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ORIGINAL RESEARCH ARTICLE
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Secretory versus non-secretory hepatocellular carcinoma: associations of serum AFP, CEA and CA19-9 levels with clinical presentation, metastatic patterns, and survival

Muhammad Emmamally[1], Urda Kotze[1], Rufaida Khan[1], Marc Bernon[1], Sanju Sobnach[1], Jake EJ Krige[1], C. Wendy Spearman[2], Mark Sonderup[2], Eduard Jonas[1]

[1]Surgical Gastroenterology Unit, Division of General Surgery, University of Cape Town Health Sciences Faculty and Groote Schuur Hospital, Cape Town - South Africa
[2]Division of Hepatology, Department of Medicine, Faculty of Health Sciences, University of Cape Town Faculty and Groote Schuur Hospital, Cape Town - South Africa

ABSTRACT

Introduction: Hepatocellular carcinoma (HCC) is a global health challenge, with disproportionately high mortality rates in low- and middle-income countries (LMICs). Tumor markers such as alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA), and carbohydrate antigen 19-9 (CA19-9) are used for diagnostic purposes and for monitoring treatment results. The relationship between these markers, individually or in combination, with clinical presentation, metastatic patterns and survival outcomes has not been extensively researched.

Methods: In this South African retrospective study, we assess the association of the tumor marker levels on presentation, diagnosis, and prognosis. Data was analyzed using chi-square tests, t-tests, and Kaplan-Meier survival analysis.

Results: The study included 501 patients, treated between 2010 and 2024. Elevated AFP levels were associated with chronic hepatitis B virus (HBV) infection, hepatomegaly, and pulmonary metastases, while elevated CA19-9 levels were associated with more advanced liver disease. Survival analysis confirmed shorter survival for patients with elevated AFP and CA19-9 levels compared to normal levels ($p < 0.001$). Elevated CEA levels were not significantly associated with survival. Patients with no elevated markers (i.e., "triple-negative" for AFP, CEA, and CA19-9) had the longest survival, compared to those with multiple elevated markers ($p < 0.001$).

Conclusion: AFP and CA19-9 elevations were associated with more advanced disease and poorer survival outcomes. We emphasize the importance of integrating tumor marker levels with imaging and histopathology for a multimodal diagnostic approach. Further research is needed to validate these associations to better define the role of biomarkers in HCC management.

Keywords: HCC, South Africa, Tumor marker, Management, Outcome

Introduction

Hepatocellular carcinoma (HCC) is a major global health issue, ranking as the third leading cause of cancer-related deaths in 2020 with 830,000 deaths, mainly impacting low- and middle-income countries (LMICs) in Asia and sub-Saharan Africa (SSA) (1-3). In these regions, HCC disproportionately affects younger populations, with chronic hepatitis B virus (HBV) infection being an important etiological factor (4-8). However, in high-income countries (HICs), HCC tends to occur in older patients, with most etiological factors largely driven by lifestyle-related factors. All HCC management guidelines emphasize imaging, with ultrasound as the primary screening tool and cross-sectional imaging essential for diagnostic confirmation (9-14). However, in LICs in SSA, there remains an understandable reliance on tumor markers as both screening and diagnostic tools due to limited access to imaging. This highlights the need for more in-depth analysis of these markers to better understand their diagnostic and prognostic value.

The most commonly used tumor markers in HCC are alpha-fetoprotein (AFP), carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) (15-19). AFP, an oncofetal glycoprotein produced during early fetal and neonatal development, is typically only detectable in trace amounts in healthy adults due to a rapid decrease after infancy (20-23). AFP has demonstrated both pro-oncogenic and antiapoptotic effects (24,25). First introduced in the 1960s for diagnostic purposes,

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Corresponding author:
Eduard Jonas
email: eduard.jonas@uct.ac.za

AFP has since been incorporated into prognostic models and liver transplant scoring systems. However, AFP levels can rise due to both malignant and non-malignant conditions affecting hepatic and non-hepatic tissues, and recent Asian studies have explored the phenomenon of AFP-negative HCC (26,27).

CEA is a glycoprotein also produced during the fetal period, with production ceasing before birth (28). Although classically associated with colorectal cancer, CEA is also linked to other malignancies, including pancreatic, gastric, breast, and lung adenocarcinomas (29). While the literature on CEA in HCC is limited, existing studies suggest CEA has no predictive or prognostic value when used in isolation (30,31). Similarly, CA19-9, which is naturally synthesized in small amounts by the gastrointestinal (GI) tract, is significantly elevated in GI malignancies, especially pancreatic cancers, and cholangiocarcinoma (32-35). Like CEA, CA19-9 lacks evidence supporting a role in the diagnosis and prognosis of HCC, and the literature suggests that CA19-9 cannot be used as a standalone marker of HCC (36).

In order to provide a deeper understanding of the utility of these markers, particularly in an SSA setting, where such analyses have not been extensively performed, we conducted a retrospective cohort study to evaluate the use of AFP, CEA, and CA19-9 in the diagnosis, clinical presentation, metastatic progression, and prognosis of HCC. We analyzed each tumor marker individually and in combination to determine whether elevated levels can predict survival, while also exploring correlations between tumor marker levels and survival outcomes.

Methods and Materials

This retrospective observational cohort study included patients with HCC who were managed at Groote Schuur Hospital (GSH), Cape Town, South Africa, between 1 January, 2010 and 31 December, 2024, in whom pre-treatment serum AFP, CEA or CA19-9 levels were available. Ethical approval was obtained from the Human Research Ethics Committee (HREC) of the University of Cape Town (UCT) (HREC number: 424/2023). Data were extracted from an ethics-approved institutional HCC registry hosted on the UCT REDCap platform (HREC Number: R003/2019) (37,38). Patients were stratified according to pre-treatment tumor marker levels, with elevated levels defined as AFP ≥ 20 ng/mL, CEA ≥ 5 ng/mL, and CA19-9 ≥ 37 U/mL.

Diagnosis of HCC was established based on either characteristic imaging criteria (arterial phase hyperenhancement with delayed washout on computed tomography/magnetic resonance imaging) as per international guidelines or histopathological confirmation in cases of atypical imaging. Patients with features suggestive of intrahepatic cholangiocarcinoma or combined hepatocellular-cholangiocarcinoma (HCC-CCA) were excluded from this analysis following multidisciplinary consensus.

Patient demographics, including age and sex, were recorded, along with comorbidities such as diabetes mellitus (DM), hypertension, and ischemic heart disease (IHD) (Supplementary Table 1). Clinical presentation data were collected, detailing the presence, nature, and duration of symptoms before diagnosis. Liver function was assessed using the Child-Pugh score (CPS) and Model for End-Stage Liver Disease-Sodium (MELD-Na) score, while tumor stage was classified according to the Barcelona Clinic Liver Cancer (BCLC) system (Supplementary Table 2) (39). The metastatic profile of each patient was reviewed, focusing on the site of metastases and the time of detection or presentation (synchronous or metachronous to the time of primary tumor diagnosis). Blood parameters, including hemoglobin, platelet count, and international normalized ratio (INR), were analyzed (Supplementary Table 3). Liver function was assessed through albumin, bilirubin, alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), and transaminase levels. Hepatic indices, including the AST-to-ALT ratio, GGT-to-ALT ratio, Albumin-Bilirubin Index (ALBI), and AST-to-Platelet Ratio Index (APRI), were calculated.

Patient demographics, clinical parameters, assessed scoring systems, metastatic patterns and blood test results were compared between patients with normal and elevated AFP, CEA, and CA19-9 levels. Survival outcomes were evaluated by comparing overall survival (OS) between patients with normal and elevated tumor markers, as well as across different combinations of elevated tumor markers.

Statistical analysis

All statistical analyses were performed on SPSS (Version 29) (40). We used various methods to analyze the relationship between tumor markers and variables. Categorical variables were assessed using Pearson's Chi-squared test. For continuous variables such as age, symptom duration, and MELD-Na score, we used paired-samples t-tests to compare the means between two related groups. Where the assumptions for chi-square tests were not met, specifically, where expected frequencies in any category were less than five, we applied Fisher's exact test to ensure the validity of our categorical data analysis. Differences in blood results and hepatic indices were calculated using paired samples t-tests. Any p-values <0.05 were regarded as statistically significant. To determine if there was a correlation between AFP levels and the development of metastases, a one-way ANOVA was performed with all the assumptions being satisfied. Overall survival was estimated using the Kaplan-Meier method. Regression analyses were conducted to explore associations between survival and AFP, CEA, and CA19-9 levels, with log 10 transformations applied to improve linearity.

Results

Demographic and comorbidity association with tumor markers

The study cohort consisted of 501 patients with AFP results, of whom 172 (34.33%) and 201 (40.11%) also had CEA and CA19-9 results, respectively. Patients with elevated AFP levels were considerably younger (49.43 ± 15.05 years) than those with normal levels (54.32 ± 12.80 years; p = 0.001), but no significant age differences were observed for CEA and CA19-9 (Supplementary Table 1). Sex distribution and performance status showed no significant variations across tumor marker groups, except that more patients in the normal CEA group were PS 1 (p = 0.040), and more patients with normal CA19-9 levels were PS 0 (p = 0.033). Significantly more patients in the elevated AFP group had chronic HBV infection (p < 0.001). No

significant associations were observed between comorbidities such as DM, hypertension, and IHD for any of the tumor markers. However, patients with elevated CA19-9 levels were more likely to have a history of alcohol over-consumption compared to those with normal levels (p = 0.043).

Clinical presentation and symptom correlation with tumor markers

A significantly higher proportion of patients in the elevated AFP and CA19-9 groups presented with symptomatic HCC (p < 0.001 and p = 0.005, respectively). In the CA19-9 group, patients with elevated levels also had a longer duration of symptoms before presentation (116.58 ± 167.44 days vs. 78.08 ± 71.43 days; p = 0.039). Pain and weight loss at presentation were present in significantly more patients in the elevated AFP group (p = 0.021 and p = 0.024, respectively). An elevated AFP was also associated with hepatomegaly (p < 0.001), while elevated CA19-9 levels were associated with encephalopathy (p = 0.043).

Tumor characteristics and metastatic patterns in relation to tumor markers

There were no significant differences in the severity of liver dysfunction, as measured by CPS and MELD-Na scores, when comparing patients with normal versus elevated AFP or normal versus elevated CEA levels (Supplementary Table 2). However, in the CA19-9 group, a higher proportion of patients with normal levels were classified as CPS stage A (p < 0.001), while elevated CA19-9 levels were associated with advanced liver failure (CPS stage C; p < 0.001). Similarly, elevated CA19-9 levels were associated with significantly higher MELD-Na scores (p < 0.001). The elevated AFP and elevated CA19-9 groups were more often associated with multifocal disease (p = 0.035 and p = 0.0499, respectively). Metastatic profiles varied with tumor marker elevations, with elevated AFP levels associated with a higher prevalence of lung metastases (p = 0.015) as well as metastases diagnosed at first presentation (p = 0.033). However, no specific AFP level correlated with an increased prevalence of metastatic disease (p = 0.679).

Liver function parameters and their association with tumor markers

Elevated AFP levels correlated with higher AST and GGT levels (p = 0.011 and p = 0.006, respectively), indicating worse underlying liver function (Supplementary Table 3). In the CEA group, an elevated GGT/ALT ratio was observed (p = 0.0495). Elevated CA19-9 levels were associated with higher ALP levels, lower albumin, and elevated INR levels (p = 0.009, p = 0.002, and p = 0.019, respectively), suggesting more severe liver dysfunction.

Survival outcomes in relation to tumor markers

Survival analysis showed that patients with normal levels of AFP and CA19-9 had significantly longer mean survival times (514.29 ± 762.18 and 335.29 ± 588.35 days, respectively; p < 0.001) compared to those with elevated levels (194.55 ± 497.43 and 128.76 ± 170.96 days, respectively; p < 0.001) (Fig. 1). However, there was no significant difference

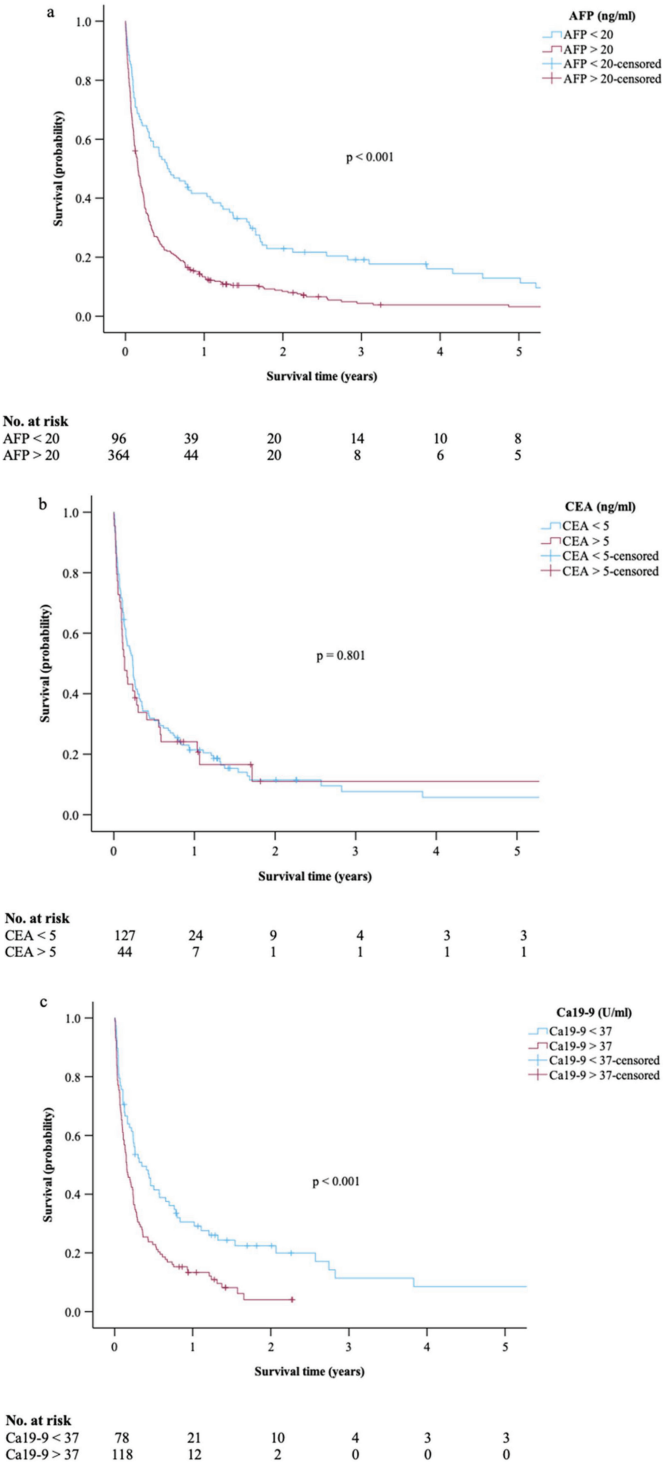


FIGURE 1 - Kaplan–Meier survival curves showing overall survival in HCC patients, comparing normal versus elevated tumor marker levels for (a) AFP (elevated levels defined as ≥20 ng/mL), (b) CEA (elevated levels defined as ≥ 5 ng/mL), (c) CA19-9 (elevated levels defined as ≥ 37 U/mL).

in survival between patients with normal and elevated CEA levels (p = 0.801). The 1-year, 3-year, and 5-year survival rates were 40.63%, 14.58%, and 8.33% for patients with normal

AFP levels; 18.90%, 3.15%, and 2.36% for patients with normal CEA levels; and 26.92%, 5.13%, and 3.85% for patients with normal CA19-9 levels, respectively. Conversely, for those with elevated AFP, CEA, and CA19-9 levels, the 1-year, 3-year, and 5-year survival rates were 12.09%, 2.20%, and 1.37%; 18.90%, 2.27%, and 2.27%; and 10.17%, 0.00%, and 0.00%, respectively.

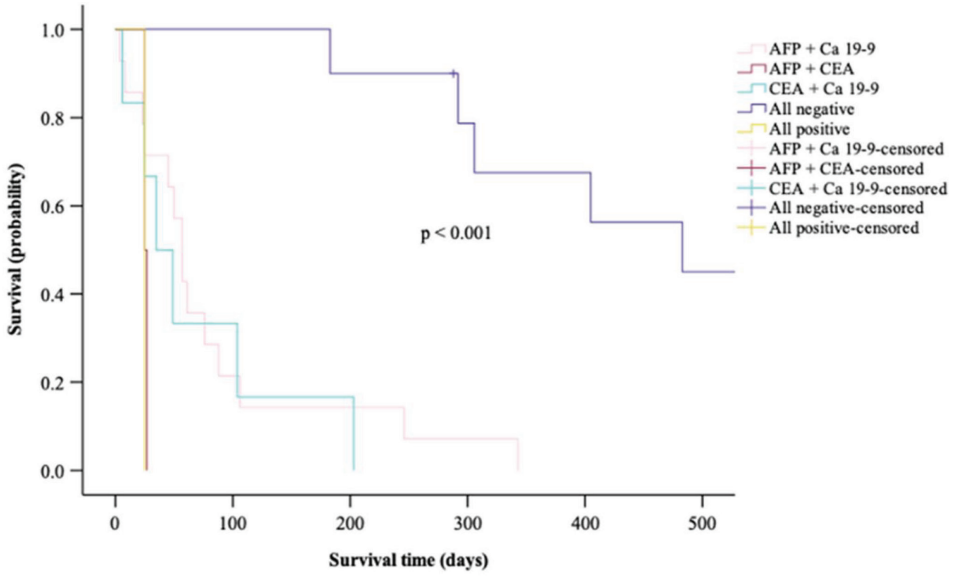
Patients with "triple-negative" tumor markers survived the longest at 564.33 ± 385.30 days, followed by those with elevated AFP and CA19-9 levels at 84.93 ± 95.24 days, elevated CEA and CA19-9 levels at 70.33 ± 72.98 days, and elevated AFP and CEA levels at 26 ± 1.41 days. The single "triple-positive patient" survived 26 days, with these survival differences being statistically significant ($p < 0.001$) (Fig. 2). Although elevated AFP and CA19-9 levels were linked to worse survival, the actual tumor marker levels within the elevated groups did not significantly correlate with survival duration. The R^2 values were 0.113 for AFP, 0.017 for CEA, and 0.03 for CA19-9, and the assumption of linearity was not met (Fig. 3).

Discussion

This study offers key insights into the diagnostic, management, and prognostic roles of AFP, CEA, and CA19-9 in South African patients with HCC. The variability in the diagnostic utility of these markers, particularly AFP, underscores the complex landscape of biomarker reliability for HCC across different geographical regions. While AFP has traditionally been regarded as a cornerstone biomarker for HCC diagnosis, our findings indicate that 19.76% of HCC patients exhibit a non-secretory AFP profile. This is consistent with reports from regions such as East Asia, Europe, and North America, raising questions about the reliability of AFP as a standalone diagnostic tool in certain populations, particularly given the increasing recognition of AFP-negative HCC as a distinct clinical entity. (26,41,42). Although AFP has been highlighted as a useful screening tool, particularly in LMICs where imaging is not readily available, the limitations of relying solely on AFP for universal screening should be recognized.

The prevalence of "triple-negative" HCC (negative for AFP, CEA, and CA19-9) in 10 patients (2%) in our cohort highlights the need for further investigation into the impact of differential tumor marker expression, both individually and in combination. The prognostic significance of these three markers has been extensively investigated in previous studies. In our study, elevated AFP levels were identified as a strong predictor of survival, consistent with findings reported in the literature (42). While the lack of impact of elevated CEA levels on survival in our patient cohort aligns with previous studies, our findings diverge from the literature by demonstrating that elevated CA19-9 levels are a strong predictor of survival (30,31,36). The differential impact of different tumor marker levels on survival was another notable finding in our study. Patients with normal levels of AFP and CA19-9 had significantly longer survival compared to those with elevated levels; however, the actual tumor marker levels within the elevated groups did not seem to impact survival. Although only one patient in our study had "triple-positive" tumor markers, the poor survival of only 26 days was notable.

Notably, elevated AFP levels correlated with increased AST and GGT levels, which are indicative of worsening liver function. It has been suggested that high GGT levels may also



No. at risk						
AFP + Ca 19-9	14	3	2	1	0	0
AFP + CEA	2	0	0	0	0	0
CEA + Ca 19-9	6	2	1	0	0	0
All negative	10	10	9	7	6	4
All positive	1	0	0	0	0	0

FIGURE 2 - Kaplan–Meier survival curves showing overall survival in patients with different combinations of tumor marker levels: double-marker elevations (AFP+CA19-9, AFP+CEA, or CEA+CA19-9), no elevated markers (triple-negative) and all three markers elevated (triple-positive). Survival differences across these groups were statistically significant ($p < 0.001$).

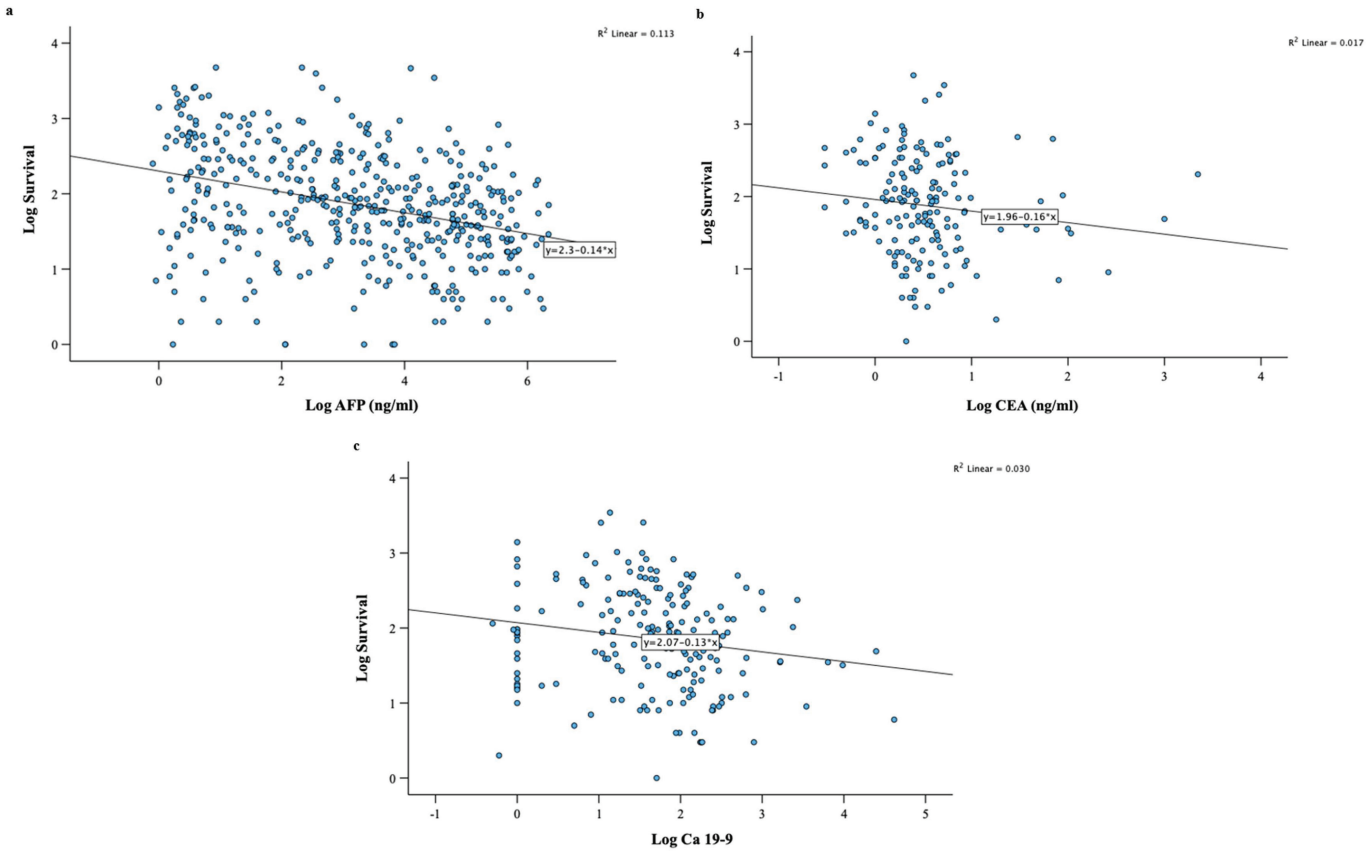


FIGURE 3 - Scatter plots showing the correlation of tumor marker levels and survival time for (a) AFP, (b) CEA, and (c) CA19-9. Log-transformed tumor marker values are plotted against log-transformed survival duration. Each plot includes a fitted linear regression line with its corresponding equation and R^2 value.

impact survival due to an association with aggressive tumor behavior (43). Experimental studies have reported that overexpression of GGT enhances the invasive capacity of cancer cells and contributes to the development of anticancer drug resistance (44,45). Our study also showed a significant association between elevated AFP levels and chronic HBV infection, which is a major risk factor for the development of HCC (46). This association has been confirmed in several previous studies, which makes AFP a particularly reliable marker for disease progression in regions with a high prevalence of chronic HBV in the population, including SSA and South-East Asia (47). Moreover, the correlation between elevated AFP and symptoms like hepatomegaly, pain, and weight loss suggests that AFP could be valuable as an indicator of tumor burden and disease severity. The significant link between AFP levels and metastatic spread, especially pulmonary metastases, observed in our cohort provides a direction for future research to explore AFP's role in predicting metastatic potential and tailoring surveillance strategies accordingly.

The findings of this study highlight the associative value of these tumor markers in relation to disease presentation, progression, and survival. Given the retrospective design, incomplete staging data, and the exploratory nature of the analysis, our results should be interpreted as suggestive. Future prospective studies with comprehensive clinical datasets are needed to validate these associations and to evaluate the independent prognostic value of tumor markers using multivariate models alongside established staging systems.

The retrospective design of the study and the relatively small proportion of the total patient cohort that was tested for CEA and CA19-9 are notable limitations. Future studies should include larger, more diverse populations to validate and potentially expand on our findings. Additionally, prospective designs may facilitate understanding the causal relationships and dynamics of tumor markers over the course of the disease. Expanding the biomarker panel to include novel markers such as glypican-3 and osteopontin may provide a deeper insight into the molecular pathogenesis of HCC and enhance the predictive accuracy of these novel markers on disease outcomes in various populations (48-50).

Our study, which focuses on the South African population, provides valuable data on the potential role of tumor markers in the management of HCC in SSA—a region where data remain scarce. In this low-resource setting, relatively inexpensive analyses, such as tumor markers assessed individually or in combination, may play an important role in prioritizing patients for limited resources, including curative-intended interventions (resection, ablation, and transplant) and life-prolonging therapies (trans-arterial treatments). As such, the association of these markers with clinical features

and survival analysis adds significant depth, influencing therapeutic approaches. For future research, we suggest larger prospective multicenter studies to validate our findings, as well as the incorporation of a broader range of biomarkers, including genetic and molecular markers, to improve diagnostic accuracy and facilitate personalized treatment approaches in HCC management.

Conclusion

This study contributes to the existing literature on HCC by providing a detailed analysis of tumor markers AFP, CEA, and CA19-9 in a South African population. The findings underscore the complexity of using these markers for diagnosis and prognosis, highlighting the need for multimodal diagnostic approaches. Future studies should include broader geographical populations, integrate novel biomarkers, and employ prospective designs to validate and expand our findings.

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Authors' Contributions

ME: Conceptualization, methodology, data analysis and writing of the original draft.; UK: Data curation, review and editing; RK: Data collection and statistical analysis; MB: Supervision and critical revision of manuscript; SS: Conceptualization, supervision, and review; JEJK: Senior supervision and manuscript review; WS: Interpretation of hepatology data, supervision and editing; MS: Interpretation of hepatology data, supervision and editing; EJ: Senior supervision, conceptualization, resources, editing and final approval.

Disclosures

Conflict of Interest: The authors declare that they have no financial or non-financial conflicts of interest relevant to this study.

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Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author (Prof. Eduard Jonas). The data is not publicly available due to ethical restrictions and patient confidentiality in line with Human Research Ethics Committee requirements at the University of Cape Town.

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