Original Article

Research on the oncogenic role of the house-keeping gene *GAPDH* in human tumors

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Background: As an internal reference gene, glyceraldehyde-3-phosphate dehydrogenase (*GAPDH*) plays an important role in glycolysis. While increasing evidence suggests that *GAPDH* plays a crucial role in tumorigenesis of some cancers, no systematic analysis of *GAPDH* has been conducted. Here, we sought to analyze the expression of *GAPDH* and its oncogenic processes in pan-cancer.

Methods: *GAPDH* was investigated in The Cancer Genome Atlas (TCGA) tumor types using several bioinformatic tools including Tumor IMmune Estimation Resource (TIMER), Gene Expression Profiling Interactive Analysis (GEPIA), University of ALabama at Birmingham CANcer (UALCAN), cBio Cancer Genomics Portal (cBioPortal), and Search Tool for Recurring Instances of Neighbouring Genes (STRING) for the expression and relationships with prognosis and immune infiltration separately.

Results: Through our analysis, we measured the higher expression of *GAPDH* across the majority of TCGA tumors. *GAPDH* overexpression predicts poor survival in patients with tumors expressing a high level of *GAPDH*. Moreover, the genetic changes in *GAPDH* contributed to an increased mRNA expression. Additionally, *GAPDH* expression was negatively correlated with immune infiltration involving cancer-associated fibroblasts, neutrophil cell and endothelial.

Conclusions: The house-keeping gene *GAPDH* might be a promising biomarker for pan-cancer prognosis. And *GAPDH* is not suitable as an internal reference gene for most cancer research, whether RNA or protein analyses.

Keywords: Glyceraldehyde-3-phosphate dehydrogenase (*GAPDH*); cancer; prognosis; survival

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Introduction

There is an increasing demand for new pan-cancer markers in order to better understand the mechanism and clinical application of tumorigenesis process. Many publicly funded bioinformatics databases, like The Cancer Genome Atlas (TCGA), could provide an outstanding convenience for people to analyze the expression and related functional genomics data of the interested gene in a variety of cancers (1-3).

Glyceraldehyde-3-phosphate dehydrogenase (*GAPDH*), which plays a role in glycolysis, has been identified as an internal reference gene to quantitate DNA, RNA and proteins in usual biological experiments (4,5). An important reason is that *GAPDH* is highly and constantly expressed in almost all tissues. However, A study of *GAPDH* protein in mouse had discovered a new side (6). It might take part in several additional nuclear functions such as nitrosylation of nuclear proteins and the regulation of mRNA stability due to its nitrosylase activity. Subsequently, more and more studies have found that *GAPDH* is unstable in some pathological stages including aging and cancer (7,8). As a

glycolytic enzyme, *GAPDH* is a significant player in cancer energy metabolism to reflect the high metabolic state of cancer, which may be further related to cancer proliferation and invasion.

Therefore, we would carry out the pan-cancer analysis to explore the expression profile of *GAPDH* and several other modules including survival status, gene regulation and related cellular pathways in various tumor types through the datasets provided by TCGA project and corresponding databases. This comprehensive work would be helpful for us to reveal the potential application value and molecular mechanism of *GAPDH* in the progression of cancers in human beings. We present the following article in accordance with the REMARK reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-1972/rc).

Methods

Analysis of GAPDH gene expression

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Tumor IMmune Estimation Resource 2 (TIMER2) database (http://timer.cistrome.org/) was used to compare an expression of *GAPDH* mRNA in tumors and nearby normal tissues across all tumors from TCGA (9).

Gene Expression Profiling Interactive Analysis 2 (GEPIA2) database (http://gepia2.cancer-pku.cn) was used to profile the expression of *GAPDH* mRNA between tumors and matched TCGA normal and Genotype-Tissue Expression (GTEx) data (10).

University of ALabama at Birmingham CANcer (UALCAN) database (http://ualcan.path.uab.edu/analysis-prot.html) was used to collect the expression of GAPDH protein in primary and normal tissues using data from Clinical Proteomic Tumor Analysis Consortium (CPTAC) dataset (11).

The Human Protein Atlas (HPA) database (http://www.proteinatlas.org/) was used to download the immunohistochemistry (IHC) images of GAPDH in normal tissues and four tumors, including ovarian serous cystadenocarcinoma (OV), kidney renal clear cell carcinoma (KIRC), lung adenocarcinoma (LUAD) and pancreatic adenocarcinoma (PAAD).

Analyses of survival prospects

The above GEPIA2 database was used to get the information about the overall survival (OS) data, disease-free survival (DFS) data and survival map of *GAPDH* throng TCGA tumors.

Analyses of genetic changes

The cBioPortal database (https://www.cbioportal.org/) was used to obtain the genetic alteration data of *GAPDH* in tumors, consisting of gene mutation, change frequency, mRNA expression and so on (12).

Analyzing immune infiltration

We analyzed TIMER2 data to determine if *GAPDH* expression correlates with immune infiltration in TCGA tumors. Fibroblasts, neutrophils and endothelial cells associated with cancer were selected for further analysis.

Analyses of genes related to GAPDH gene

Search Tool for Recurring Instances of Neighbouring Genes (STRING) website (https://string-db.org/) was used to collect no more than 50 interactors of GAPDH protein based on experiments (13).

The GEPIA2 database was again used to collect the top 100 *GAPDH*-correlated genes across all the TCGA tumors. For a few genes of interest, we conducted a paired Pearson correlation analysis to *GAPDH*.

The R language software (Clusterprofiler package, version 3.14.3) was used to conduct the enriched Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway of the above two sets of

Highlight box

Key findings
- *GAPDH* may be a promising biomarker for pan-cancer diagnosis.

What is known and what is new?
- Normally, *GAPDH* is used as an internal reference gene to quantify DNA, RNA, and proteins, but it is unstable at some pathological stages, including cancer and aging;
- *GAPDH* overexpression is found in the majority of TCGA tumors. High levels of *GAPDH* are associated with poor survival.

What is the implication, and what should change now?
- *GAPDH* has a potential role in cancer progression in human beings. RNA or protein analyses using *GAPDH* are not compatible with most cancer research.

GAPDH binding and interacted genes.

Statistical analysis

We used Spearman correlation analysis as the statistical approach. And P<0.05 was considered meaningful.

Results

GAPDH gene expression increases in the majority of TCGA tumors

Using the TIMER2, we compared *GAPDH* expression in the TCGA repository among tumors and normal tissues adjacent to them. *Figure 1A* shows that *GAPDH* is expressed at a higher level in almost all tumor tissues like bladder urothelial carcinoma (BLCA) and lung squamous cell carcinoma (LUSC) than in tissues that serve as controls. Incredibly, only one tumor type, prostate adenocarcinoma (PRAD), did not exhibit differential expression.

In cases in which the TCGA does not have any data on normal tissues, further analysis of *GAPDH* expression was conducted in tumors using GTEx data. For adrenocortical carcinoma (ACC), lymphoid neoplasm diffuse large B-cell lymphoma (DLBC), OV, skin cutaneous melanoma (SKCM), testicular germ cell tumors (TGCT), thymoma (THYM) and uterine carcinosarcoma (UCS), we found higher expression in tumor tissues (*Figure 1B*, P<0.05). Tumors like acute myeloid leukemia (LAML) or Brain lower grade glioma (LGG) did not show a significant difference in expression. As a whole, we found that human tumors expressed a high level of *GAPDH*.

Apart from transcription, we evaluated *GAPDH* at the protein level using the CPTAC proteome dataset. Tumor tissues from OV, KIRC, LUAD and PAAD were significantly more likely to express *GAPDH* than normal tissues (*Figure 1C*, P<0.05). Also, we analyzed IHC results obtained from HPA and compared them to data from CPTAC. The results of the analyses of the two databases were in agreement. The IHC staining of normal ovary, kidney, lung and pancreas tissues was low or medium, while the staining of tumor tissues was medium or strong (*Figure 1C*).

Survival analysis data of GAPDH gene

Next, we were interested in determining whether *GAPDH* expression correlated with prognosis and OS. Based on *GAPDH* expression levels in cancer cases, we divided the cases into high and low groups, and then TCGA and GEO datasets were used to investigate the relationship between *GAPDH* expression and prognosis among different tumor types. It has been found that tumors expressing high levels of *GAPDH* have poor OS. This is true for cervical squamous cell carcinoma and endocervical adenocarcinoma (CESC) (P=0.0022), glioblastoma multiforme (GBM) (P=0.023), LGG (P=1.7e–05), liver hepatocellular carcinoma (LIHC) (P=2.1e–05), LUAD (P=3e–04) and mesothelioma (MESO) (P=0.00061) (*Figure 2A*). Further, *Figure 2B* shows the association between the *GAPDH* gene expression and the DFS rates in KIRC (P=0.039), kidney renal papillary cell carcinoma (KIRP) (P=0.0089), LGG (P=0.003), MESO (P=0.036), PAAD (P=0.0081), sarcoma (SARC) (P=0.038) and THYM (P=0.026).

Genetic alteration analysis data

As a consequence of genetic alterations in human cancers, we would like to analyze how the genetic changes in *GAPDH* are reflected in tumors. The *GAPDH* gene is altered in 2.1% (231/10,967) of queried TCGA tumor samples, and the classification of genetic alterations was shown in *Figure 3A*. Further, a high frequency of *GAPDH* alteration (>6%) was found in seminoma where "amplification" is the primary type (*Figure 3B*). Additionally, to find out whether the highest degree of "amplification" of *GAPDH* is related to mRNA expression, we systematically studied and correlated these in Seminoma. Compared with samples without copy number changes in *GAPDH*, those with *GAPDH* alterations had an increased mRNA expression (*Figure 3C*).

Immune infiltration analysis data

Because *GAPDH* participates in the regulation of nitrosylation and nuclear functions, alterations in expression levels of *GAPDH* or mutations in the gene may alter how immune cells respond to tumors. Therefore, we examined the correlation between various levels of endothelial and immune cell infiltration and *GAPDH* expression in a variety of tumor types studied in the TCGA using TIMER, XCELL, QUANTISEQ and so on. It is interesting to note that expression of *GAPDH* negatively correlates with the estimated infiltration of cancer-associated fibroblasts (CAFs) in the breast invasive carcinoma (BRCA), SARC and THYM. Also, HNSC neutrophil cell infiltration and

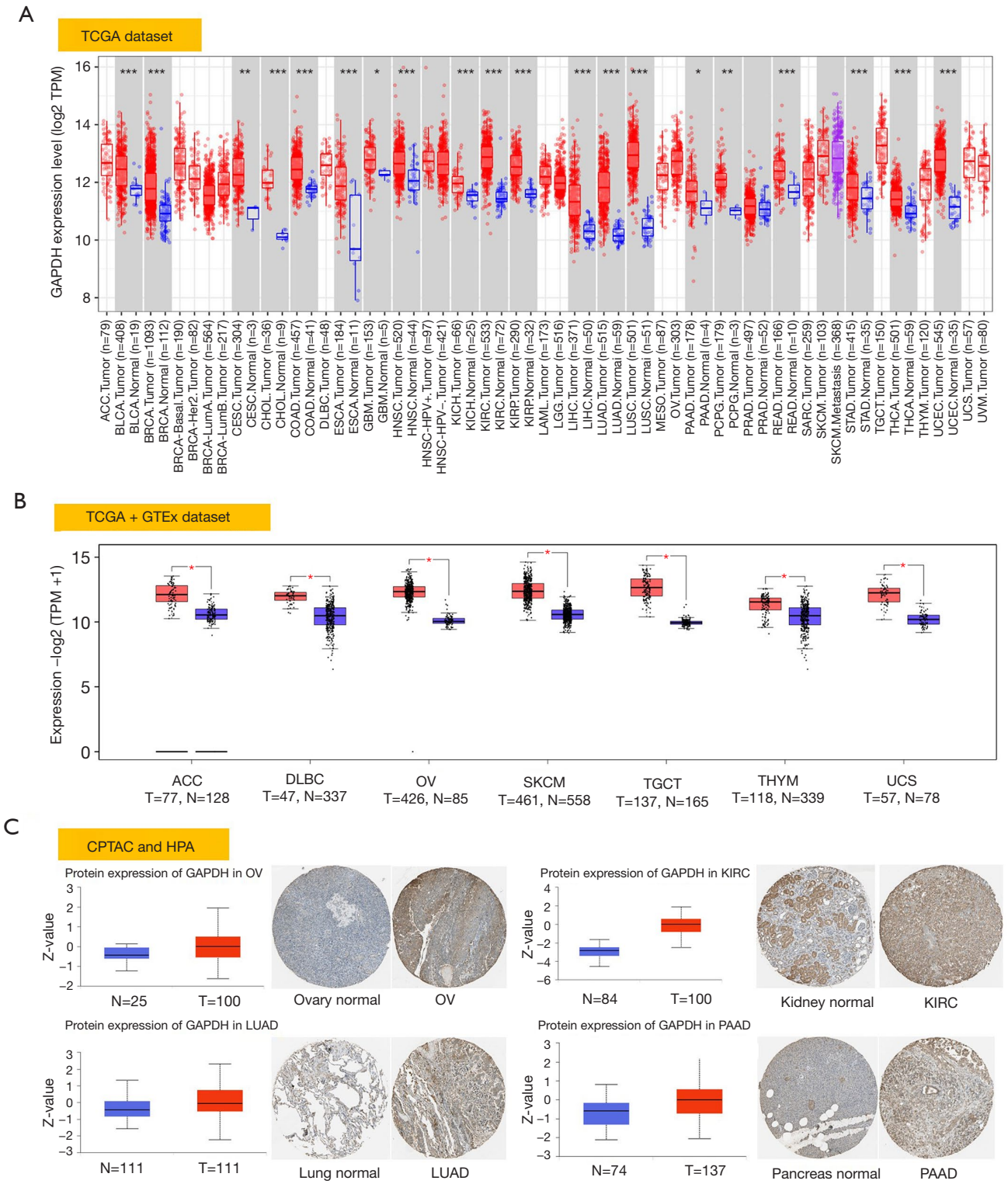

Figure 1 The analysis of *GAPDH* expression. (A) The comparison of *GAPDH* mRNA expression between TCGA tumors and adjacent normal tissues. (B) The comparison of *GAPDH* mRNA expression between TCGA tumors and GTEx data. (C) GAPDH protein expression data from CPTAC and the IHC images from HPA database. *, P<0.05; **, P<0.01; ***, P<0.001. Ovary normal: https://www.proteinatlas.

org/ENSG00000111640-GAPDH/tissue/ovary#img; Kidney normal: https://www.proteinatlas.org/ENSG00000111640-GAPDH/tissue/kidney#img; Lung normal: https://www.proteinatlas.org/ENSG00000111640-GAPDH/tissue/lung#img; Pancreas normal: https://www.proteinatlas.org/ENSG00000111640-GAPDH/tissue/pancreas#img; OV: https://www.proteinatlas.org/ENSG00000111640-GAPDH/pathology/ovarian+cancer#img; KIRC: https://www.proteinatlas.org/ENSG00000111640-GAPDH/pathology/renal+cancer#img; LUAD: https://www.proteinatlas.org/ENSG00000111640-GAPDH/pathology/lung+cancer#img; PAAD: https://www.proteinatlas.org/ENSG00000111640-GAPDH/pathology/pancreatic+cancer#img. ACC, adrenocortical carcinoma; BLCA, bladder urothelial carcinoma; BRCA, breast invasive carcinoma; CESC, cervical squamous cell carcinoma and endocervical adenocarcinoma; CHOL, cholangiocarcinoma; COAD, colon adenocarcinoma; CPTAC, Clinical Proteomic Tumor Analysis Consortium; DLBC, lymphoid neoplasm diffuse large B-cell lymphoma; ESCA, esophageal carcinoma; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; GBM, glioblastoma multiforme; GTEx, Genotype-Tissue Expression; HNSC, head and neck squamous cell carcinoma; HPA, Human Protein Atlas; HPV, human papillomavirus; IHC, immunohistochemistry; KICH, kidney chromophobe; KIRC, kidney renal clear cell carcinoma; KIRP, kidney renal papillary cell carcinoma; LAML, acute myeloid leukemia; LGG, brain lower grade glioma; LIHC, liver hepatocellular carcinoma; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; MESO, mesothelioma; OV, ovarian serous cystadenocarcinoma; PAAD, pancreatic adenocarcinoma; PCPG, pheochromocytoma and paraganglioma; PRAD, prostate adenocarcinoma; READ, rectum adenocarcinoma; SARC, sarcoma; SKCM, skin cutaneous melanoma; STAD, stomach adenocarcinoma; TCGA, The Cancer Genome Atlas; TGCT, testicular germ cell tumors; THCA, thyroid carcinoma; THYM, thymoma; TPM, transcripts per million; UCEC, uterine corpus endometrial carcinoma; UCS, uterine carcinosarcoma; UVM, uveal melanoma.

GAPDH expression exhibited negative correlations. For BLCA, BRCA, colon adenocarcinoma (COAD), esophageal carcinoma (ESCA), KIRC, LUAD, LUSC, PAAD, SARC, stomach adenocarcinoma (STAD), THYM and UCS as well, *GAPDH* expression and endothelial infiltration showed negative correlations, as well as a positive correlation in THCA tumors (*Figure 4*).

Enrichment analysis of GAPDH gene-related partners

Finally, to determine the molecular mechanism for how the *GAPDH* gene affects tumorigenesis and development, a series of pathway enrichment analyses were carried out based on the proteins that interact with *GAPDH* and the *GAPDH* expression correlation genes. With the STRING tool, we obtained a total of 50 experimentally detected *GAPDH*-binding proteins. *Figure 5A* shows the interaction network of these 50 proteins. Then, GEPIA2 combined the data of all TCGA tumors, allowing us to acquire genes ranking in the top 100 that correlate with *GAPDH* expression. A positive correlation existed between *GAPDH* expression and that of triosephosphate isomerase 1 (TPI1) (R=0.80), enolase 1 (ENO1) (R=0.57), prohibitin 2 (PHB2) (R=0.56) and pyruvate kinase M1/2 (PKM) (R=0.53) (*Figure 5B*). And the heatmaps indicated that *GAPDH* correlated strongly with the four genes listed above in most cancer types (*Figure 5C*).

After combining the two datasets, we performed GO and KEGG enrichment analyses, which identified "Pyruvate metabolic process" and "Glycolysis/gluconeogenesis" on the list of top hits (*Figure 5D*), indicating that these pathways might be involved in *GAPDH*-induced cancer.

Discussion

The *GAPDH* gene on chromosome 12 encodes a single mRNA species that results in the production of a polypeptide comprising 335 amino acids, as a homo tetramer made up of four identical subunits of 37 kDa. Even though a lot of companies use *GAPDH* for internal control, it is expressed differently in several kinds of human cells (14). Levels of *GAPDH* are also reported to be unusually elevated in some types of cancer in humans (15,16).

In addition to its glycolytic function, *GAPDH* is involved in numerous cellular functions, including DNA repair and apoptosis (17,18). Hence, the *GAPDH* deregulation in cancers suggests that this enzyme has inconsistent roles in determining cell fate. However, it remains unclear whether *GAPDH* plays a role in certain types or common pathways involved in the development of tumors. Therefore, we conducted a pan-cancer analysis of *GAPDH*. According to the TCGA data, we examined *GAPDH* gene expression in 33 different tumors. A systematic collection of protein data, as well as molecular and genetic characteristics, was also

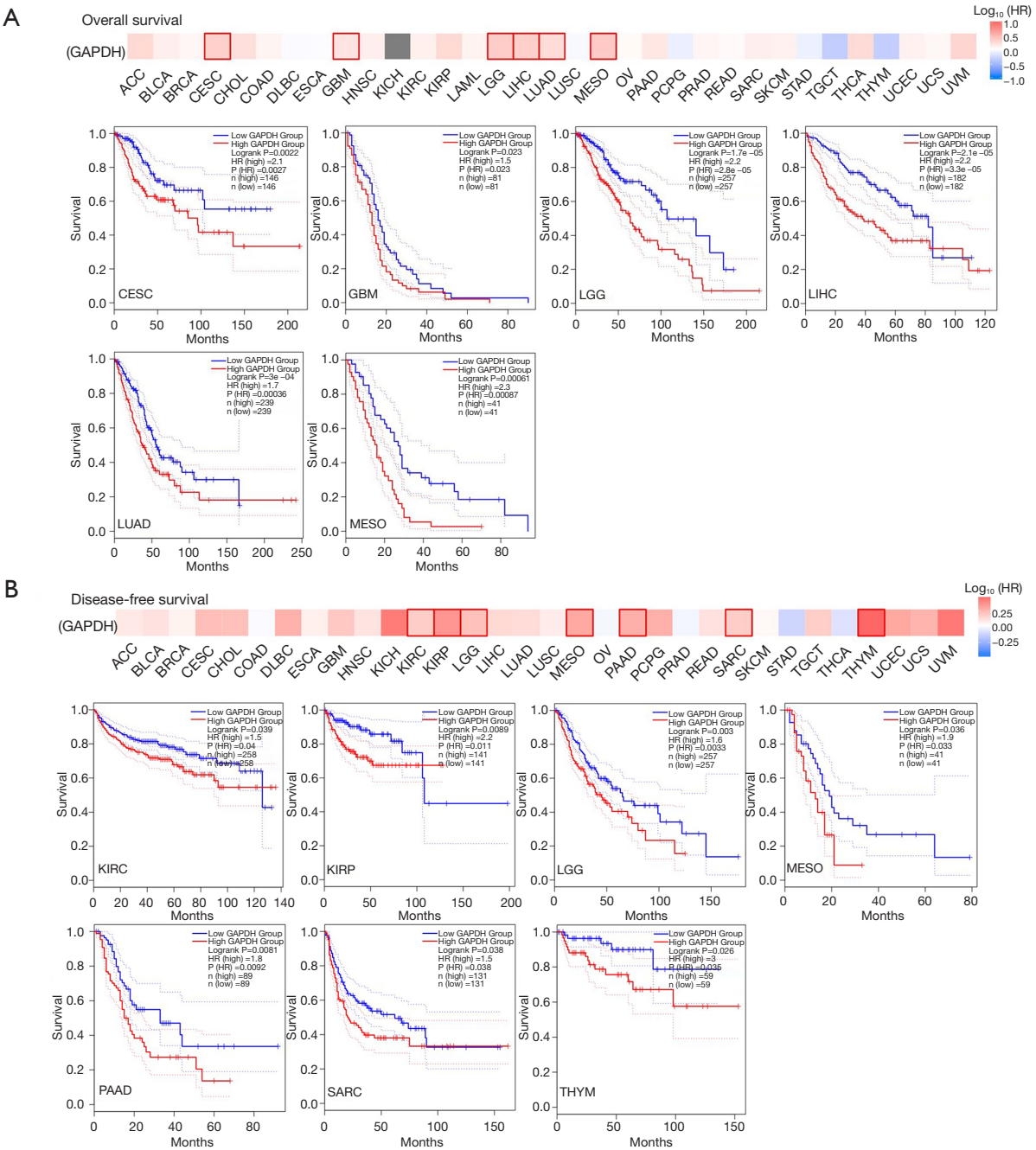

Figure 2 *GAPDH* high expression correlates with poor overall survival (A) and disease-free survival (B) in some TCGA tumors. ACC, adrenocortical carcinoma; BLCA, bladder urothelial carcinoma; BRCA, breast invasive carcinoma; CESC, cervical squamous cell carcinoma and endocervical adenocarcinoma; CHOL, cholangiocarcinoma; COAD, colon adenocarcinoma; DLBC, lymphoid neoplasm diffuse large B-cell lymphoma; ESCA, esophageal carcinoma; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; GBM, glioblastoma multiforme; HNSC, head and neck squamous cell carcinoma; HR, hazard ratio; KIRC, kidney renal clear cell carcinoma; KIRP, kidney renal papillary cell carcinoma; LAML, acute myeloid leukemia; LGG, brain lower grade glioma; LIHC, liver hepatocellular carcinoma; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; MESO, mesothelioma; OV, ovarian serous cystadenocarcinoma; PAAD, pancreatic adenocarcinoma; PCPG, pheochromocytoma and paraganglioma; PRAD, prostate adenocarcinoma; READ, rectum adenocarcinoma; SARC, sarcoma; SKCM, skin cutaneous melanoma; STAD, stomach adenocarcinoma; TCGA, The Cancer Genome Atlas; TGCT, testicular germ cell tumors; THCA, thyroid carcinoma; THYM, thymoma; UCEC, uterine corpus endometrial carcinoma; UCS, uterine carcinosarcoma; UVM, uveal melanoma.

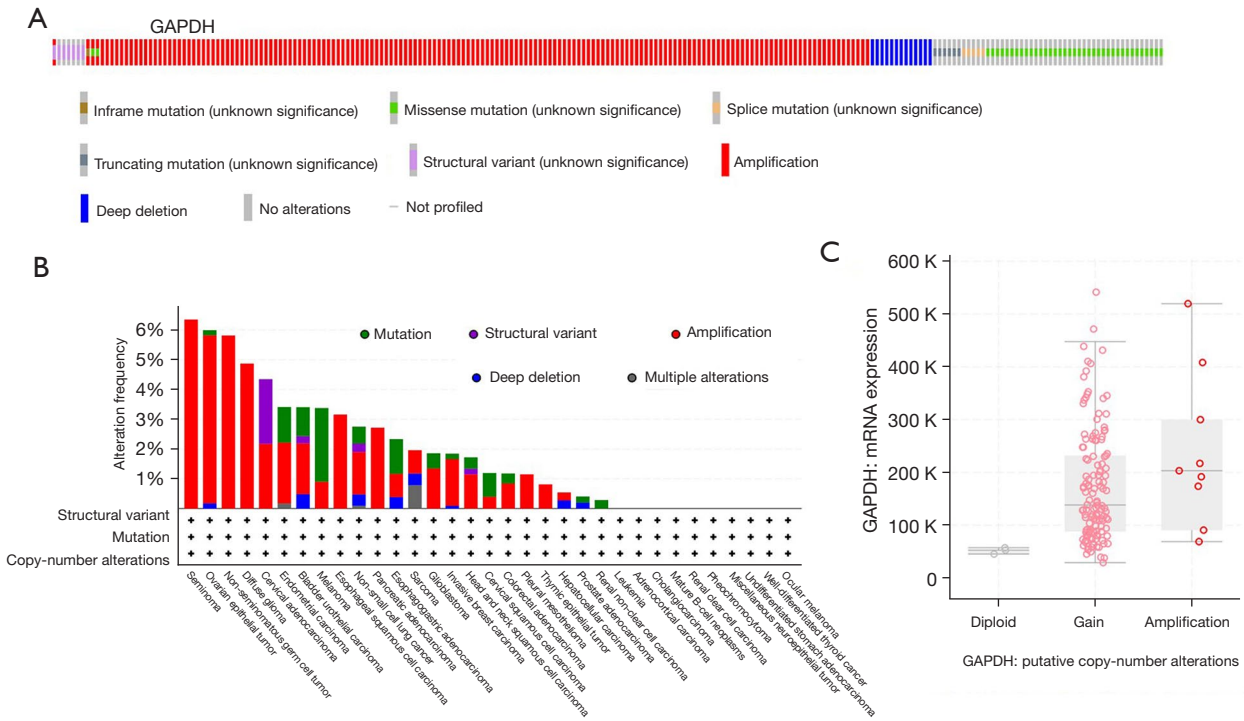

Figure 3 The analysis of *GAPDH* genetic alterations. (A) The overall genetic alterations of *GAPDH* in TCGA tumors. (B) The types of *GAPDH* genetic changes in specific cancers. (C) Corrections between *GPADH* mRNA expression and *GAPDH* copy number alterations in seminoma. GAPDH, glyceraldehyde-3-phosphate dehydrogenase; TCGA, The Cancer Genome Atlas.

conducted using other databases.

Based on our results, *GAPDH* expression levels in 27 tumor tissues are higher than those in the control tissues, regardless of the presence of PRAD, LAML, MESO, SARC and uveal melanoma (UVM). The similar expression levels of *GAPDH* in different tumor types may be due to common underlying functions and mechanisms. At the same time, we also compared the expression level of GAPDH total protein and found a higher level of GAPDH protein in the tumor tissues of OV, KIRC, LUAD and PAAD patients than in their corresponding control tissues. This difference suggests that *GAPDH* might not be suitable as an internal reference gene for several cancer research. Furthermore, we found that overexpression of *GAPDH* generally predicted a poor prognosis for patients with cancers expressing high levels of *GAPDH*, such as LGG and MESO. In MESO, a high *GAPDH* level was related to poor OS (P=0.00061) and DFS (P=0.036). *GAPDH* was rarely reported to be associated with MESO. The results of our study may lead to a prospective clinical biomarker for the prediction of survival rates among patients with MESO.

Evidence is growing that cancer metabolism not only has a critical role to play in cancer signaling for maintenance of tumors and survival, but also contributes to regulating the antitumor immune response by affecting both metabolites and immune cells (19,20). In this study, there is statistically significant evidence of negative or positive comparison of *GAPDH* expression and CAF, neutrophil, endothelial counts in a few types of tumors, which indicate that *GAPDH* would be of great significance in tumor immunity. Besides, the hyperoxia signaling pathway is involved in aggressive tumor behavior (21), and the *GAPDH* gene contains a hypoxia response element with a hypoxia inducible factor-1 (HIF-1) transcription factor binding site. By activating HIF-1, the expression of enzymes involved in glycolysis, such as *GAPDH*, could be enhanced by p-AKT in cancer cells of the colon, kidney and liver (22-24). Corresponding to this, our analysis of KEGG pathways identified "Glycolysis/gluconeogenesis" and "HIF-1 signaling pathway" as the enriched hits.

Conclusions

As a result of our analysis, we found a statistically significant

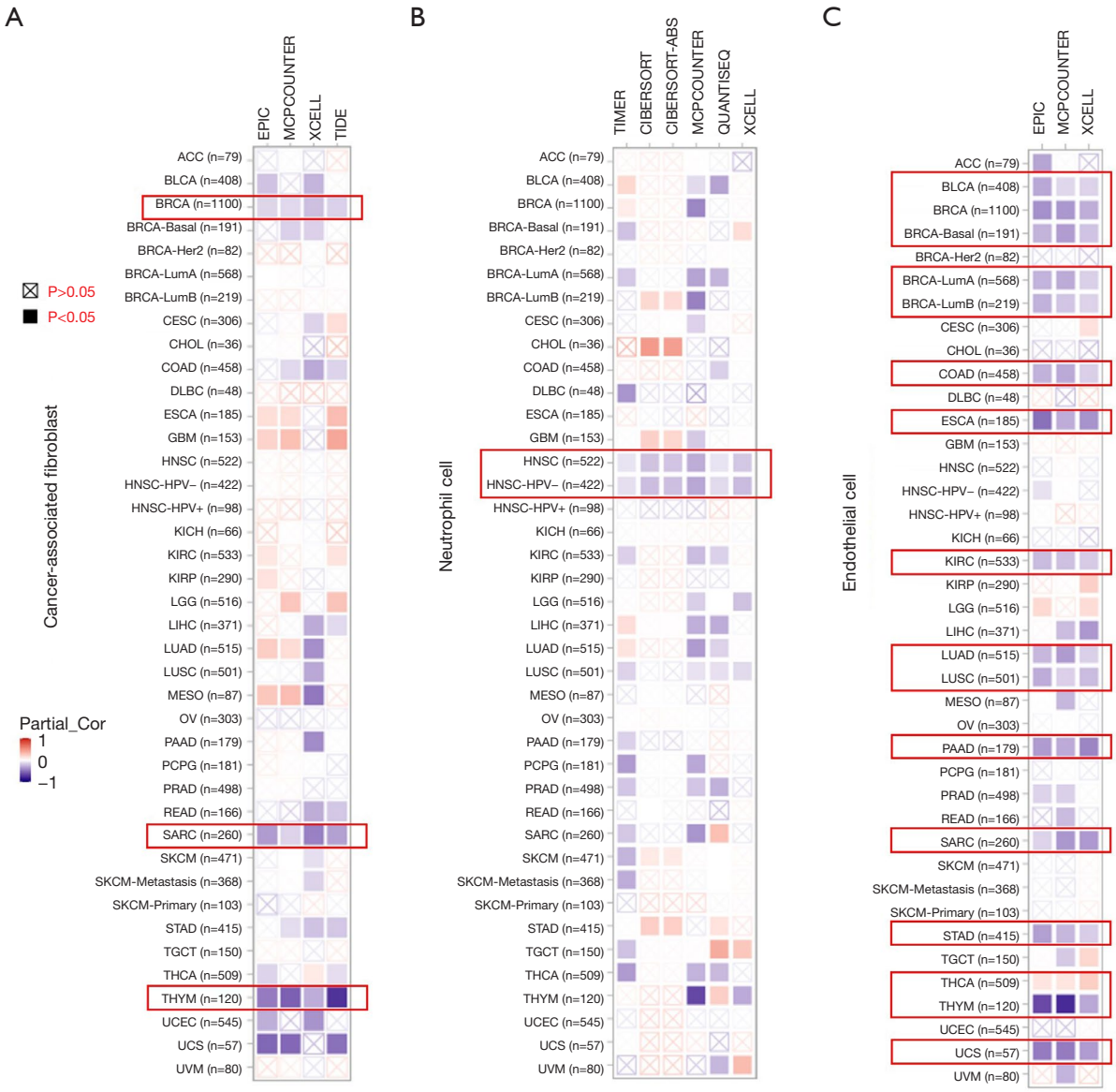

Figure 4 The correction between GAPDH expression and immune cell infiltration including cancer-associated fibroblasts (A), neutrophil cell (B) and endothelial (C). ACC, adrenocortical carcinoma; BLCA, bladder urothelial carcinoma; BRCA, breast invasive carcinoma; CESC, cervical squamous cell carcinoma and endocervical adenocarcinoma; CHOL, cholangiocarcinoma; COAD, colon adenocarcinoma; DLBC, lymphoid neoplasm diffuse large B-cell lymphoma; ESCA, esophageal carcinoma; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; GBM, glioblastoma multiforme; HNSC, head and neck squamous cell carcinoma; HPV, human papillomavirus; KICH, kidney chromophobe; KIRC, kidney renal clear cell carcinoma; KIRP, kidney renal papillary cell carcinoma; LAML, acute myeloid leukemia; LGG, brain lower grade glioma; LIHC, liver hepatocellular carcinoma; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; MESO, mesothelioma; OV, ovarian serous cystadenocarcinoma; PAAD, pancreatic adenocarcinoma; PCPG, pheochromocytoma and paraganglioma; PRAD, prostate adenocarcinoma; READ, rectum adenocarcinoma; SARC, sarcoma; SKCM, skin cutaneous melanoma; STAD, stomach adenocarcinoma; TGCT, testicular germ cell tumors; THCA, thyroid carcinoma; THYM, thymoma; UCEC, uterine corpus endometrial carcinoma; UCS, uterine carcinosarcoma; UVM, uveal melanoma.

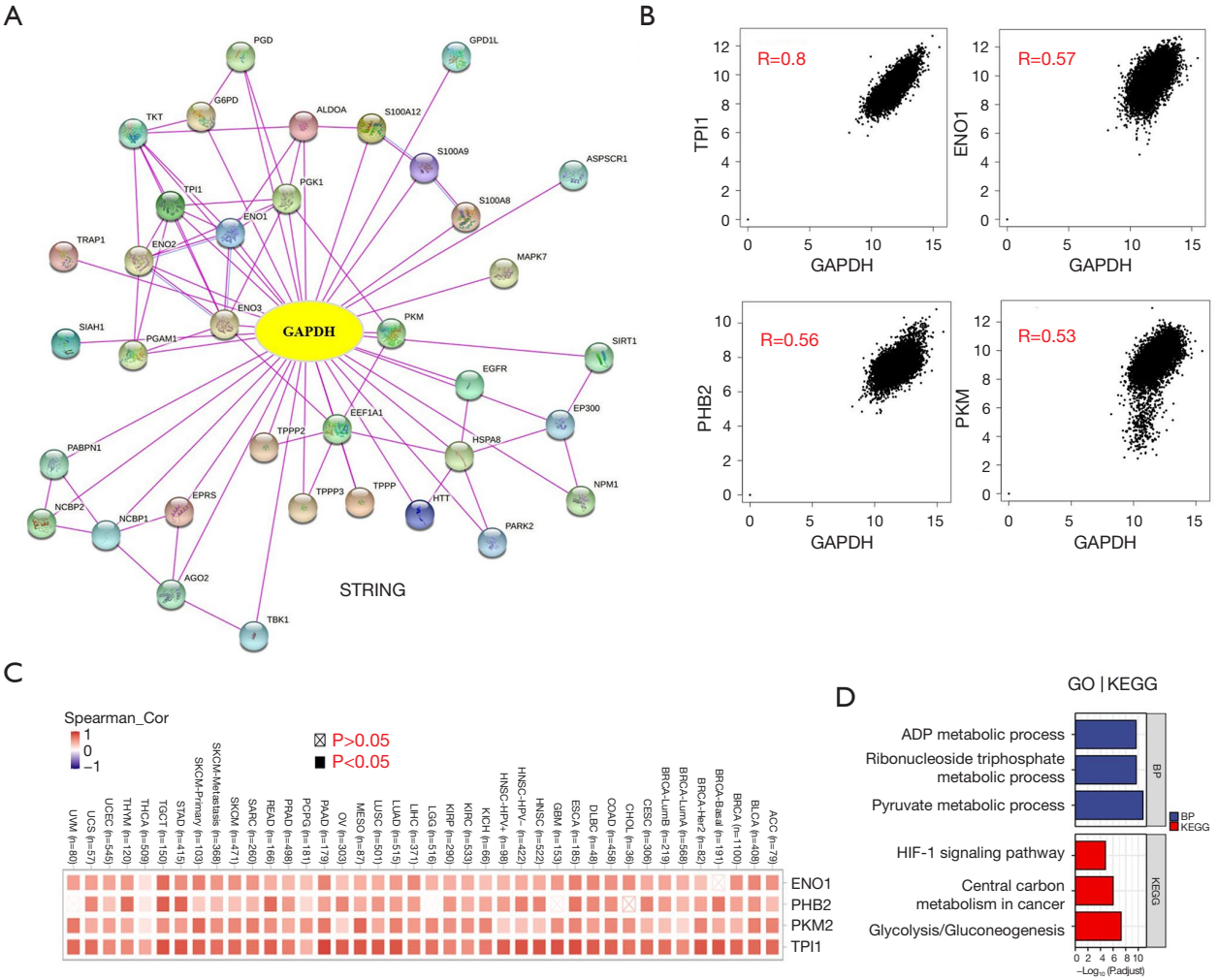

Figure 5 Enrichment analysis of *GAPDH* related partners. (A) The protein-protein network of GAPDH protein based on STRING. (B,C) The top 4 genes corrected with *GAPDH* mRNA in TCGA tumors were shown in scatter diagram (B) and heatmaps (C). (D) GO and KEGG enrichment analyses of *GPADH*-related genes. ACC, adrenocortical carcinoma; ADP, adenosine diphosphate; BLCA, bladder urothelial carcinoma; BP, biological processes; BRCA, breast invasive carcinoma; CESC, cervical squamous cell carcinoma and endocervical adenocarcinoma; CHOL, cholangiocarcinoma; COAD, colon adenocarcinoma; DLBC, lymphoid neoplasm diffuse large B-cell lymphoma; ENO1, enolase 1; ESCA, esophageal carcinoma; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; GBM, glioblastoma multiforme; GO, Gene Ontology; HIF-1, hypoxia inducible factor; HNSC, head and neck squamous cell carcinoma; HPV, human papillomavirus; KEGG, Kyoto Encyclopedia of Genes and Genomes; KICH, kidney chromophobe; KIRC, kidney renal clear cell carcinoma; KIRP, kidney renal papillary cell carcinoma; LAML, acute myeloid leukemia; LGG, brain lower grade glioma; LIHC, liver hepatocellular carcinoma; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; MESO, mesothelioma; OV, ovarian serous cystadenocarcinoma; PAAD, pancreatic adenocarcinoma; PCPG, pheochromocytoma and paraganglioma; PHB2, prohibitin 2; PKM, pyruvate kinase M1/2; PRAD, prostate adenocarcinoma; READ, rectum adenocarcinoma; SARC, sarcoma; SKCM, skin cutaneous melanoma; STAD, stomach adenocarcinoma; STRING, Search Tool for Recurring Instances of Neighbouring Genes; TGCT, testicular germ cell tumors; THCA, thyroid carcinoma; THYM, thymoma; TPI1, triosephosphate isomerase 1; UCEC, uterine corpus endometrial carcinoma; UCS, uterine carcinosarcoma; UVM, uveal melanoma.

link between *GAPDH* expression, clinical outcome and immune cell infiltration for a variety of tumors, providing a variety of viewpoints regarding *GAPDH*'s role in tumorigenesis.

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Footnote

Reporting Checklist: The authors have completed the REMARK reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-1972/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-1972/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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