Pan-cancer analysis highlights the role of \textit{PSENEN} in the prognosis and immunology of cancer

YANG Zerui\textsuperscript{1,4}\textsuperscript{*}, WEN Dingsheng\textsuperscript{1,3}\textsuperscript{*}, YE Yubing\textsuperscript{1,3}, CHEN Kai\textsuperscript{5}, QIU Zhikun\textsuperscript{1*}, LIU Xingyun\textsuperscript{2*}, LI Xiong\textsuperscript{1,3,4}\textsuperscript{*}

\textsuperscript{1}Key Specialty of Clinical Pharmacy, The First Affiliated Hospital of Guangdong Pharmaceutical University, Guangzhou 510000, China;
\textsuperscript{2}The Affiliated Nanhua Hospital, Hengyang Medical School, University of South China, Hengyang 421000, China;
\textsuperscript{3}School of Clinical Pharmacy, Guangdong Pharmaceutical University, Guangzhou 510086, China;
\textsuperscript{4}NMPA Key Laboratory for Technology Research and Evaluation of Pharmacovigilance, Guangdong Pharmaceutical University, Guangzhou 510086, China;
\textsuperscript{5}Department of Cardiothoracic Surgery, The First Affiliated Hospital of Guangdong Pharmaceutical University, Guangzhou 510000, China

\textsuperscript{*}These authors contributed equally to this work.

\textsuperscript* Corresponding authors] E-mail: lixiong@gdpu.edu.cn.

[Abstract] Background Presenilin enhancer-2 (\textit{PSENEN}, PEN-2), one of the four components of the $\gamma$-secretase complex, has been increasingly revealed to be significant in cancer types such as pancreatic cancer, gastric cancer, and breast cancer. However, the pan-cancer clinical relevance of \textit{PSENEN} remains unclear. Methods Raw data on \textit{PSENEN} expression in normal and cancer tissues were obtained from The Cancer Genome Atlas (TCGA) database and Genotype-Tissue Expression Project (GTEx). The difference of \textit{PSENEN} expression was analyzed using data from the TCGA repository and TIMER2 database. Meanwhile, Cox regression analysis and KM plotter were used to analyze the pan-cancer prognostic significance of \textit{PSENEN}. We also analyzed the correlation between \textit{PSENEN} expression and tumor immune infiltration using the TIMER and XCELL algorithms. Moreover, we used the TISIDB database to determine \textit{PSENEN} expression in different immune and molecular subtypes of human cancers. Pan-cancer analysis of genetic alteration of \textit{PSENEN} was performed using online tools such as cBioPortal and UALCAN. Finally, six Gene Expression Omnibus datasets from the Gene Expression Profiling Interactive Analysis database were used to validate the expression level of \textit{PSENEN} in lung adenocarcinoma (LUAD). Results Contrary to nonmalignant tissues, the expression level of \textit{PSENEN} was significantly upregulated in the cancerous tissues in 22 cancer types. Elevated \textit{PSENEN} expression was correlated with worse overall survival in 7 cancer types and with worse disease-specific survival in 8 of them. By using xCell algorithm, TIMER algorithm, and Spearman’s correlation analysis, we found that \textit{PSENEN} expression was closely correlated with the infiltration of immune cells across all cancer types. Moreover, aberrant \textit{PSENEN} expression was associated with 60 immune checkpoint pathway-related genes, microsatellite instability, and tumor immunity.

BIOINFORMATICS
1 Introduction

Cancer is the leading cause of morbidity and mortality worldwide, imposing major healthcare-related economic burdens on society\cite{1}. Numerous oncogenes and tumor suppressor genes have been identified, which have been linked to signaling pathways that govern cell growth or death. This enabled the exploration of anti-tumor agents and therapeutic techniques. However, there is still a long way to go to eradicate cancer due to the increasing drug resistance\cite{2}. Therefore, there is urgent need to identify new diagnostic biomarkers and therapeutic targets\cite{3}.

Notch, one of the most evolutionarily conserved pathways, plays a role in the regulation of a wide range of developmental processes, such as cell proliferation, cell death, and differentiation\cite{4-5}. Dysregulation of Notch has been shown to be closely associated with various diseases, including Alzheimer's disease and a range of malignancies\cite{4-6}. Many studies have demonstrated that abnormal activation of Notch plays a key role in tumorigenesis\cite{7-8}. γ-Secretase mediates the proteolytic cleavage of components involved in Notch signaling, including type I transmembrane proteins, amyloid precursor protein, and Notch receptors\cite{5}. Hence, γ-secretase is a potential cancer therapeutic target\cite{9-10}. Presenilin enhancer-2 (\textit{PSENEN}, PEN-2), along with presenilins, nicastrin, and anterior pharynx defective 1A (APH-1), is one of four essential components of the γ-secretase complex\cite{11-12}. Several studies have revealed the overexpression of \textit{PSENEN} in various cancer types, such as pancreatic, gastric, and breast cancers\cite{13-15}, suggesting that \textit{PSENEN} plays a role in tumor development. Moreover, a recent study suggested that PEN-2 is a direct molecular target of metformin\cite{16}. Notably, it was reported that metformin reduced the incidence of certain cancer types, including colon, liver, breast, pancreatic, and lung cancers\cite{17-18}. Metformin was also found to greatly promote anti-cancer efficacy and improve patient survival\cite{19-20}. Recent studies have also shown that \textit{PSENEN} is differentially expressed in many cancers types, and its role in low-grade gilomas (LGG) has been comprehensively analyzed\cite{21}. Nevertheless, the role of \textit{PSENEN} in other cancers is still far from being comprehensively clarified.

With the development of public databases, pan-cancer analysis is an important approach for researchers to analyze genes of interest and their associations with clinical prognosis, and to clarify the possible molecular mechanisms involved in tumorigenesis\cite{22}. In the present study, we performed a comprehensive systemic review of the roles of \textit{PSENEN} in various cancer types, including its expression, functions, and prognostic value. We also investigated the associations of \textit{PSENEN} with the tumor microenvironment, immune cell infiltration, and other immune-related biomarkers based on online web servers and the R program. This study highlighted the potential and critical roles of \textit{PSENEN} as a pan-cancer prognostic and immunotherapeutic biomarker, laying the foundation for subsequent prospective studies as well as functional and mechanistic experimental studies.
2 Materials and methods

2.1 Data collection and differential gene expression analysis

Pan-cancer RNA sequencing (RNA-seq) expression data, together with corresponding clinical follow-up information of 33 cancer types [including adrenocortical carcinoma (ACC), bladder urothelial carcinoma (BLCA), breast invasive carcinoma (BRCA), cervical squamous cell carcinoma and endocervical adenocarcinoma (CESC), cholangiocarcinoma (CHOL), colon adenocarcinoma (COAD), lymphoid neoplasm diffuse large B-cell lymphoma (DLBC), esophageal carcinoma (ESCA), glioblastoma multiforme (GBM), head and neck squamous cell carcinoma (HNSC), kidney chromophobe (KICH), kidney renal clear cell carcinoma (KIRC), kidney renal papillary cell carcinoma (KIRP), acute myeloid leukemia (LAML), brain lower-grade glioma (LGG), liver hepatocellular carcinoma (LIHC), lung adenocarcinoma (LUAD), lung squamous cell carcinoma (LUSC), mesothelioma (MESO), ovarian serous cystadenocarcinoma (OV), pancreatic adenocarcinoma (PAAD), pheochromocytoma and paraganglioma (PCPG), prostate adenocarcinoma (PRAD), rectal adenocarcinoma (READ), sarcoma (SARC), skin cutaneous melanoma (SKCM), stomach adenocarcinoma (STAD), stomach and testicular germ cell tumors (TGCT), thyroid carcinoma (THCA), thymoma (THYM), uterine corpus endometrial carcinoma (UCEC), uterine carcinosarcoma (UCS), and uveal melanoma (UVM)] of The Cancer Genome Atlas (TCGA), were downloaded from the UCSC Xena database (https://xenabrowser.net/datapages/). The sequencing data of PSENEN was also acquired from GTEx Project. The expression data was log2-transformed (TPM +1), and the missing data and duplicated values were excluded[23]. We compared the mRNA differences of PSENEN between cancerous and normal tissues by t-tests; \( P<0.05 \) was set as a threshold for statistical significance, and calculations were performed using R software (version 4.0.2, https://www.Rproject.org). The TIMER2 database was also used to analyze the difference in expression of PSENEN between normal and cancer tissues.

2.2 Survival analysis

Overall survival (OS) and disease-specific survival (DSS) were used for survival analysis, and Cox proportional hazard models and Kaplan–Meier (KM) plotter analysis were carried out using the "survival" packages in R to explore the association between PSENEN expression and patient prognosis. The log-rank test was used to compare the survival times between two groups with high or low PSENEN expression[23]. The results were displayed as forest plots (using the “forestplot” package in R) and survival curves.

2.3 Analysis of correlation between PSENEN expression and tumor immune microenvironment

The infiltration scores of B cells, CD4+ T cells, CD8+ T cells, neutrophils, macrophages, and dendritic cells (DC) were analyzed using the TIMER algorithms of the R software package. XCELL algorithms were used to estimate the abundance scores of 64 immune cell types. Next, we calculated the Spearman’s correlation coefficients between the expression level of PSENEN and immune cell infiltration scores in each tumor using the corr.test function of the psych R package (version 2.1.6).

2.4 Analysis of correlation between PSENEN expression and immune checkpoints

We downloaded sets of two types of genes involved in immune checkpoint-based pathways from the literature, including 24 genes associated with immune suppression and 36 genes associated with immune enhancement, and obtained their pan-
cancer expression profiles. Then, we analyzed the correlation of *PSENEN* with these 60 genes by using Spearman correlation analysis in R.

The gene mutation data of 33 cancer types were derived from TCGA database in UCSC Xena. The TMB of each tumor was calculated using the R package maftools (version 2.8.05). We obtained the MSI score of each tumor from a previous study.[24] Spearman’s correlation coefficient was used to elaborate the correlations between the expression level of *PSENEN* and MSI/TMB.[23]

### 2.5 Analysis of correlation between *PSENEN* expression and immune/molecular subtypes of human cancers

The TISIDB database (http://cis.hku.hk/TISIDB/index.php) is an online integrated repository portal collecting abundant human cancer datasets from TCGA database.[25] The associations between the expression level of *PSENEN* and immune or molecular subtypes of various cancer types were assessed using this database. A *p*-value of < 0.05 was considered to reflect a statistically significant difference.

### 2.6 Mutation analysis

Mutation analysis was conducted using the cBioPortal (http://www.cbioportal.org/). The mutation or variant data were obtained from TCGA PanCancer Atlas Studies.[26] Survival data, including on OS, DSS, DFS, and PFS, were compared in all TCGA cancer types, without or with *PSENEN* genetic alteration. We also used the UALCAN databases to compared DNA methylation levels of *PSENEN* between normal and cancer tissues.

### 3 Results

#### 3.1 *PSENEN* expression was significantly upregulated in 22 cancer types

We analyzed the differential expression of *PSENEN* between normal and cancer tissues using the data from TCGA and the TIMER2 database. The results showed that *PSENEN* was significantly overexpressed in 17 cancer types. In detail, its expression level was significantly higher in cancer tissues than in the adjacent nonmalignant tissues in cancer types such as BLCA, BRCA, CESC, CHOL, ESCA, GBM, HNSC, KICH, KIRP, LIHC, LUAD, LUSC, SKCM, STAD, and UCEC datasets, while the opposite pattern was found in PRAD (Fig. 1A, 1B).

For those cancer types lacking data on corresponding normal tissues in TCGA, we further analyzed the differences in expression of *PSENEN* between normal and cancer tissues by merging the data from the GTEx dataset. We found that the expression level of *PSENEN* was much higher in cancer tissues than in normal tissues for DLBC, GBM, LGG, OV, THYM, and UCS, while the opposite results were found for TGCT (Fig. 1C, 1D, *P*<0.05).

#### 3.2 *PSENEN* could serve as a prognostic predictor for certain cancers

We performed a survival association analysis, including OS and DSS, to identify the association between *PSENEN* expression level and prognosis in 33 cancer types. The results of OS analysis showed that *PSENEN* was significantly correlated with worse OS in ACC, KIRC, LGG, LIHC, LUAD, SKCM, and UVM, especially in UVM (hazard ratio=4.06). In contrast, *PSENEN* was associated with better OS in DLBC and PCPG (Fig. 2A). K-M plotter analysis also demonstrated that a higher *PSENEN* expression level was associated with worse OS among patients with KIRC, LGG, LIHC, LUAD, READ, SKCM, and UVM (Fig. 3).

As for DSS, the results of Cox regression analysis showed that *PSENEN* was a risk factor in the patients with ACC, KIRC, KIRP, LGG, LIHC, LUAD, THCA, and UVM, and a protective factor in the patients with BRCA and PCPG (Fig. 2B). K-M plotter analysis indicated that elevated *PSENEN* expression was correlated with poorer
Fig. 1  *PSENEN* expression levels in diverse human cancers.
A. The difference in expression of *PSENEN* in normal and pan-cancer samples from TCGA database; B. *PSENEN* expression level in cancer samples from TCGA analyzed by the TIMER2 database; C, D. Box plot data of DLBC, GBM, LAML, LGG, OV, TGCT, THYM, and UCS in TCGA cohorts compared with the levels in normal tissues in GTEx. *P*<0.05, "*P*<0.01, ""*P*<0.001.
Fig. 2 Univariate Cox regression analysis of PSENEN.
A. Forest map shows the univariate Cox regression results of PSENEN for OS in TCGA pan-cancer types; B. Forest map shows the univariate Cox regression results of PSENEN for DSS in TCGA pan-cancer types.
DSS in patients with KIRC, KIRP, LGG, LUSC, SKCM, and UVM, while BRCA patients with higher PSENEN expression had a longer DSS time (Fig. 4).

3.3 Correlation of PSENEN expression with tumor immune microenvironment

We investigated PSENEN's effects on the immunological milieu of tumors by assessing the
association of its expression with the degree of immune cell infiltration. We analyzed immune cell infiltration data using TIMER algorithms and of the XCELL algorithms of the R software package. The results of TIMER algorithms demonstrated associations in various cancer types between the expression of PSENEN and the infiltration scores of six immune cell types (B cells, CD4+ T cells, CD8+ T cells, neutrophils, macrophages, and dendritic cells). BCRA, LGG, LIHC, and THCA were the
top four tumor groups. Interestingly, \textit{PSENEN} expression level was positively associated with the amount of immune cell infiltration in LGG and LIHC, but negatively associated in BCRA and THCA (Fig. 5A). Furthermore, the xCell algorithms were used to analyze the relationship between \textit{PSENEN} expression and the infiltration of 64 immune cell subtypes. The results indicated that the \textit{PSENEN} expression level was positively associated with most of the subtypes in THYM, LGG, UVM, and LIHC, but negatively associated with those in ACC, BRCA, and THCA. The data analyzes of immune cell infiltration from the two different sources were consistent, implying the existence of an association between \textit{PSENEN} expression and the degree of immune cell infiltration in different types of tumors (Fig. 5B).

3.4 Correlation of \textit{PSENEN} expression with immune checkpoints implicates \textit{PSENEN} in the tumor immune response

Several genes have been identified as components of immune response checkpoints, allowing us to determine whether \textit{PSENEN} expression correlates with the expression of such checkpoint genes\textsuperscript{[2]}. The results indicated that, in various cancer types, especially in UVM, GBM, LGG, COAD, OV, PAAD, LIHC, and HNSC, \textit{PSENEN} expression was positively correlated with the expression levels of most of the immune-inhibitory genes (e.g., BTLA, VEVFB, TGFB1) and most of the immune-stimulatory genes (e.g., TLR4, SELP, BTN3A1, \(P<0.05\); Fig. 6). Meanwhile, in THYM, THCA, ACC, BRCA, and READ, the expression levels of most of the immune-inhibitory genes and immune-stimulatory genes were negatively correlated with the expression level of \textit{PSENEN}.

3.5 \textit{PSENEN} is associated with TMB and MSI in some cancers

A large number of studies have shown that the tumor mutational burden (TMB) and microsatellite instability (MSI) play important roles in tumor development. As new kinds of biomarkers, they are widely used to evaluate the therapeutic effect of immune checkpoint inhibitors\textsuperscript{[3,27]}. Therefore, we further explored the relationships of \textit{PSENEN} expression with TMB and MSI across all cancer types represented in TCGA. We observed a significant correlation between \textit{PSENEN} expression and TMB in 13 of the 33 cancer types. In detail, the expression of \textit{PSENEN} was positively correlated with TMB in LGG (\(P<0.001\)), LUAD (\(P<0.001\)), ESCA (\(P<0.01\)), SARC (\(P<0.001\)), KIRC (\(P<0.01\)), PAAD (\(P<0.001\)), and BLCA (\(P<0.001\)), whereas it was negatively correlated in LAML (\(P<0.01\)), BRCA (\(P<0.05\)), HNSC (\(P<0.05\)), THYM (\(P<0.001\)), UCS (\(P<0.05\)), and DLBC (\(P<0.05\)) (Fig. 7A). As for MSI, the results demonstrated that \textit{PSENEN} expression was positively associated with MSI in KIRC (\(P<0.001\)), LIHC (\(P<0.01\)), THCA (\(P<0.05\)), and ACC (\(P<0.05\)), but negatively associated with it in GBM (\(P<0.05\)), LGG (\(P<0.05\)), CESC (\(P<0.001\)), COAD (\(P<0.05\)), KIRP (\(P<0.001\)), and PRAD (\(P<0.001\)) (Fig. 7B).

3.6 Correlation of \textit{PSENEN} expression with immune subtypes and molecular subtypes

We also used the TISIDB online tool to analyze the relationship between \textit{PSENEN} expression and pan-cancer immune subtypes and molecular subtypes. The results obtained from the TISIDB indicated that the expression level of \textit{PSENEN} was significantly associated with different immune subtypes in 14 kinds of cancers, namely, BLCA, BRCA, COAD, HNSC, KIRC, LGG, LIHC, LUAD, OV, PAAD, PRAD, READ, SKCM, and STAD (Fig. 8). In addition, the expression level of \textit{PSENEN} differed significantly among the different immune subtypes of a cancer type. For example, \textit{PSENEN} showed higher expression in C1 and C6 types but lower expression in the C3 type. As for different molecular subtypes of cancers,
Fig. 5  Relationship between PSENEN expression and immune cell infiltration in different cancer types.
Fig. 6 Pan-cancer analysis of correlation of PSENEN expression with expression of immune checkpoint genes. $^*$$P<0.05$

we found that there were significant correlations between the expression level of PSENEN and different molecular subtypes in ACC, BRCA, HNSC, KIRP, LGG, LUSC, OV, PCPG, PRAD, STAD, and UCEC (Fig. 9). From the above results, we concluded that the expression level of PSENEN differs among the immune subtypes and molecular subtypes of various human cancers.

3.7 Pan-cancer analysis of genetic alteration of PSENEN

The dysregulation of DNA methylation has been implicated in the development of cancer, and used for cancer diagnosis and therapy.$^{[28-29]}$. 
Fig. 7  Pan-cancer analysis of the correlation of PSENEN expression with immune TMB (A) and MSI (B).
Therefore, we compared the DNA methylation level of \( PSENEN \) between normal and cancer tissues by using the UALCAN databases. As shown in Fig. 10, we found that the methylation level of \( PSENEN \) significantly decreased in BLCA, COAD, HNSC, LIHC, LUAD, PRAD, READ, TGCT, and UCEC tissues compared with that in normal tissues. However, a considerable elevation of DNA methylation level of \( PSENEN \) has been observed between KIRC tissues and matched normal tissues (Fig. 10).

The accumulation of genetic mutations is another factor that drives carcinogenesis\(^{[30-31]}\). Hence, we used the cBioPortal online tool to explore \( PSENEN \) gene alterations in human tumor samples. We found that the mutation frequency of \( PSENEN \) is the highest in ovarian epithelial tumors (>8%). Among the types of genetic alterations, amplification was the most common type. Furthermore, our results showed that certain
Fig. 9 Pan-cancer analysis of the correlation of PSENEN expression with molecular subtypes.

Genetic alterations of PSENEN were closely related to the clinical prognosis in terms of the survival of patients. Cancer patients with mutations of the PSENEN gene had worse PFS, DFS, OS, and DSS than those without mutations (Fig. 11).

### 4 Discussion

Notch signaling is a key regulator of immune cell differentiation, and is closely linked to autoimmune diseases, tumorigenesis, and tumor-induced immunomodulation. Cancer features such as tumor angiogenesis, stemness, and epithelial–mesenchymal transition are almost always associated with aberrant activation of Notch signaling\(^{[32]}\). Notch receptor–ligand interactions are mediated by \(\gamma\)-secretase for secondary cleavage, releasing the intracellular structural domain (NICD). The NICD subsequently translocates to the nucleus, where it regulates the transcription of target genes\(^{[33]}\). Therefore, \(\gamma\)-secretase is a potential target for cancer therapy. The \(\gamma\)-secretase protein complexes are assembled from four hydrophobic proteins, presenilin, PEN-2, nicastrin, and anterior pharynx defective 1 (APH1), which are encoded...
by PSEN1/PSEN2, PSENEN, NCSTN, and APH1A/APH1B, respectively. Mutations of the PSENEN gene have been reported to be a risk factor for Alzheimer's disease\textsuperscript{[34-35]} and acne\textsuperscript{[36]}. Additionally, emerging studies have reported that PSENEN is overexpressed in pancreatic cancer\textsuperscript{[15]}, gastric cancer\textsuperscript{[14]}, and breast cancer\textsuperscript{[13]}. Although recent studies by Chen have indicated that PSENEN is differentially expressed in various cancer types and its role in LGG has been comprehensively analyzed, the role of PSENEN in other cancers is still far from being comprehensively understood. For example, it remains to be explored whether PSENEN influences the pathogenesis of various
Fig. 11  Pan-cancer analysis of PSENEN gene mutations.
A. The frequency of different types of mutations was examined using the cBioPortal database; B–E. The effect of PSENEN mutation status on disease-free, disease-specific, progression-free, and OS of cancer patients was investigated using the cBioPortal database, respectively.
cancer types through certain molecular pathways. Therefore, we analyzed the data from 33 cancer types in TCGA and performed a pan-cancer analysis of PSENEN. Our comprehensive pan-cancer analysis included a range of factors, such as gene expression levels, prognostic value, genetic alteration, and immune infiltration. The aim of our review is to explore the potential molecular mechanism behind the involvement of PSENEN in the pathogenesis or clinical prognosis of different cancer types.

Our data from several databases, including TCGA, GTEx, and TIMER, indicated that PSENEN expression was significantly elevated in 21 cancer types, namely, BLCA, BRCA, CESC, CHOL, ESCA, GBM, HNSC, KICH, KIRP, LIHC, LUAD, LUSC, SKCM, STAD, UCEC, DLBC, GBM, LGG, OV, THYM, and UMS, while it was downregulated in PRAD and TGCT, compared with the level in normal tissues. In summary, the expression of PSENEN was significantly upregulated in most human cancer types, suggesting that PSENEN plays important roles in tumorigenesis. We also found that the overexpression of PSENEN was associated with worse OS and DSS in several cancer types, indicating that PSENEN can be used as a prognostic biomarker for certain cancer types. Indeed, the prognostic value of PSENEN has been reported in lower-grade glioma\textsuperscript{[21]} and breast cancer\textsuperscript{[13]}. This study additionally reported the association of PSENEN with survival in eight cancer types, expanding the range of cancer types in which PSENEN might be applied for prognostic prediction.

In the present study, we for the first time displayed evidence of the potential association between the expression of PSENEN and the tumor immune microenvironment, immune checkpoints, MSI, and TMB. By using the TIMER algorithm, we found positive associations between the PSENEN expression level and the amount of immune cell infiltration in LGG and LIHC, but negative ones in BCRA and THCA. Furthermore, the xCell algorithm indicated that the expression level of PSENEN was positively correlated with these subtypes in THYM, LGG, UVM, and LIHC, but negatively associated with them in ACC, BRCA, and THCA. These findings indicated that our results obtained using immune cell infiltration data from two different sources were consistent. We also found that, in a variety of cancer types, PSENEN expression was significantly correlated with a variety of immune checkpoint-related genes, MSI and TMB. These results suggested that PSENEN may have direct or indirect effects on the tumor immune microenvironment and may act as an immune checkpoint. Therefore, in the future, we can develop targeted therapy for PSENEN and combine it with conventional immunotherapy to improve its efficacy.

Gene mutations promote carcinogenesis and confer a selective growth advantage for cancer cells\textsuperscript{[37-39]}. We analyzed the data from the cBioPortal platform and found PSENEN mutations in most cancer types. In particular, the rate of such mutations was the highest in ovarian epithelial tumor, sarcoma, endometrial cancer, non-small cell lung cancer, and cervical cancer. It is interesting for us to further investigate the relationship between PSENEN gene mutations and gynecological cancer.

DNA methylation is a key epigenetic mechanism that influences gene expression without altering the DNA sequence\textsuperscript{[40]}, and further determines cell fate and cancer development\textsuperscript{[41-42]}. In the present study, we found a lower level of DNA methylation of the PSENEN gene promoter in most cancer types, which is consistent with the higher PSENEN gene expression. The molecular mechanisms by which DNA methylation silences PSENEN gene expression require in-depth study.

In a recent study by Ma et al., PSENEN was shown to be a target of metformin\textsuperscript{[16]}. Accumulating studies have demonstrated that metformin has anti-cancer properties and amplifies cell death
mechanisms, especially apoptosis, in a broad spectrum of cancer cells. The present study provides insights into the notable strength of PSENEN as a prognostic and immunotherapeutic biomarker across cancer types. Therefore, we infer that metformin may play a targeted therapeutic role by targeting PSENEN in tumor cells, although this needs to be verified in future work.

The present study has several limitations. More in vivo experiments should be conducted to identify the roles of PSENEN in tumorigenesis and cancer progression. Furthermore, a multicenter clinical trial should be conducted to validate the immune checkpoint role of PSENEN in the near future.

5 Conclusions

In summary, we performed a comprehensive evaluation of PSENEN, revealing its potential role as an indicator of patient prognosis and its immunoregulatory effect. PSENEN may serve as a prognostic biomarker and warrants in-depth exploration of its oncogenic role in various cancer types.

6 Conflicts of interest

The authors have no conflicts of interest to declare.

7 Author contributions

YANG Zerui analyzed the data, prepared the figures and tables, and wrote the manuscript. WEN Dingsheng participated in analyzing the data. CHEN Kai and YE Yubing participated in the preparation of the figures and tables, and interpretation of data for the work. LI Xiong, LIU Xingyun, and QIU Zhikun reviewed, edited, and revised the manuscript. All authors contributed to the article and approved the submitted version.

8 Data availability

The datasets presented in this study can be found in online repositories.

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