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Original Article

Differential expression of *ABO* in normal and tumor tissues: Implications for cancer biology and prognosis

Hind M. Albadrani, PhD [a], Munerah Hamed, PhD [b], Abeer Zakariyah, PhD [c], Samar Binkheder, PhD [d], Saeed M. Kabrah, PhD [e,*] and Arwa F. Flemban, PhD [b]

[a] *Department of Clinical Laboratory Sciences, College of Applied Medical Sciences, Imam Abdulrahman Bin Faisal University, Dammam, Eastern Province, KSA*
[b] *Department of Pathology, Faculty of Medicine, Umm Al-Qura University, Makkah, KSA*
[c] *Department of Medical Genetics, Faculty of Medicine, University of Jeddah, Jeddah, KSA*
[d] *Medical Informatics Unit, Department of Medical Education, College of Medicine, King Saud University, Riyadh, KSA*
[e] *Department of Clinical Laboratory Sciences, Faculty of Applied Medical Sciences, Umm Al-Qura University, KSA*

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الملخص

أهداف البحث: تعرف فصيلة ABO في المقام الأول بتحديد فصائل الدم، وأظهرت الدراسات أنماط تعبير متغيرة في الأنسجة المختلفة وأنواع السرطان. وتهدف هذه الدراسة البحث في العلاقة بين التعبير الجيني للفصيلة والسرطان، وتقييم تأثيره المحتمل على بقاء المريض على قيد الحياة.

طرق البحث: باستخدام قاعدة بيانات GEPIA، قمنا بتحليل تعبير ABO في الأنسجة الطبيعية والأورام عبر أنواع السرطان المختلفة باستخدام أدوات التحاليل الجينية المتاحة عبر الإنترنت لإجراء تقييم شامل.

النتائج: كشف التحليل عن تباينات كبيرة في التعبير عن ABO بين أنواع الأنسجة المختلفة. والجدير بالذكر أن أنسجة المبيض والغدة الدرقية أظهرت أعلى تعبير عن ABO، في حين أظهرت أنسجة الكبد والغدة الصعترية والدماغ تعبيرًا منخفضًا نسبيًا. وتباينت أنماط التعبير عن ABO بشكل واضح بين أنواع السرطان، حيث أظهرت سرطانات المبيض والغدة الدرقية الاختلافات الأكثر أهمية بين أنسجة الورم والأنسجة الطبيعية. كما أظهرت أنواع أخرى من السرطان، بما في ذلك سرطان قشرة الكظر، وسرطان الدم النقوي الحاد، وسرطان الخلايا الكلوية، اختلافات ملحوظة في التعبير عن ABO. وارتبط انخفاض التعبير عن ABO بانخفاض معدلات البقاء على قيد الحياة في سرطان الغدة الدرقية القولون والمستقيم، وسرطان الغدة الدرقية في المعدة، وسرطانات الكلى، وغيرها.

الاستنتاجات: تشير هذه النتائج إلى الدور المحتمل لـ ABO في تطور الورم وتطور السرطان والتشخيص. كما تؤكد هذه الدراسة على قيمة ABO كمؤشر حيوي لمختلف أنواع السرطان وتتطلب إجراء المزيد من البحث لفهم أدواره الوظيفية وتأثيراته العلاجية لتطوير علاجات السرطان المستهدفة وأدوات التشخيص.

الكلمات المفتاحية: فصيلة ABO؛ التعبير الجيني؛ سرطان؛ ورم؛ تحليل السيليكو

Abstract

Objectives: *ABO*, which is primarily recognized for determining blood types, shows variable expression patterns in different tissues and cancer types. This study investigated the relationship between gene expression and cancer, and assessed its potential impact on patient survival.

Methods: Utilizing the GEPIA database, we analyzed *ABO* expression in normal and tumor tissues across various cancer types using online *in silico* tools for comprehensive evaluation.

Results: The analysis revealed significant disparities in *ABO* expression among different tissue types. Notably, ovarian and thyroid tissues exhibited the highest expression of *ABO*, whereas the liver, thymus, and brain tissues showed relatively low expression. The expression patterns of *ABO* varied distinctly among cancer types, with ovarian and thyroid carcinomas demonstrating the most significant differences between tumor and normal tissues. Other cancers, including adrenocortical carcinoma, acute

* Corresponding address: Department of Clinical Laboratory Sciences, Faculty of Applied Medical Sciences, Umm Al-Qura University, KSA.
E-mail: smkabrah@uqu.edu.sa (S.M. Kabrah)

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myeloid leukemia, and renal cell carcinoma, also exhibit notable variations in *ABO* expression. Low *ABO* expression was correlated with reduced survival rates in colorectal adenocarcinoma, stomach adenocarcinoma, and renal cancers, among others.

Conclusions: These findings suggest the potential role of *ABO* in tumor development, as well as cancer progression and prognosis, underscoring the value of *ABO* as a biomarker for various cancers. This warrants further research for understanding the functional roles of *ABO* and its therapeutic implications to develop targeted cancer therapies and diagnostic tools.

Keywords: *ABO*; Cancer; Gene expression; *In silico, tissue*; Tumor

Introduction

Cancer is a leading cause of morbidity and mortality worldwide and significantly affects the quality of life of individuals. The global burden of cancer continues to rise, with millions of new cases diagnosed annually[1]. Studies have revealed intriguing links between the ABO blood groups and risk of certain cancers. *ABO* has become the focus of increased attention owing to its involvement in a diverse range of health conditions including urinary tract infections,[2] infectious diseases,[3–5] and type 2 diabetes mellitus.[6] Recent advances in genomic research have uncovered a broad spectrum of functions associated with the ABO system. One area of growing interest is the association between *ABO* and cancer development.[7]

ABO is located on the ninth chromosome (9q34.2) in humans. It encodes glycosyltransferases that are responsible for the construction of ABO blood group antigens on the surface of red blood cells and other tissues.[8–10] The ABO blood groups are characterized by their polymorphic, antigenic, and genetic properties.[8] *ABO* is known for its critical role in determining blood types[9] and is the primary human blood typing system.[11] The distributions of the four *ABO* blood types (A, B, AB, and O) and their antigens vary worldwide. The ABO blood type is determined by the frequency of the three alleles of *ABO* in different populations.[8] Blood type O is the most common worldwide, followed by A, B, and AB which is the least common.[8]

Several studies have investigated the relationship between *ABO* expression and cancer. Specific ABO blood types may be associated with varying susceptibilities to cervical cancer.[12] The relationship between ABO blood groups and gastric cancer has also been explored, suggesting that individuals with certain blood types may exhibit a varied extent of predisposition to developing gastric cancer.[13] Moreover, *ABO* has been implicated in lymphoma, a group of blood cancers that affect the lymphatic system.[14] The ABO blood type may influence the risk and prognosis of lymphoma, offering valuable insights into the complex interplay between genetic factors and cancer susceptibility.[15] Beyond these specific cancer types, the involvement of *ABO* in systemic inflammation and modulation of immune response may contribute to its broad impact on cancer risk. For instance, individuals with blood types A, B, or AB have a higher risk of developing pancreatic cancer than those with blood type O, probably owing to the regulation of proinflammatory and adhesion molecules.[16] Chronic inflammation is a recognized factor in developing various cancers, and the influence of *ABO* on inflammatory processes may provide a mechanistic link between blood types and cancer susceptibility.

Based on these facts, this study explored the association between ABO expression and cancer to elucidate its potential role in tumorigenesis and its impact on patient survival. The primary hypothesis posits that distinct patterns of ABO expression exist across various types of normal and cancerous tissues. Furthermore, we investigated whether these differential expression profiles correlate with clinical outcomes, particularly patient survival rates. While this study focuses on *in silico* analysis, future research should include protein-level validation and ethnicity-specific studies to more comprehensively understand the role of ABO. Additionally, a comprehensive comparison between ABO and traditional cancer biomarkers is suggested to evaluate its utility as a prognostic biomarker further. By utilizing these approaches, we aim to shed light on the broader molecular links between ABO and cancer and its potential implications in clinical practice.

Materials and Methods

This retrospective observational study investigated *ABO* expression in normal and cancerous tissues. This study used data from multiple publicly available databases, including the Human Protein Atlas (HPA), Genotype-Tissue Expression (GTEx) project, ARChS4 atlas, and Gene Expression Profiling Interactive Analysis (GEPIA2) tool. This study utilized the following strategy to assess *ABO* expression in normal and cancerous tissues. A list of the tumors is provided. The strategy for evaluating the expression and function of *ABO* is shown in Figure 1.

Validation of ABO expression in normal tissues

GeneCards (https://www.genecards.org/) was used to identify the genomic location of *ABO* on chromosome 9 using a free online platform (http://www.genecards.org). This online tool includes genomic data from over 150 databases, such as GeneLoc, HGNC, Entrez Gene, Nature, and miRBase, and a genomic view from the UCSC and Ensembl annotation databases (https://link.springer.com/chapter/10.1007/978-981-16-5812-9_2). The validation of *ABO* expression was assessed using DNA sequencing, RNA sequencing, and microarray data internally generated by the HPA (https://www.proteinatlas.org/) and GTEx (https://www.genome.gov/Funded-Programs-Projects/Genotype-Tissue-Expression-Project). The ARChS4 atlas (http://maayanlab.cloud/archs4/index.html) was used to analyze the mRNA expression of *ABO* in normal tissues. This platform groups tissues into different levels and includes various cellular contexts.

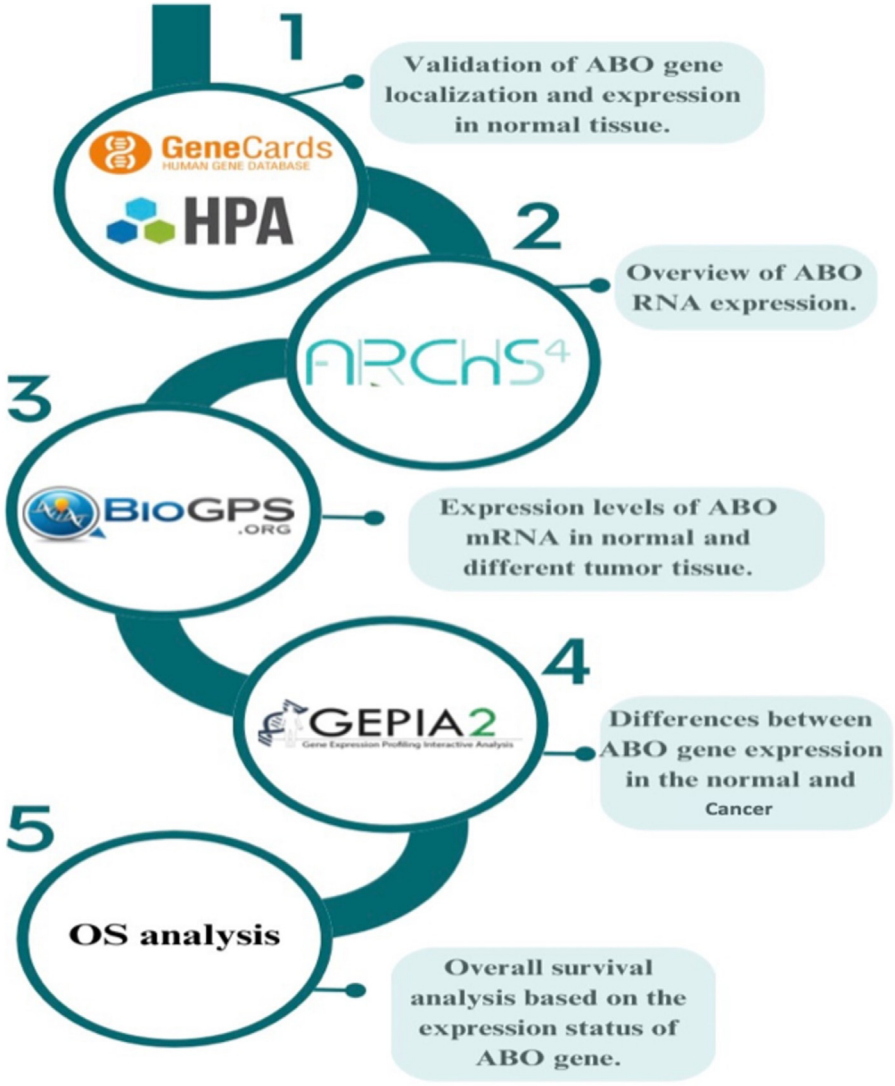


Figure 1: Overall strategy for evaluating *ABO* expression.

Transcriptomic data obtained from the HPA (https://www.proteinatlas.org/) were used to evaluate *ABO* expression in normal tissues. This tool uses various data sources, including data from the Single Cell Expression Atlas, Human Cell Atlas, Gene Expression Omnibus, Allen Brain Map, and European Genome-phenome Archive.

BioGPS, a free online platform (http://biogps.org/#goto=welcome), was used to analyze mRNA expression of *ABO* in human tissues. This platform contains high-density oligonucleotide arrays obtained from the GeneAtlas (U133A, German) dataset to investigate *ABO* expression in 79 human tissues from 176 samples in 31 normal and cancer tissues.

Analysis of ABO expression in cancer tissues

GEPIA2 (http://gepia2.cancer-pku.cn) was used to evaluate differences in *ABO* expression between normal and cancer tissues. This platform measures gene expression in cancer by producing boxplots. Differential expression was calculated using disease state (tumor or normal) as a variable. A box plot illustrates the median normal vs. tumor expression using The Cancer Genome Atlas (TCGA) (https://www.cancer.gov/ccg/research/genome-sequencing/tcga) and GTEx data.

Survival analysis

To assess the impact of ABO gene expression on the survival of cancer patients, we utilized the GEPIA2 platform (http://gepia2.cancer-pku.cn/#index), which integrates data from TCGA and GTEx databases. Overall survival analysis was performed using Kaplan–Meier (KM) survival plots to compare patient groups with high and low ABO expression.

The survival data were analyzed using the log-rank test (also known as the Mantel–Cox test) to evaluate statistical differences in survival between the groups. Additionally, GEPIA2 calculates the Cox proportional hazard ratio (HR) and the 95 % confidence interval (CI), which are included in the survival plots. These hazard ratios provide an estimate of the relative risk of death based on ABO gene expression levels.

Results

ABO expression profile in different normal tissue types

The data presented in Figure 2 demonstrate that *ABO* expression substantially varied across different tissue types. The highest expression of *ABO* was observed in ovarian tissue, with a median expression of 23.43. This was closely followed by expression in thyroid tissue with a median expression of 22.5. These findings suggest a potential role for *ABO* in the physiology and pathology of these tissues. Several other tissue types also displayed notable *ABO* expression. ABO expression in adrenocortical tissue was 13.56, and those in esophageal and myeloid tissues were 13.37 and 10.93, respectively. *ABO* expression in renal and papillary renal tissues was 7.99 and 7.65, respectively. These results suggest a potential association between *ABO*, and renal tissue physiology or pathogenesis.

In contrast, tissues of the liver, diffuse large B-cell, bile duct, thymus, and brain exhibited relatively low *ABO* expression, with median expression ranging between 0.06 and 0.55. These findings implied that *ABO* is minimally regulated in these tissues. Colon, bladder urothelial, head and neck squamous cell, and uterine corpus endometrial tissues showed moderate *ABO* expression, ranging between 2.07 and 3.99. Overall, analysis of *ABO* expression profile across different tissue types revealed significant variations.

Assessment of ABO expression in normal and cancer tissues

The differences in *ABO* expression between normal and tumor tissues are shown in Figure 3. Among the cancer types analyzed, the most considerable difference observed in *ABO* expression between normal and cancer tissues was in ovarian carcinoma (OV), with a difference of 21.21. This was followed by thyroid carcinoma (THCA), with a difference of 14.19. These findings suggested a substantial alteration in *ABO* expression during tumor progression in these tissue types. Several other cancer types exhibit notable differences in *ABO* expression. Adrenocortical carcinoma (ACC)

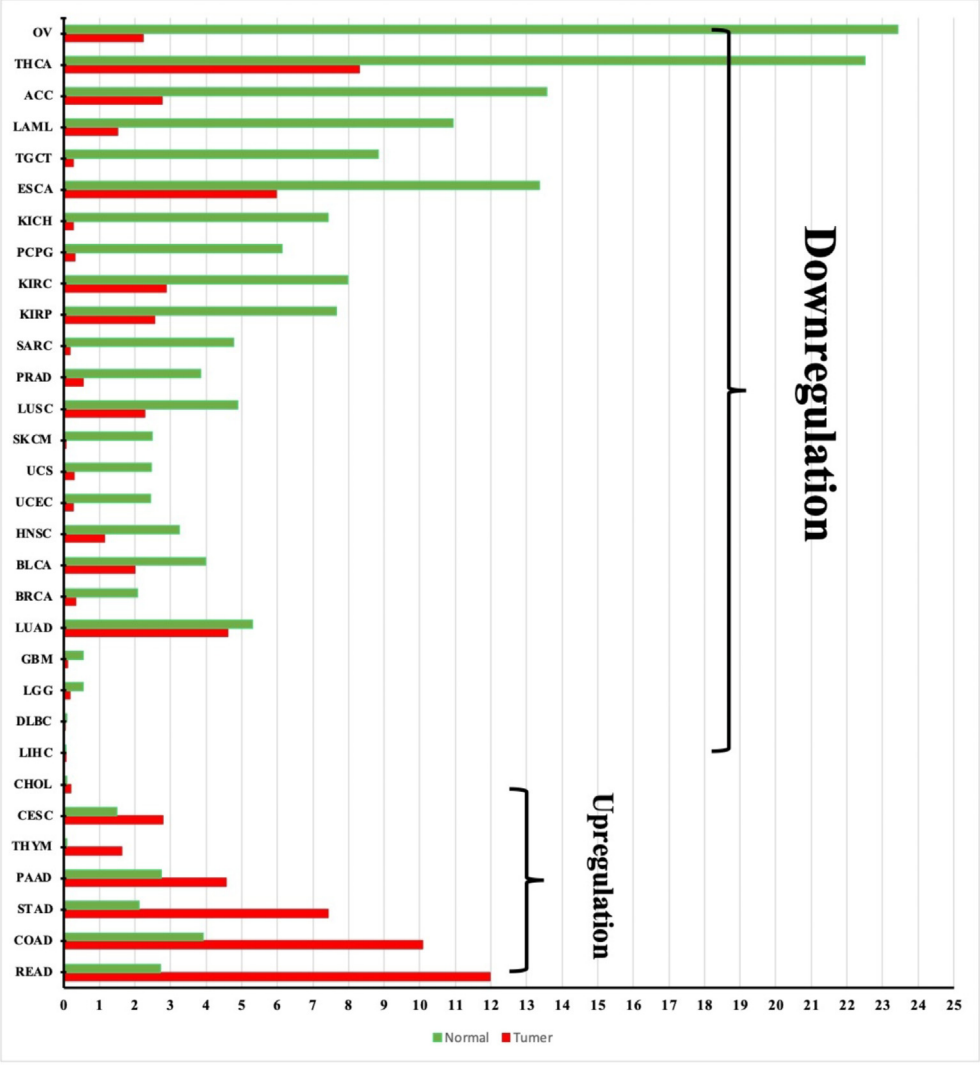


Figure 2: *ABO* expression profile across normal tissues. mRNA expression of *ABO* across different normal human tissues, generated by the ARChS4 online database.

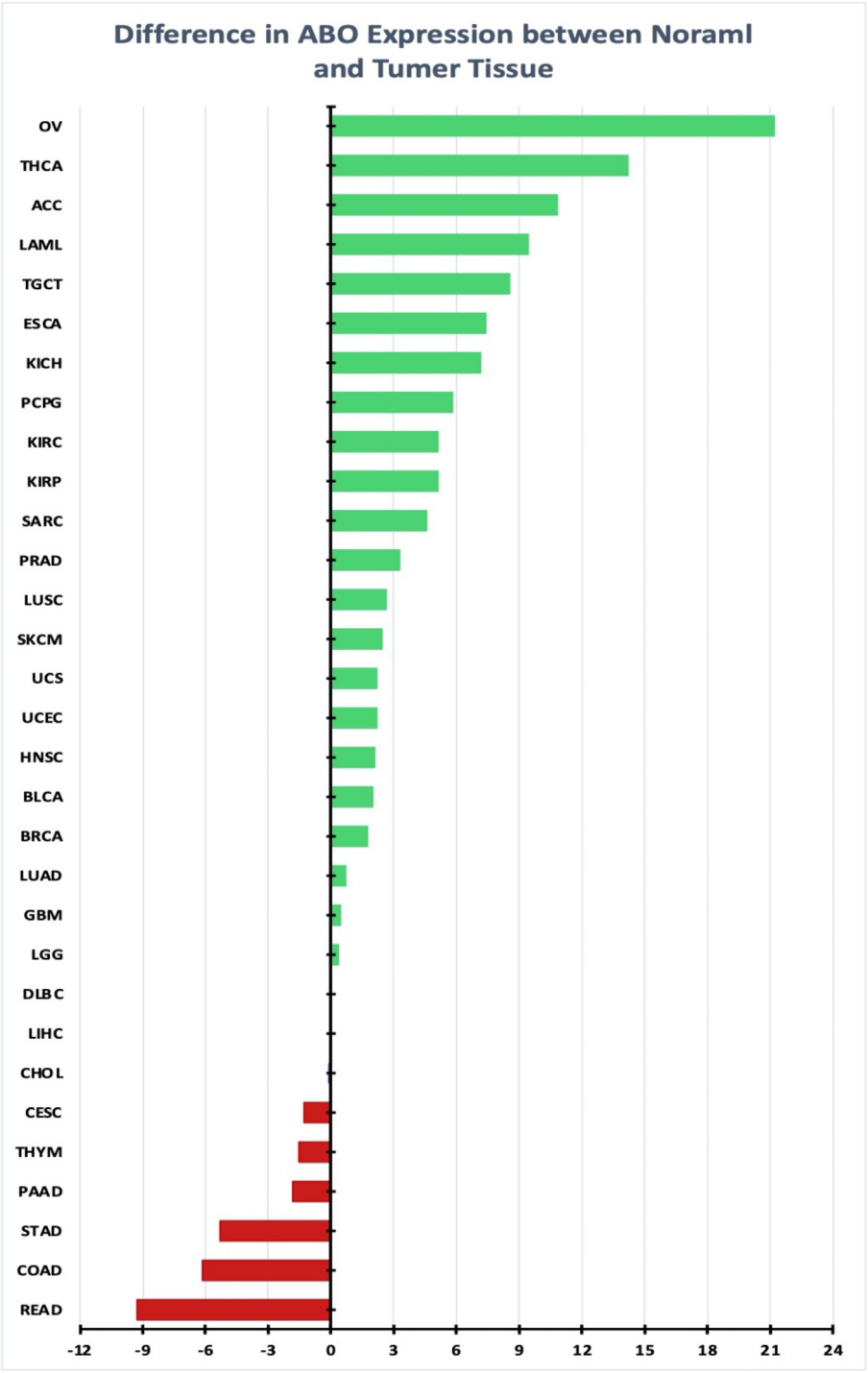


Figure 3: *ABO* expression in normal and tumor tissues. Differences in *ABO* expression between normal and tumor tissues. The left panel shows a reduction in expression from that of normal tissues, while the right panel shows an increased expression in tumor tissues, highlighting significant variations in *ABO* expression associated with tumoral transformation.

demonstrated a difference of 10.8, while acute myeloid leukemia (LAML) and testicular germ cell tumors (TGCT) showed differences of 9.41 and 8.56, respectively. Renal clear cell carcinoma (KIRC) and papillary renal cell carcinoma (KIRP) displayed differences of 5.12 and 5.1, respectively, in *ABO* expression. These findings suggest a potential role of *ABO* in the development or progression of renal cell carcinoma.

In contrast, some cancer types showed relatively minor differences in *ABO* expression than that of the normal tissues. These included hepatocellular carcinoma (LIHC), diffuse large B-cell lymphoma (DLBC), cholangiocarcinoma (CHOL), and thymoma (THYM) with differences ranging

from −0.12 to 0.05. These results implied a limited alteration in *ABO* expression during the pathogenesis of these cancer types. Invasive breast carcinoma (BRCA), colorectal adenocarcinoma (COAD), bladder urothelial carcinoma (BLCA), and lung squamous cell carcinoma (LUSC) displayed moderate differences in *ABO* expression, ranging between 1.74 and 2.62. These findings suggest a potential association between *ABO* and progression of these cancer types.

Comparison of mRNA expression of ABO between normal and tumor tissues

The scatter boxplot in Figure 4 shows the median values of mRNA expression of *ABO* in different tumor types, with significant differences observed between the two groups. *ABO* was significantly overexpressed in the following tumors compared to that in the normal tissue; READ (median 3.7 vs. 1.9, $p < 0.05$), COAD (median 3.47 vs. 2.3, $p < 0.05$), STAD (median 3.07 vs. 1.64, $p < 0.05$), and THYM (median 1.40 vs. 0.11, $p < 0.05$). Conversely, *ABO* expression was significantly downregulated in the following tumors; BRCA (0.41 vs. 1.61, $p < 0.05$), UCEC (0.35 vs. 1.78, $p < 0.05$), UCS (0.36 vs. 1.79, $p < 0.05$), SKCM (0.08 vs. 1.8, $p < 0.05$), SARC (0.22 vs. 2.53, $p < 0.05$), KIPR (1.83 vs. 3.11, $p < 0.05$), KIRC (1.95 vs. 3.17, $p < 0.05$), PCPG (0.39 vs. 2.83, $p < 0.05$), KICH (0.33 vs. 3.08, $p < 0.05$), ESCA (2.80 vs. 3.84, $p < 0.05$), TGCT (0.34 vs. 3.3, $p < 0.05$), LAML (1.33 vs. 3.58, $p < 0.05$), ACC (1.91 vs. 3.86, $p < 0.05$), THCA (3.22 vs. 4.55, $p < 0.05$), and OV (1.69 vs. 4.61, $p < 0.05$). These data suggest that the mRNA expression of *ABO* is altered in various cancer types.

The prognostic role of ABO on the survival of patients with cancer

The prognostic role of *ABO* is shown in Figure 5. Low *ABO* expression was negatively associated with patient survival in multiple types of cancer including READ, COAD, STAD, CHOL, SARC, ACC, KIRP, KIRC, and KICH. However, the association was not significant for all types of cancers, except KIRP, KIRC, and KICH ($p < 0.05$). In contrast, high *ABO* expression was negatively and non-significantly associated with patient survival in PAAD, THYM, UCEC, ESCA, and LAML.

Discussion

This study explored the association between *ABO* and various tumor types. Our findings showed that *ABO* expression varies between normal and tumor tissues, and that *ABO* expression and patient survival rates are correlated among different types of cancer.

Generally, *ABO* is expressed on the surface of blood cells.[17] Furthermore, *ABO* is prominently expressed in tissues, including the digestive, respiratory, and genitourinary tracts, and epithelial cell lining, which interact with the external environment. We found that *ABO* is expressed in several tissues, including THCA, OV, ACC, ESCA, LAML, KICH, KIRK, and KIRP, as was previously observed. The expression profile of *ABO* varied among different tissue types, suggesting tissue-specific regulation. Therefore, understanding the expression and potential functions of *ABO* holds promise for advancements in personalized medicine and cancer prevention.

ABO is associated with various diseases including inflammatory diseases,[18] cardiovascular disorders,[19–21] and cancer.[21] However, the association between *ABO* expression and cancer remains unclear. *ABO* has been implicated in some cancers such as pancreatic cancer,[22,23] colorectal carcinoma,[24,25] and gastric cancer.[26] Consistent with previous studies, we found that *ABO* expression was upregulated in various types of cancers. In contrast, reduced *ABO* expression has been observed in some cancers such as bladder carcinoma[26] and leukemia, including LAML chronic myeloid leukemia, and acute lymphoblastic leukemia.[27] Similarly, our *in silico* analysis showed that *ABO* expression was downregulated in some cancers such as bladder urothelial carcinoma, acute myeloid leukemia, breast invasive carcinoma, and renal carcinoma. This suggests an association between *ABO* expression and specific cancer types. A possible explanation may be that *ABO* is directly or indirectly regulated by tumor suppressor genes or oncogenes. Previously, a regulatory element downstream of *ABO* exclusive to epithelial cells has been discovered. The transcription factor Elf5, an epithelial-specific member, plays a role in enhancing the activity of this regulatory element, and *ABO* expression depends on the binding of a downstream positive regulatory element to Elf5 in epithelial cells.[28] Polymorphisms in *ABO* contribute to the susceptibility and risk of cancer. For example, two single nucleotide polymorphisms in *ABO* (rs505922 and rs657152) have been found to be associated with pancreatic cancer.[29]

Moreover, the differential expression of *ABO* may be attributed to hypermethylation of the *ABO* promoter region, which results in transcriptional activation of the gene.[30,31] Promoter methylation is linked to the inactivation of numerous cancer-associated genes.[32,33] The differential expression of *ABO* in normal and tumor tissues implies cell-specific activation/inactivation of *ABO* expression during tumorigenesis.[30]

We found that low *ABO* expression was associated with reduced patient survival in a wide range of cancer types. The ABO blood group influences the progression and metastasis of cancer by manipulating systemic inflammatory response.[18] An association between *ABO* and circulating levels of inflammatory factors, such as tumor necrosis factor alpha,[34] P-selectin 35, and soluble intercellular adhesion molecule,[35] has been reported. These adhesion molecules play a critical role in chronic inflammation and recruitment of immune cells[12] and could explain the potential connection between the ABO blood group and cancer survival by linking the ABO blood group with tumor onset and dissemination.[36]

Differential expression of *ABO* can be utilized as a prognostic biomarker for different cancers. The prognostic impact of ABO blood type on survival has been studied in various types of cancers such as colorectal[37] and ovarian cancers.[38] Patients diagnosed with colon cancer, who underwent surgical resection and had blood type AB, exhibit a higher likelihood of improved survival outcomes than those with blood types other than AB.[37] Individuals

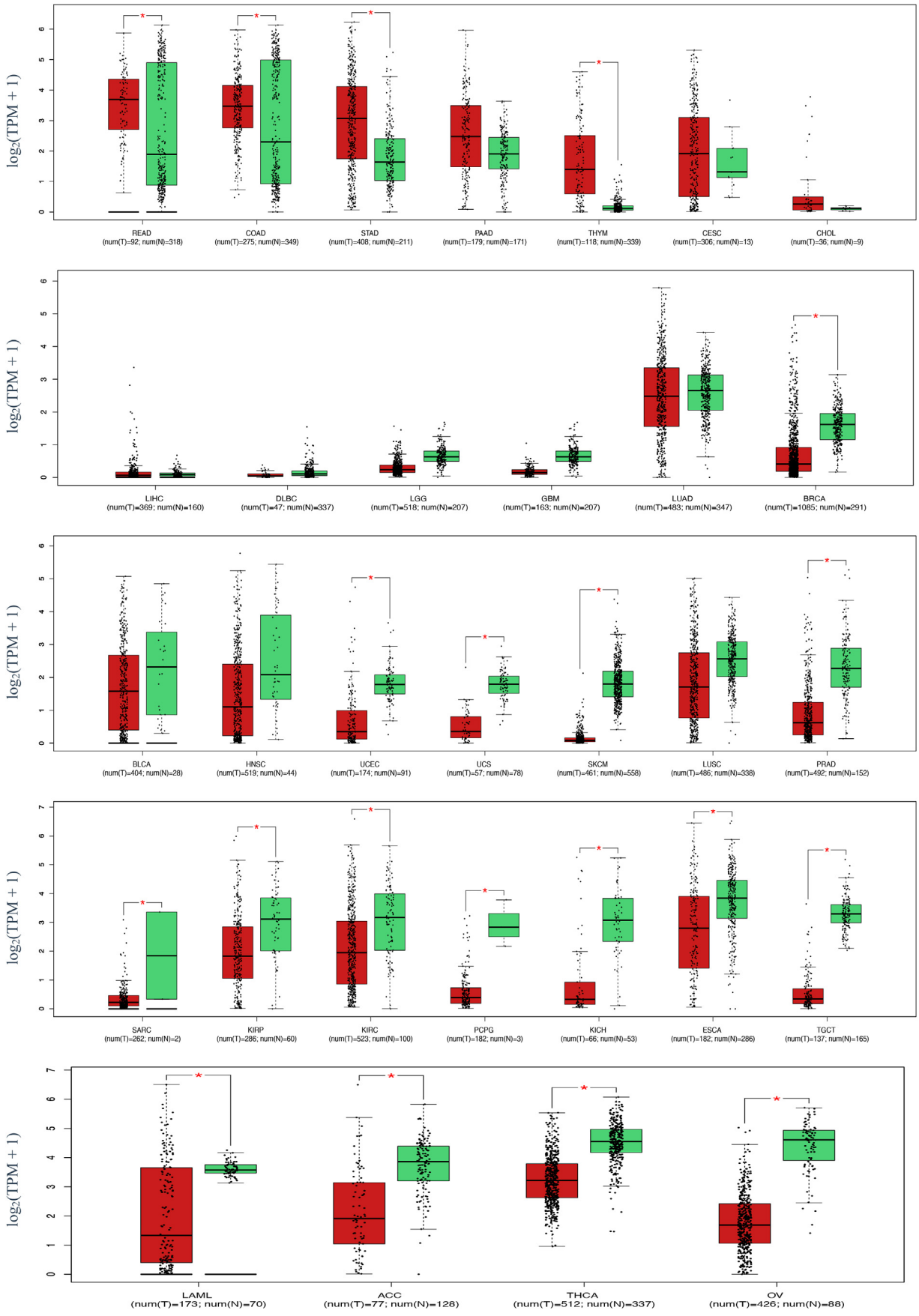
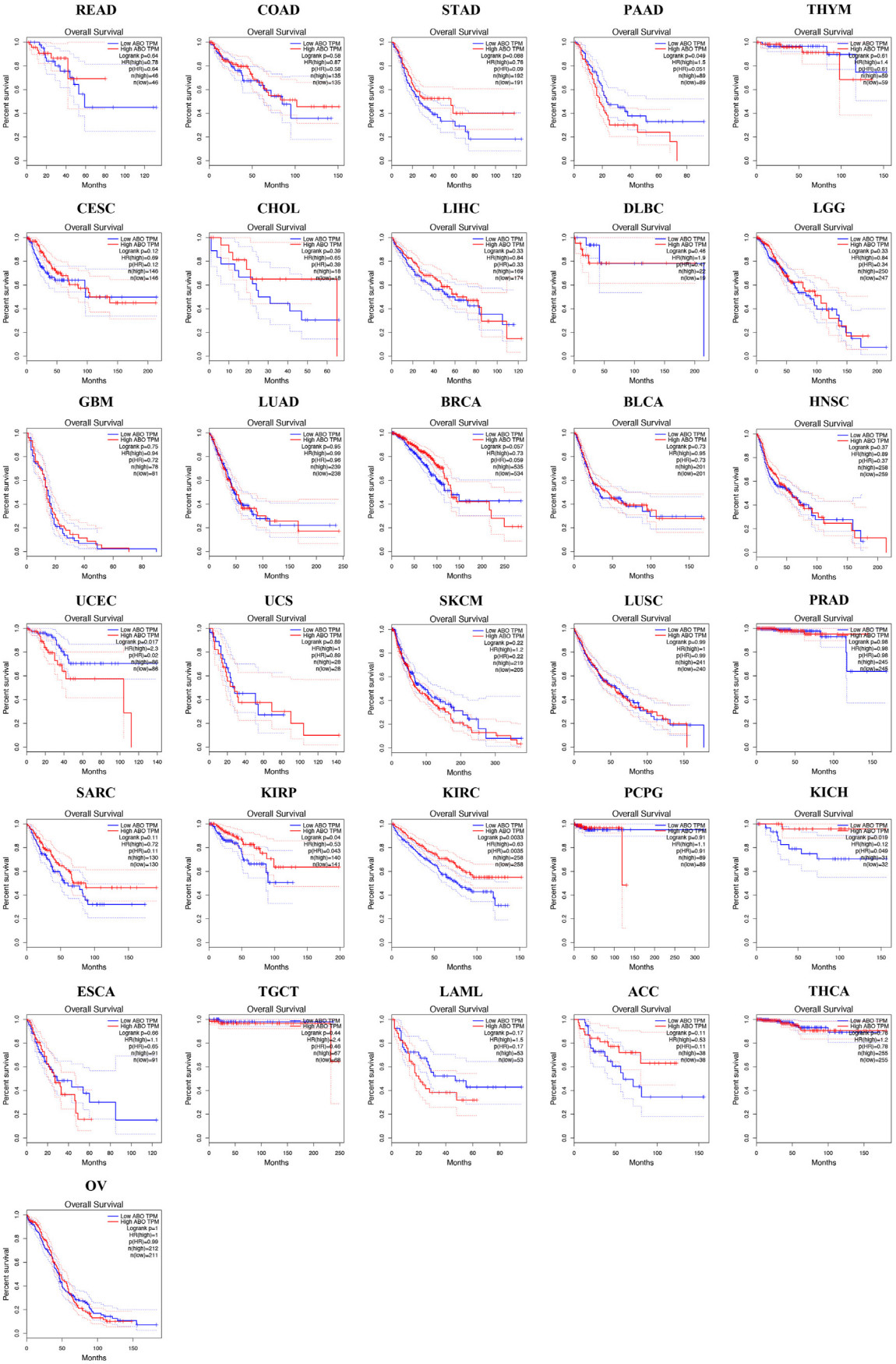


Figure 4: mRNA expression of *ABO* using scatter blot. Box plots with jitter for comparing *ABO* expression [$\log_2$ (TMP+1)] in normal (green) and cancer (red) tissues. Red star indicates a significant correlation with $p < 0.05$.


READ
COAD
STAD
PAAD
THYM
CESC
CHOL
LIHC
DLBC
LGG
GBM
LUAD
BRCA
BLCA
HNSC
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UCS
SKCM
LUSC
PRAD
SARC
KIRP
KIRC
PCPG
KICH
ESCA
TGCT
LAML
ACC
THCA
OV
Overall Survival
Percent survival
Months
Low ABO TPM
High ABO TPM

with blood type A exhibit a significantly elevated probability of developing colorectal cancer compared to individuals with other blood types.[39]

The ABO blood group has also been studied in ovarian cancer. However, the correlation between *ABO* and ovarian cancer remains unclear and requires further investigation. Several studies have revealed a correlation between blood type A and increased survival rates in individuals with ovarian cancer.[38] In contrast, an association between blood group A and an elevated risk of epithelial ovarian cancer in Chinese women has been noticed.[40] The presence of B antigen has been found to be positively linked to the occurrence of ovarian cancer.[41] We found that *ABO* was downregulated in ovarian cancer, which was consistent with previous findings.[40]

A prospective study on a middle Chinese cohort has reported that individuals with blood types B and AB have reduced susceptibility to gastrointestinal cancers, such as stomach and colorectal cancers, compared to those with blood type A. Moreover, blood type AB was associated with a relatively high risk of liver cancer, whereas blood type B was associated with a reduced risk of bladder cancer. The results of this study align with the concept that, in addition to red blood cells, ABO blood-type antigens are present in the epithelial cells of the gastrointestinal and urinary tracts and ovaries. Therefore, the ABO blood type may play a role in the progression of epithelial cancers in these areas.[39]

A meta-analysis of the ABO blood group and the risk of different cancers from four databases conducted on 100,554 cases at 30 cancer sites has revealed that blood group A is significantly associated with an increased risk of gastric, nasopharyngeal, pancreatic, ovarian, and breast cancers. Nonetheless, blood group O is associated with a reduced risk of these cancers, along with colorectal and esophageal cancers. Interestingly, blood groups B and AB were not significantly correlated with any cancer risk in this study.[42] A recent meta-analysis of 231,737 patients with 20 different cancers has reported that blood group A is significantly associated with pancreatic, oral cavity, liver, cervical, breast, gastric, bladder, colorectal, and ovarian cancer. Blood group AB has been linked to pancreatic, gastric, and ovarian cancers, whereas blood group B has been connected to non-melanoma and esophageal cancer. Furthermore, patients with pancreatic cancer and having blood groups A, B, and AB were primarily Caucasians and Asians..[43] The differences between the findings of different meta-analyses may be owing to the selection of datasets and ethnicity-specific studies.

This study has some limitations. These include its reliance on *in silico* analysis of mRNA expression rather than protein expression, which may not fully capture the functional activity of ABO in cancer progression. Additionally, we did not perform external validation using independent datasets, though we ensured the reliability of the findings through cross-platform comparisons and the use of well-validated datasets (TCGA and GTEx). Furthermore, the lack of consideration for ethnicity-specific differences in ABO expression and cancer outcomes could impact the generalizability of our results. Future studies should incorporate protein-level validation, ethnic diversity in cohorts, and external validation with independent datasets to strengthen these findings. Another limitation is the potential inflation of hazard ratios (HR) observed in Figure 5, likely due to sparse events and a small sample size in the subgroup analysis. This limitation can result in instability of HR estimates and an exaggeration of effect sizes. Sparse data are known to bias proportional hazards models by amplifying minor differences between groups, which can lead to wide confidence intervals and inflated HR values. This issue has been well-documented in the literature.[44] We recommend cautious interpretation of these results and propose that future research should employ larger datasets to mitigate these limitations and confirm the findings.

Conclusions

The diversity in ABO gene expression across different tissues is likely due to its specialized functions in various biological processes. Our study on the variations in the association of ABO expression with distinct cancer types highlights the complexity of ABO regulation and its tissue-specific nature. These findings raise important questions regarding the potential roles of ABO beyond its classical functions in blood compatibility, particularly its involvement in cancer biology.

However, the underlying mechanisms and the relationship between ABO expression and cancer risk remain unclear. While this study demonstrates the correlation between ABO expression and patient survival, further research is needed to explore the role of ABO in cancer initiation, progression, and metastasis. Future studies should investigate ABO expression at the protein level, examine its mechanistic pathways, and conduct validation across diverse ethnic populations.

Our findings suggest that differential expression of ABO in normal and tumor tissues may indicate cell-specific activation or inactivation, making ABO expression a potential prognostic biomarker for various cancers. However, it should be noted that the role of ABO as a biomarker should be further explored in external cohorts and compared with traditional cancer biomarkers for a more comprehensive evaluation of its clinical utility as a biomarker.

Source of funding

This research received no external funding.

Figure 5: Role of *ABO* in the survival of patients with cancer. Survival analysis based on *ABO* expression in patients with cancer using GEPIA2. Kaplan−Meier curves for depicting the survival probability over time by categorizing patients into groups based on their *ABO* expression profiles (low and high). The solid and dotted lines represent the survival curve and 95 % confidence interval. The *p*-values of a log-rank test for trend and High Risk (HR).

Conflict of interest

The authors listed in this manuscript certify that they have no conflict of interests.

Ethical approval

The present study utilized data that were publicly available, and the tools were available freely online. Ethical approval was obtained from the Biomedical Ethical Committee at Umm Al-Qura University (HAPO-02-K-012-2023-03-1531, and HAPO-02-K-012-2023-06-1693). This study uses data from publicly available databases that have been collected with the consent of the participants.

Author contributions

SK conceived the presented idea, designed the study, validated it, and conducted the experiment. All authors contributed to the design of the article's concept, data interpretation, writing, and revising the manuscript critically for important intellectual content. The authors contributed equally to the final version of the manuscript. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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