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The primary aim of *World Journal of Gastrointestinal Oncology* (*WJGO*, *World J Gastrointest Oncol*) is to provide scholars and readers from various fields of gastrointestinal oncology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGO mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal oncology and covering a wide range of topics including liver cell adenoma, gastric neoplasms, appendiceal neoplasms, biliary tract neoplasms, hepatocellular carcinoma, pancreatic carcinoma, cecal neoplasms, colonic neoplasms, colorectal neoplasms, duodenal neoplasms, esophageal neoplasms, gallbladder neoplasms, *etc*.

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LETTER TO THE EDITOR

Elevated *ETV4* expression in cholangiocarcinoma is linked to poor prognosis and may guide targeted therapies

Uchenna E Okpete, Haewon Byeon

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Abstract

Cholangiocarcinoma (CCA), a highly aggressive bile duct cancer, is associated with late-stage diagnosis and limited treatment options, leading to poor patient outcomes. Early detection and personalized treatment strategies are crucial. The study by Wang *et al* highlights the prognostic potential of the PEA3 subfamily genes (*ETV1*, *ETV4*, and *ETV5*) in CCA, identifying ETV4 as a particularly promising biomarker. Their bioinformatic analysis revealed that elevated *ETV4* expression correlates with poorer survival, positioning it as a strong indicator of disease progression. These findings suggest that ETV4 could enhance prognostic precision and guide personalized therapies, although further validation through large-scale clinical trials is essential. Challenges in clinical application include the need for comprehensive experimental validation and addressing the tumor heterogeneity in CCA. Future research should focus on validating these biomarkers in diverse cohorts and developing targeted therapies, especially in regions where CCA is endemic.

Key Words: Prognostic biomarkers; Cholangiocarcinoma; Survival rates; *ETV4* expression; PEA3 subfamily; Precision medicine; Targeted therapy

Core Tip: Cholangiocarcinoma is a highly aggressive cancer with limited treatment options. The recent study by Wang *et al* highlights the prognostic value of the PEA3 subfamily genes (*ETV1*, *ETV4*, and *ETV5*), especially *ETV4*, as key indicators of poor survival. Elevated *ETV4* expression is linked to aggressive tumor behavior and worse outcomes. These findings offer potential for personalized treatment strategies, but further large-scale validation is required to integrate *ETV4* as a prognostic biomarker and therapeutic target in clinical practice, particularly in high-incidence regions.

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TO THE EDITOR

Cholangiocarcinoma (CCA) is one of the most aggressive and lethal gastrointestinal cancers, largely due to its late detection and limited treatment options. The global burden of CCA varies significantly, with the highest incidence rates found in parts of Asia[1]. Northeast Thailand reports age-standardized rates of 85 cases *per* 100000, followed by North and Central Thailand (14.5 *per* 100000), and Gwangju, South Korea (8.8 *per* 100000). In contrast, Western countries exhibit lower incidence rates, ranging from 0.5 to 3.4 *per* 100000[2].

Mortality trends show a similar pattern, with intrahepatic CCA (iCCA) mortality rates rising over the past decade in Europe, North America, and Oceania. Countries like Ireland, the United Kingdom, and Portugal have some of the highest rates, while Baltic nations, including Latvia and Lithuania, have seen sharp increases, with annual mortality changes exceeding 18%. Given the rising global burden and median survival rates often less than 24 months in advanced stages, early detection and precision oncology approaches are pivotal. In this context, the identification of novel prognostic markers is critical to advancing personalized medicine in CCA. The recent study by Wang *et al*[3] provides valuable insights into the potential role of the PEA3 subfamily genes (*ETV1*, *ETV4*, and *ETV5*) as biomarkers for CCA prognosis, offering a promising avenue for personalized medicine.

The PEA3 subfamily, part of the E26 transformation-specific family of transcription factors, plays a significant role in cancer progression, influencing proliferation, invasion, and metastasis. While these genes have been implicated in other cancers like liver, colorectal, and lung cancer, Wang *et al*'s study uniquely highlights the prognostic significance of *ETV1*, *ETV4*, and *ETV5* in CCA[3]. These findings are especially valuable for improving diagnosis and treatment, particularly in high-incidence regions like Asia.

KEY FINDINGS AND CLINICAL IMPLICATIONS

Through bioinformatic analysis of data from the Cancer Genome Atlas and Genotype-Tissue Expression project, Wang *et al*[3] discovered that *ETV1*, *ETV4*, and *ETV5* were significantly overexpressed in CCA tissues compared to healthy controls. Notably, high expression levels of *ETV1* and *ETV4* were associated with shorter overall survival, positioning these genes as potential indicators of disease progression. Among these, *ETV4* emerged as a particularly strong predictor of poor prognosis, with higher expression levels correlating with significantly worse survival outcomes. The high *ETV4* expression group had a *P*-value of 0.04, indicating a statistically significant association.

Mechanistically, *ETV4* has been implicated in driving tumorigenesis through its involvement in key oncogenic pathways, particularly in prostate and breast cancers[4]. It promotes cancer cell proliferation, migration, and invasion by influencing signaling pathways such as MAPK/ERK and PI3K/Akt. These pathways are crucial for regulating cell survival, growth, and differentiation, making *ETV4* a potent driver of aggressive tumor behavior in CCA. *ETV4* can also influence epithelial-mesenchymal transition (EMT), a process that enhances metastatic potential and resistance to apoptosis, further contributing to its role in poor prognosis.

In terms of clinical relevance, the identification of these genetic markers holds promise for more personalized therapeutic approaches in CCA. Stratifying patients based on *ETV4* expression could allow for tailored treatment plans, as those with high *ETV4* expression may be identified as a high-risk group likely to experience more aggressive disease progression and thus benefit from intensified therapeutic regimens. Integrating ETV4 expression analysis into routine diagnostic and prognostic workflows could provide valuable tools for early risk stratification, particularly through its incorporation into initial biopsy assessments and companion diagnostic tests. This can be achieved *via* immunohistochemistry or quantitative polymerase chain reaction to assess *ETV4* expression levels in CCA tissue samples.

For prognostic purposes, *ETV4* levels could serve as biomarkers to estimate overall survival and guide decision-making regarding aggressive *vs* conservative treatment approaches. Moreover, longitudinal tracking of *ETV4* expression through non-invasive techniques, such as liquid biopsy [*e.g.*, circulating tumor DNA (ctDNA) from blood samples], could allow clinicians to monitor changes over time without the need for repeated tissue biopsies. This would aid in assessing treatment response and detecting early signs of recurrence, enabling more dynamic and responsive clinical management.

Additionally, ETV4 has been shown to potentially induce treatment resistance in CCA, particularly chemoresistance, through its activation of pathways such as PI3K/Akt and MAPK/ERK, which promote survival and growth in tumor cells. Hence, therapeutic strategies targeting ETV4 could prove beneficial in overcoming this resistance, and future studies could explore the role of PEA3 gene silencing to enhance chemosensitivity and improve the efficacy of CCA therapies.

IMPLICATIONS FOR PROGNOSTIC PRECISION

The identification of *ETV4* as a prognostic biomarker is particularly significant in light of CCA's treatment challenges. Current therapeutic options for CCA have shown limited efficacy, and no established prognostic markers are routinely used in clinical practice. Early attempts to target the vascular endothelial growth factor and epidermal growth factor receptor pathways with agents such as bevacizumab, cediranib, erlotinib, sunitinib, and vandetanib failed to improve survival outcomes[5]. Therefore, the discovery of *ETV4* as a strong predictor of poor survival in CCA patients marks a critical advancement. Wang *et al*'s functional assays in animal models demonstrated that silencing PEA3 subfamily genes, particularly *ETV4*, effectively suppressed invasion and metastasis in CCA cells, leading to reduced tumor proliferation and growth[3]. This suggests a promising therapeutic target for future treatment.

Several strategies for targeting *ETV4* in CCA treatment approach are promising. One potential approach includes gene silencing techniques such as RNA interference or *CRISPR-Cas9* gene editing, which could directly inhibit the expression of *ETV4*, thereby reducing its pro-tumorigenic effects on invasion and metastasis. Additionally, small molecule inhibitors that disrupt the *ETV4* transcriptional activity or block its interactions with key regulatory proteins in cancer pathways may offer another therapeutic avenue. Such inhibitors could reduce *ETV4*-driven signaling cascades involved in tumor proliferation, migration, and EMT, processes that are critical for metastasis[6].

The Cox regression analysis conducted in this study further validated the prognostic relevance of *ETV4*, showing that high *ETV4* expression is associated with a significantly higher risk of early mortality in CCA patients. Specifically, the analysis revealed that patients with elevated *ETV4* expression had a hazard ratio of 3.00 (1.05-8.58, $P = 0.004$), indicating more than double the risk of poor survival compared to those with lower *ETV4* expression. While these findings are promising, they remain preliminary and require validation in larger clinical trials before broad clinical application.

CHALLENGES IN CLINICAL APPLICATION AND FUTURE DIRECTIONS

The integration of *PEA3* genes, particularly *ETV4*, into clinical practice faces several challenges. CCA is a highly heterogeneous disease, both anatomically and genetically, which could impact the reliability of *ETV4* as a prognostic biomarker. CCA tumors are classified into intrahepatic (iCCA) and extrahepatic subtypes (eCCA), with eCCA further subdivided into perihilar and distal. Each subtype presents distinct molecular and histological characteristics. For instance, tumors may harbor varying mutations, such as K-ras, TP53, and others, with mutations differing based on underlying etiologies like parasitic infections or chronic inflammation. The heterogeneity of CCA means that *ETV4* expression may not be uniform across all subtypes, potentially affecting its reliability as a universal biomarker.

To address this challenge, several strategies should be considered. Subgroup analysis based on CCA subtype and genetic mutations (*e.g.*, TP53, K-ras) could provide a more precise understanding of how *ETV4* expression correlates with outcomes across different tumor types. Combining *ETV4* with other biomarkers, such as those related to genetic mutations or tumor morphology, could create a more robust prognostic tool. Validating *ETV4* expression across diverse populations and genetic backgrounds is also critical, particularly given the variation in CCA incidence and etiology across regions, such as Southeast Asia *vs* Western countries. Additionally, longitudinal tracking of *ETV4* expression through non-invasive methods like ctDNA could offer a dynamic approach to monitoring disease progression and treatment response, enhancing its clinical applicability despite tumor heterogeneity. Demographic and genetic diversity may significantly influence the applicability of *ETV4* profiling across different populations. In East Asia, where CCA is often linked to liver fluke infection and hepatitis[7,8], *ETV4* expression patterns could vary compared to Western populations, where CCA arises from different risk factors like primary sclerosing cholangitis[9]. In high-incidence regions such as Southeast Asia, the use of *ETV4* as a biomarker could be particularly impactful by enabling earlier diagnosis and risk stratification in populations facing endemic CCA. These areas have the highest global rates of CCA due to environmental and infectious risk factors, and the aggressive nature of the disease makes early detection vital. Implementing *ETV4* testing in these regions could significantly improve clinical outcomes by identifying high-risk patients sooner and enabling more personalized treatment plans.

Future studies should validate *ETV4* as a biomarker across diverse populations and CCA subtypes, ensuring its global relevance. Additionally, developing *ETV4*-targeted therapies and conducting clinical trials tailored to genetic diversity will be crucial for personalized CCA treatment. Ethical considerations such as cost, accessibility, and patient consent for genetic testing must also be addressed as the field advances toward clinical implementation. This is particularly urgent in CCA-endemic regions, where early diagnosis could have the greatest impact on patient survival. Moreover, leveraging advanced technologies like CRISPR for gene editing, coupled with machine-learning algorithms for predictive modeling, could enhance the precision of genetic screening and targeted treatment in CCA.

CONCLUSION

The expression of *PEA3* subfamily genes, particularly *ETV4*, represents a significant advancement in the understanding and treatment of CCA. This study highlights the potential of *ETV4* as a key prognostic marker and emphasizes the therapeutic value of targeting *PEA3* genes in clinical practice. However, further comprehensive clinical studies are needed due to limited experimental validation. As the molecular mechanisms of this aggressive cancer are further unraveled, integrating such biomarkers into routine care could lead to improved prognosis, personalized treatments, and better survival outcomes for CCA patients.

In this regard, the next steps for researchers looking to build upon Wang *et al*'s findings would involve several key areas of focus[3]. First, conducting large-scale, multi-center clinical trials to validate the prognostic utility of *ETV4* and other *PEA3* subfamily genes across diverse CCA populations is essential. Additionally, studies should aim to explore the therapeutic potential of targeted therapies against these genes, particularly investigating their role in modulating tumor progression and resistance mechanisms. In parallel, researchers should delve deeper into combinatorial treatment strategies, where *PEA3*-targeted therapies are integrated with current standards of care such as chemotherapy or immunotherapy, to determine synergistic effects. Furthermore, leveraging advanced molecular tools like CRISPR-based gene editing and RNA interference could offer new insights into how *PEA3* genes contribute to CCA pathogenesis and reveal novel drug targets.

By building on these findings, this research lays a strong foundation for future therapeutic developments, ushering in a new era of precision oncology for CCA, where biomarker-driven approaches could greatly enhance personalized treatment plans and improve survival outcomes.

FOOTNOTES

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