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Review and Meta-analysis

Prognostic Significance of Tumor-Stroma Ratio in Hepatocellular and Gall Bladder Carcinoma: Protocol for a Systematic Review and Meta-analysis

Sana Ahuja	Department of Pathology, Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi, India.
Sufian Zaheer	Department of Pathology, Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi, India.
Marzieh Fattahi-Darghlou	Department of Epidemiology, School of Public Health, Hamadan University of Medical Sciences, Fahmideh Ave, Hamadan, Iran.
Alireza Mosavi Jarrahi	Department of Social Medicine, Medical School, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
Seyed Saeed Hashemi Nazari	Department of Epidemiology, School of Public Health and Safety Prevention of Cardiovascular Disease Research Center, Imam Hossein Hospital Shahid Beheshti University of Medical Sciences, Iran.
Amina Mohammed Al Marzouqi	Vice Chancellor University of Sharjah, College of Health Sciences, University of Sharjah, Sharjah, UAE.
Syed Aziz Rahman	College of Health Sciences, University of Sharjah, Sharjah, UAE.
Nabeel Al-Yateem	College of Health Sciences, University of Sharjah, Sharjah, UAE.
Zalikha Khamis Darwish Al-Marzouqi	Oman College of Health Sciences, North Batinah Branch, Oman.
Maria Pramila D' Costa	Department of Nursing, Oman College of Health Sciences North Batinah Branch Suhar, Sultanate of Oman.

Background: The tumor-stroma ratio (TSR) has emerged as a crucial prognostic marker in various cancers, including breast, colorectal, and lung cancers. However, evidence for its prognostic value in hepatocellular carcinoma (HCC) and gallbladder carcinoma (GBC) remains limited and inconsistent. This systematic review and meta-analysis will assess the prognostic significance of TSR in patients with HCC and GBC, determining its potential to guide clinical decision-making and improve patient outcomes.

Methods: The PubMed, Scopus, and Web of Science databases will be comprehensively searched, with no language or publication date restrictions. Studies eligible for inclusion are cohort studies, and case-control studies, that evaluate the prognostic value of TSR in patients diagnosed with HCC or GBC. The TSR is defined as the proportion of stromal tissue relative to tumor cells, with a cut-off value of 50% used to categorize patients as TSR-high or TSR-low. Data extraction and quality assessment will be independently performed by three researchers, with extracted data including study details, patient demographics, and outcomes (overall survival). The quality of each study will be assessed using the Newcastle Ottawa Scale.

Results: The results will be pooled in a meta-analysis, calculating hazard ratios (HR) for survival outcomes. Statistical heterogeneity will be assessed using the I^2, Q test, tau^2, and prediction intervals. Subgroup analyses and meta-regression will explore potential sources of heterogeneity, and sensitivity analyses will be conducted to test the robustness of the

findings. Publication bias will be evaluated using Begg's funnel plot and Egger's test.

Conclusion: This study will evaluate the prognostic significance of TSR in hepatocellular carcinoma and gallbladder carcinoma.

Introduction

The tumor microenvironment (TME), comprising various non-cancerous cells and the extracellular matrix surrounding the tumor, plays a crucial role in tumor progression, invasion, and metastasis [1]. Within this microenvironment, the tumor-stroma ratio (TSR) has emerged as a significant prognostic factor for several solid tumors. TSR is defined as the proportion of tumor cells relative to the surrounding stromal tissue [2]. A low TSR, indicating a high proportion of stroma, has been associated with poor clinical outcomes in cancers such as colorectal carcinoma, gastric carcinoma, breast cancer, oral tongue squamous cell carcinoma, and epithelial ovarian cancer. Numerous studies have demonstrated that a higher stromal content (low TSR) is associated with poorer patient outcomes, while a lower stromal content (high TSR) indicates better prognosis [3-11]. The stroma comprises fibroblasts, endothelial cells, immune cells, and the extracellular matrix, which interact with tumor cells through paracrine signaling, influencing tumor growth and metastatic potential [1].

Hepatocellular Carcinoma (HCC), a primary liver cancer, ranks among the top causes of cancer-related mortality worldwide. Various prognostic factors, including tumor size, vascular invasion, and tumor stage, are routinely assessed to guide treatment decisions. Among emerging prognostic indicators, the tumor-stroma ratio (TSR) has garnered attention as a potential independent predictor of survival in HCC [12, 13]. Studies investigating the association between TSR and prognosis in HCC have yielded varied results, highlighting the need for further research to elucidate its clinical significance fully.

Gallbladder Carcinoma (GBC) represents a relatively rare but highly aggressive malignancy of the biliary tract. Often diagnosed at an advanced stage due to nonspecific symptoms and lack of effective screening tools, GBC carries a dismal prognosis with limited treatment options. The tumor-stroma ratio (TSR), reflecting the proportion of tumor cells to fibrotic stroma, has emerged as a potential prognostic marker in GBC, with higher stromal content suggestive of a poorer prognosis [14, 15]. However, further validation studies are warranted to establish the clinical utility of TSR in GBC and to elucidate its underlying mechanisms.

This meta-analysis aims to systematically evaluate the prognostic significance of TSR in hepatocellular carcinoma and gallbladder carcinoma. By aggregating and synthesizing data from existing studies, we seek to elucidate the relationship between TSR and clinical outcomes in these malignancies. Through this comprehensive analysis, we hope to provide a clearer understanding of TSR's impact on HCC and GBC prognosis, thereby contributing to more informed clinical decision-making and potentially guiding future research into therapeutic strategies targeting the tumor stroma.

Research Question

What is the prognostic significance of tumor stroma ratio (TSR) in hepatocellular and gall bladder carcinoma?

Methods and Analysis

The protocol complies with the Preferred Reporting Items for Systematic Reviews and Meta-

Analyses Protocol 2015 statement for reporting [16]. It has been registered in PROSPERO [registration number: CRD42024547011].

Search strategy

PubMed, Scopus, Web of Science The databases were searched without applying filters for language or publication date. The search strategy was as follows: “Hepatocellular carcinoma” OR “Liver cancer” OR “Gall bladder carcinoma” AND “Tumor stroma ratio”. In addition, a grey literature search will be carried out in Google Scholar (Supplementary Table 1)

Anticipated or actual start date

20th June 2024

Anticipated completion date

15th December 2024

Eligibility criteria

Cohort studies (both prospective and retrospective) and case-control studies that evaluated the prognostic value of TSR in patients diagnosed with hepatocellular or gall bladder carcinoma

Type of participants: Patients with hepatocellular or gall bladder carcinoma will be included in the study

Exposure: The exposure factor was patients with a high tumor stroma ratio, defined as TSR ≥ 50% based threshold in the original study.

Comparison: Comparison between patients categorized as TSR- high and TSR- low (based on a cut-off of 50%) Outcome: Determination of prognostic significance of tumor stroma ratio in hepatocellular and gall bladder carcinoma (overall survival)

Selecting studies

SA, SZ and MF extracted and assessed the data independently. At least 2 researchers evaluated each citation. The extracted data included the first author, country, year of publication, number of patients, age, gender and outcome. The primary outcome included overall survival. Any discrepancy was discussed, till a consensus was reached. The PRISMA flow diagram will be applied to summarise and synthesise the selection procedure and process of the articles.

Risk of bias assessment

The quality of each study was independently rated by two researchers (SA, SZ) using the Newcastle Ottawa Scale [17].

Strategy for data synthesis

We will perform a meta-analysis for HR. We will use STATA software version 17 (StataCorp, College Station, TX, USA). The model to be adopted will be random and we will evaluate the statistical heterogeneity through the I^2, Q test, tau^2 and prediction interval. Subgroup analysis and meta-regression will be used to explore heterogeneity. We will also perform sensitivity analysis considering the methodological quality of the studies.

All the survival results were estimated as the hazard ratio (HR) for each study. If possible, the HR and 95% confidence intervals (95% CI) were obtained directly from each study publication. When the data was not directly reported, a mathematical estimation was done by calculating the necessary data according to the methods published by Parmer et al. Cochran's Q test and Higgins I^2 statistic were undertaken to evaluate the heterogeneity of pooled results. A $p<0.10$ for Qtest suggested significant heterogeneity among studies and the random-effects model (DerSimonian-Laird method) was performed to calculate the pooled HRs. Otherwise, the fixed-effects model (Mantel- Haenszel method) was applied. To explore the potential source of heterogeneity among studies, meta-regression was conducted utilizing variables as year of publication, gender, cancer type, analysis method and cutoff value. To validate the credibility of outcomes in this metaanalysis, sensitivity analysis was performed by sequential omission of each individual study using the ''metaninf'' STATA command. Begg's funnel plot and the Egger's linear regression test was conducted to examine publication bias of literatures and a $p<0.05$ was considered significant. All statistical analyses were performed with STATA software version 15.0. And all P values were two-sided.

Analysis of subgroups or subsets

Subgroup analysis was conducted to investigate potential sources of heterogeneity among studies and to assess the consistency of conclusions among different subpopulations of patients [18]. We performed subgroup analyses stratified by analysis method and patient characteristics.

Patient and public involvement

Patients and/or the public were not involved in this research's design, conduct, reporting or dissemination plans.

Discussion

The investigation into the prognostic significance of the tumor-stroma ratio (TSR) in hepatocellular carcinoma (HCC) and gallbladder carcinoma (GBC) addresses a critical gap in current oncological research. This protocol promises to provide valuable insights into the prognostic utility of TSR, which has shown potential in several solid tumors such as colorectal, breast, and lung cancers but remains underexplored in HCC and GBC [3, 6, 7, 19]. Given the aggressive nature of these cancers and their poor prognosis, identifying reliable prognostic markers is paramount for improving clinical outcomes. The proposed systematic review and meta-analysis aim to consolidate existing data, thus providing a clearer understanding of TSR's prognostic value in these malignancies. To our knowledge this is the first systematic review and meta-analysis protocol evaluating the role of TSR in HCC and GBC.

Ethics And Dissemination

Ethical approval is not required for this study as it is a review based on published studies. The results of this study will be presented at a scientific conference and submitted to a peer-reviewed journal for publication.

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Contributors

SA, MF and SZ jointly contributed to the study aims, research design and methodology. SA and SZ produced the first draft of the article outline with the guidance of MF. SA and MF designed the search strategy. SA will be the guarantor for the manuscript. All authors contributed substantially to the manuscript and critically revised the content. All authors read and approved the final version of the manuscript.

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Competing interests

None declared.

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