape by mediating immune suppression or directly accelerating tumor growth. The expansion of Treg cells was demonstrated in gastric cancer patients with HPD.[14] PD-1 blockade enhanced the activity of Treg cells, although ICI were previously thought to inhibit tumor immune escape.

Some researchers believe that the occurrence of HPD may not be caused by PD-1 blockade since it can inhibit tumor growth in theory but by the Fc fragment of anti-PD-1 antibody. In a mouse model of HPD, the group treated with Nivolumab $F(ab)_2$ fragments showed a significantly lower rate of tumor growth compared with the group treated with whole antibody. And HPD-like growth was observed in whole antibody-treated group, but not in $F(ab)_2$ fragments-treated group. Immunohistochemical staining of tumor tissues in patients with HPD also showed the presence of $CD163^+CD33^+PD\text{-}L1^+$ epithelioid macrophages in the tumor, and similar macrophage aggregation was observed in mouse tumors. This study indicates that Fc fragments of anti-PD-1 antibody triggered the aggregation of epithelioid macrophages, and finally accelerated tumor growth speed and led to HPD by unknown signaling pathways.[11] When combined with Fc fragments of anti-PD-1 antibody, macrophages could recognize and phagocytose CD8+PD-1+ T cells, which is unfavorable to immunotherapy and even convert the blockade of PD-1 to activation.[20] Nivolumab belongs to the IgG4 subtype, and anti-PD-L1 antibody belongs to the IgG1 subtype. Thus, the affinity for Fc receptor of them is different. This study can't explain the non-significant difference in the incidence of HPD between anti-PD-1 antibody and anti-PD-L1 antibody. Although the removal of the Fc fragments inhibited the lung metastasis of mouse tumors, the growth rate of primary tumor was similar to that of the control group. And whether the deletion of Fc fragments would affect the efficacy of ICI and the occurrence of HPD also required more research to prove.[21]

Prognosis of patients with HPD

Compared with other patients, the prognosis of patients with HPD was poor. In the studies of HNSCC, the progression-free survival (PFS) was significantly shortened in patients with HPD (2.9 vs 5.1 months, $P = 0.02$).[13] In a study of various cancers, there was no significant difference in OS, although there was a tendency for OS to be worse in patients with HPD (4.6 vs 7.6 months, $P = 0.19$). And the non-significant difference in the OS of HPD and non-HPD patients is partly due to the small number of patients with HPD ($n = 12$).[7] In another study of NSCLC, OS in patients with HPD was significantly worse (3.4 vs 6.2 months, $P = 0.003$). However, these HPD patients were related to more metastatic sites, which may also contribute to the bad prognosis.[16] In another study of NSCLC, HPD patients had significantly shorter PFS (19 vs 48 days, $P < 0.001$) and OS (50 vs 205 days, $P < 0.001$), compared with non-HPD patients. And this study also showed that HPD patients had more metastatic sites, liver metastasis, and high level of LDH. In addition, prognostic scores (RMG, GRIM, and LIPI score) of HPD patients were higher than those with non-HPD[12] (Table 1). Upon reviewing the data from these studies, we found that although the OS and PFS of HPD patients were different in various tumor types and studies, it is shorter

than non-HPD patients in general.[7,12,13,16] The specific mechanism of HPD is not clarified, but the immunosuppression in tumor microenvironment, which can't be inhibited by anti-PD-1/PD-L1 antibody, was demonstrated in several studies.[11,14,20] Thus, the worse outcomes of patients with HPD was not unexpected. It is intriguing that the incidence of new lesions of HPD patients was significantly lower in 1 study (33% vs 84%, $P = 0.0019$).[7] We expect that further studies will provide more information about the prognosis of patients with HPD.

Predictive biomarkers

Considering the poor outcome of HPD patients, identifying them before treatment is necessary. *MDM2/4* amplification and *EGFR* mutations are considered to contribute to predicting the occurrence of HPD. In 1 study, all 6 patients with *MDM2/4* amplifications had a TTF of no more than 2 months, 4 of whom demonstrated HPD. And 2 of 10 patients with *EGFR* mutations had HPD, with TGR increased up to 40 times. The researchers believed that ICI can elevate interferon-gamma (IFN-γ), which eventually induced *MDM2* expression. In patients with *MDM2* amplification, ICI may lead to overexpression of *MDM2*.[18] However, other studies suggested that there was no significant association between *MDM2/4* amplification and HPD, as well as *EGFR* mutations and HPD.[11,12] Champiat et al.[7] found that 19% of patients over 65 years old presented HPD, compared with only 5% of patients younger than 64 years($P = 0.018$). On the other hand, there is no association between advanced age and HPD in other studies.[12,18] Local recurrence after exposure may also be a risk factor for HPD in HNSCC (90% vs 37%, $P = 0.008$),[13] but the relevant mechanisms are not yet clear. The expression of PD-L1 is used as a predictor of the response to PD-1/PD-L1 blockade in several cancers, such as NSCLC and bladder cancer.[22] But the PD-L1 positivity may not be able to predict the occurrence of HPD since there are also reports of HPD in urothelial bladder cancer and HNSCC, which with relatively high expression of PD-L1.[13,15]

Chromosome number instability (CNI) score showed good accuracy in predicting the response to immunotherapy. The CNI score was calculated by analyzing plasma cell-free DNA (cfDNA) via next-generation sequencing. Tumor cfDNA can be detected in plasma, which is mainly from necrotic or apoptotic tumor cells. Tumor cfDNA can provide references for the estimate of tumor mutational burden, microsatellite instability, and therapeutic efficacy.[23] Patients with no significant reduction in CNI score were 90% more likely to suffer from disease progression. In 6 patients with HPD, the CNI score predicted 5 of them would demonstrate HPD in about 6-9 weeks.[24] As a noninvasive method, detection of cfDNA and CNI score seems to be a good way to predict the occurrence of HPD, but more prospective studies are needed to further prove its role and accuracy.

How to deal with HPD

The occurrence of HPD brings some challenges to the management of patients receiving ICI since the prognosis of patients with HPD was poor. How to reduce harm to patients with HPD is an urgent problem to be solved, according to the Hippocratic oath: first, do no harm. When using ICI, it is the first thing to fully inform patients about the risk of HPD.[19] The incidence of 4%-29% is high enough, and some patients may not be able to bear the consequence, especially in patients with HNSCC and NSCLC.

In addition, the existence of pseudoprogression is also one of the interference factors in the identification of HPD. Pseudopregression was reported in melanoma, NSCLC, urothelial carcinoma and, renal cell carcinoma.[5,25-28] It is a phenomenon that the tumor is infiltrated by inflammatory cells, including CD103+CD8+ lymphocytes, and seems to grow fast.[29] HPD and pseudoprogression are both difficult to be described by RECIST criteria. Modified RECIST1.1 for immune based therapeutics (iRECIST) were proposed in 2017 and patients with unconfirmed

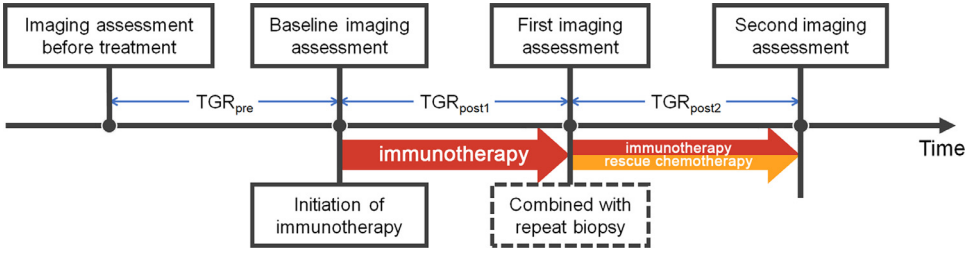

Fig. 2. Evaluation procedure for patients receiving ICI. When patients tend to present HPD in the first imaging assessment after the initiation of immunotherapy, TGR calculated before the treatment (TGRpre) or the results of biopsy might be helpful to identify HPD so that ICI can be replaced by rescue therapy to protect patients from further impairment. Otherwise, TGR calculated at the second evaluation (TGRpost2) is needed for the identification of HPD, and patients have to receive ICI until the second imaging assessment. Abbreviations: ICI, immune checkpoint inhibitors; TGR, tumor growth rate.

progression disease are recommended to perform reassessment earlier than planned.[19,30] In addition, another study showed that a large number of CD103+ lymphocytes infiltration is an indicator for good prognosis in patients with squamous NSCLC.[31] Thus, the progression of tumor observed at the first imaging assessment after initiation of immunotherapy did not mean that the therapy must be discontinued, as patients with pseudoprogression could benefit significantly from the following treatment.[32] But continuing immunotherapy is obviously inappropriate for patients with HPD, especially for those who do not have melanoma since they rarely experienced pseudoprogression. Biopsy when disease progress is useful for distinguishing between pseudoprogression and HPD status.[33]

Predicting the occurrence of HPD by *MDM2/4* amplification, *EGFR* mutation and CNI score before treatment is useful for patients who probably demonstrate HPD. But the predictive value of these biomarkers has not been validated. Thus, in clinical practice, early identification of HPD and timely replacement of ICI might be the only methods to avoid the potential risk for patients at present. It is reported that HPD patients had lower frequencies of CCR7-CD45RA-CD8+ T cells (effector/memory T cells) and higher frequencies of TIGIT+PD-1+CD8+ T cells (exhausted T cells). Monitoring tumor-associated immune cells might be helpful for the identification of patients with HPD.

TGR or TGK is an intuitive indicator for the identification of HPD, and most studies use it as criteria. In some clinical studies, the first assessment is usually performed 8 weeks after the initiation of immunotherapy, and the second assessment is performed in 4 weeks to determine whether HPD is presented. It may cause irreversible harm to patients who have already developed HPD if the treatment isn't interrupted. Furthermore, the OS of some HPD patients is less than 50 days,[12] which means that they have no chance to receive a rescue therapy, because they are not able to survive long enough for the first imaging evaluation. For patients receiving ICI as first-line therapy, shortening the time between the first and second assessments and performing biopsy timely will help to identify HPD status as early as possible.[19] For patients treated with ICI in second or subsequent lines of therapy, imaging records before immunotherapy is important. Pretreatment TGR is one of the keys to the early identification of HPD (Fig 2). For high-risk patients with *MDM2/4* amplification, *EGFR* mutations, or over 65 years old, assessment or monitoring should be performed at an early time. Combined assessment with biopsy to confirm the diagnosis, patients could stop immunotherapy or replace it with other therapy in time.[34] Rescue chemotherapy could be a choice for patients who already present HPD, although there is no powerful evidence that chemotherapy can reverse it.[35]

Conclusions

With the wider use of ICI in the clinical practice, immune-related adverse events and HPD have shown that immunotherapy may be harmful to patients. Clinicians should pay attention

to screening patients who cannot benefit or even demonstrated HPD when receiving ICI.[36] The lack of uniform criteria in the identification of HPD led to large differences in the incidence of HPD in different studies. TGR and TGK, which are used to assess changes in tumor growth speed, seem to be reasonable as criteria, but ignore the changes in tumor growth speed under natural conditions. And they are also limited in patients receiving immunotherapy as first-line therapy. As there are no consistent predictors of HPD at present, early identification is the only way to avoid risk when patients experience paradoxical disease progression. Patients will take unnecessary risks if they continue therapy when already have a tendency to present PD, as the prognosis was reported to be worse. Prediction is always the optimal solution for HPD. The association among *MDM2/4* amplification, *EGFR* mutation, CNI score and HPD needs more research to prove. And more HPD predictors need to be studied to improve predicting accuracy.

The Fc fragment of anti-PD-1 antibody has been shown to be involved in the occurrence of HPD.[11] Furthermore, the increase in IFN-γ secretion, upregulation of other immune checkpoints, and proliferation of Treg cells caused by PD-1/PD-L1 blockade suggest that the function of PD-1/PD-L1 in immune system might be more complicated and macrophages, Treg cells, and cytokines all take part in the occurrence of HPD. Considering the mechanism that the proliferation of Treg cells is involved in HPD, ICI are supposed to block PD-1 in effector T cells instead of Treg cells. Pathological biopsy, while distinguishing between HPD and pseudoprogression, is also helpful in studying the mechanisms and solutions of HPD.

CRediT authorship contribution statement

Haochen Zhang: Data curation, Writing - original draft. **Xuefeng Fang:** Writing - review & editing. **Dan Li:** Investigation. **Mengyuan Yang:** Investigation. **Linzhen Yu:** Data curation. **Yuwei Ding:** Data curation. **Hong Shen:** Supervision. **Ying Yuan:** Writing - review & editing.

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