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EVALUATION OF BIPHASIC COMPUTED TOMOGRAPHY AND TUMOR MARKERS IN DETECTING RESIDUAL HEPATOCELLULAR CARCINOMA AFTER MICROWAVE ABLATION

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Abstract

Background: *HCC is a serious type of liver cancer related to chronic liver diseases and cirrhosis. MWA is a useful procedure for treating this condition; however, when partial ablation takes place, residual tumor cells may be present. Contrast-enhanced CT in two phases, especially the arterial phase, plays a crucial role in identifying such residual HCC tumors. Moreover, AFP and PIVKA-II could give some extra information on the state of the tumor. Thus, this study aimed to find out whether the combined use of the above-mentioned methods could be helpful for detecting residual HCC.*

Objective: *To assess the effectiveness of biphasic CT and tumor markers (AFP and PIVKA-II) in detecting residual hepatocellular carcinoma after microwave ablation.*

Methodology: *A cross-sectional design was employed among 72 HCC patients who had previously undergone microwave ablation at the Department of Radiology and Imaging, Aznostics Diagnostic Centre. Patient selection was done using convenience non-probability sampling, while non-HCC lesions and those without complete history were excluded. Correlation between biphasic CT results and serum levels of AFP and PIVKA-II was made using pre-designed data collection sheet and SPSS software. Statistical analysis was performed using Wilcoxon signed rank test, Mann Whitney U test, and Fisher's exact test. Sensitivity, specificity, PPV, NPV, and accuracy of AFP and PIVKA-II variations were calculated against residual tumor on CT.*

Results*: In total, the research involved 72 HCC patients undergoing MWA, whose average age was 66.5 years, and the majority of whom were male patients. Residual tumors were found mostly during the arterial phase (18.1%) and were rarely found during the portal venous phase (1.4%). There was a significant reduction in the levels of AFP and PIVKA-II after MWA; however, there was no significant relationship between the reductions and residual tumors. According to the results of the study, the arterial phase of biphasic CT was more important for the diagnosis of residual HCC.*

Conclusion: *Among the imaging modalities, arterial-phase CT is the most sensitive modality in diagnosing residual HCC following MWA. On the other*

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hand, portal venous phase did not have additional diagnostic significance over arterial-phase CT. Decrease in the serum levels of AFP and PIVKA-II suggested the presence of treatment response, however, it was not sufficient to diagnose residual HCC. There was no significant correlation between larger tumor size and the residual HCC.

INTRODUCTION

The liver is the biggest organ in the human body and has a key function in metabolism, toxin removal, protein production, bile synthesis, nutrient storage, and immunity. Due to constant exposure to metabolic waste products, toxins, and pathogens, the liver is prone to a wide variety of diseases such as fibrosis, cirrhosis, fatty liver disease, viral hepatitis, and tumors [1]. Hepatocellular carcinoma is the most frequent type of liver cancer and is associated with liver disease and cirrhosis. Major risk factors include chronic hepatitis B and C infections, alcohol abuse, and liver damage [2].

The contrast enhanced CT is widely utilized for diagnosing and evaluating the treatment of HCC because of its high-resolution capacity and assessment of the vascular nature of the liver masses. Biphasic CT comprises mainly of the arterial and portal venous phases [3]. There is usually hyperenhancement on the arterial phase and washout in the portal venous phase in most HCC patients. Post-microwave ablation (MWA), there is a clearly defined, low-attenuation, and non-enhancing area reflecting the coagulative necrosis of the treated lesion [4].

The MWA is a minimally invasive treatment method whereby microwave energy is applied to produce thermal heat, which causes the necrosis of the tumor by ablation. Post-treatment surveillance is critical in order to detect any recurrence of the cancer or any complications from the treatment process [5]. Tumor markers such as the Alpha-fetoprotein (AFP) and PIVKA-II could offer some additional information on the status of the cancer and its response to the treatment. Any decrease in these markers indicates good results while any increase may suggest disease recurrence or residuals [6].

In addition to developments like dual-energy CT and perfusion imaging, advancements in technology have contributed towards better characterization of tumor vascularity, and these might help in the identification of small regions of residual viable tumors [7]. In spite of all these advancements, contrast-enhanced CT still remains a critical part of post-ablation evaluation. Imaging studies are done at proper intervals in order to assess the ablation region for any changes, and for the presence of any complications [8].

An accurate evaluation of the therapeutic effect can be done using the combination of the results from the imaging studies and tumor biomarkers [9]. The arterial phase CT is especially important in detecting viable residual HCC with the aid of abnormal enhancement patterns, while the use of AFP and PIVKA-II can be used to confirm any changes in tumor activity. Follow up is especially crucial in patients with liver diseases such as cirrhosis since the disease is usually silent at an early stage [10].

CT with biphasic scanning and serum tumor markers like AFP and PIVKA-II are useful in identifying the residual hepatocellular carcinoma post-microwave ablation. However, their combined use has not been studied in Pakistan, despite the country's high burden of HCC. This study aims to evaluate the effectiveness of biphasic CT alongside tumor markers for identifying residual disease after ablation in Pakistani patients, providing valuable local evidence to guide post-procedural monitoring and management.

Methodology

The prospective cross-sectional analysis was carried out at the Aznostics Diagnostic Centre, Lahore, in four months among 72 patients of HCC who were under treatment by MWA. Sampling of the population was done conveniently on non-probability sampling basis using Cochran's formula at 95% confidence interval and 10% margin of error.

$$n = \frac{Z^2 \times p \times (1-p)}{d^2}$$

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(p) = 0.25
Z = 95% (Z = 1.96)
d = 10% =0.10

$$n = \frac{(1.96)^2 \times 0.25 \times (1 - 0.25)}{(0.10)^2}$$

n=72 patients.

Adequate pre- and post-ablation biphasic CT scans with AFP and PIVKA-II data were enrolled. Cases of incomplete information, extra-hepatic metastasis, other cancers, and non-informative images were excluded from the study. Data were gathered via a prepared questionnaire and analyzed by SPSS version 26. Descriptive and inferential statistics were used for the comparison of the markers with residual hepatocellular carcinoma. The diagnostic value of the serum AFP level and PIVKA-II was determined based on sensitivity, specificity, PPV, NPV, and accuracy against CT findings.

Results

1. Overview

The below paper has the results of a study that involved the measurement of tumor markers (alpha-fetoprotein [AFP] and protein induced by vitamin K absence or antagonist-II [PIVKA-II]) in a prospective cohort of 72 patients diagnosed with HCC who underwent microwave ablation, which comprised of arterial and portal venous phases in CT. The aim of this research was to analyze the presence of residual tumor in each phase of CT and the correlation between tumor markers and residual tumor.

2. Patient Demographics and Tumor Characteristics

Table 4.1: Patient Demographics and Tumor Characteristics

Variable	Summary	Detail
Age (years)	Mean ± SD: 66.5 ± 7.5	Range 48–81; median 67
Gender	Male: 43 (59.7%)	Female: 29 (40.3%)
Tumor size (mm)	Mean ± SD: 31.6 ± 14.4	Range 9–83 mm; median 30 mm
Liver lobe	Right: 54 (75.0%)	Left: 18 (25.0%)
Underlying liver disease	Cirrhosis: 47 (65.3%)	Hepatitis C: 20 (27.8%); Fatty change: 5 (6.9%)
Number of lesions	1 lesion in all patients	Solitary-lesion cohort (100%)

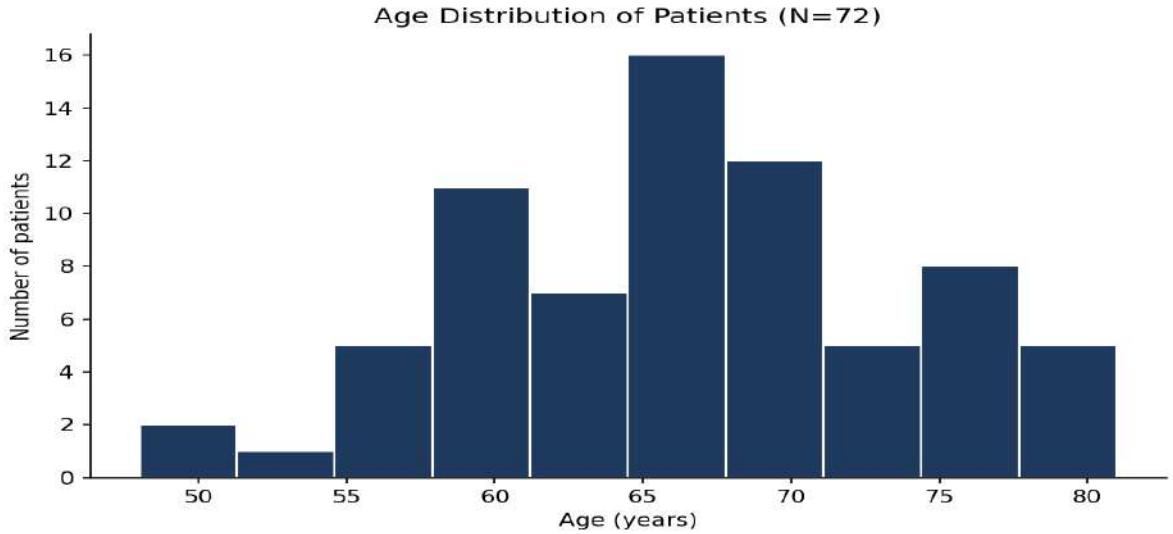


Figure 4.1 Age distribution of patients.

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The age distribution of 72 individuals with an age range of approximately 48 to 81 years is shown in the histogram above. Most of the individuals fall within the 60-70 years range, which indicates that this is the predominant age range in the study. The peak of the age distribution is where there is the highest number of individuals ranging between 65 and 67 years old. Very few individuals are below 55 years or above 78 years old.

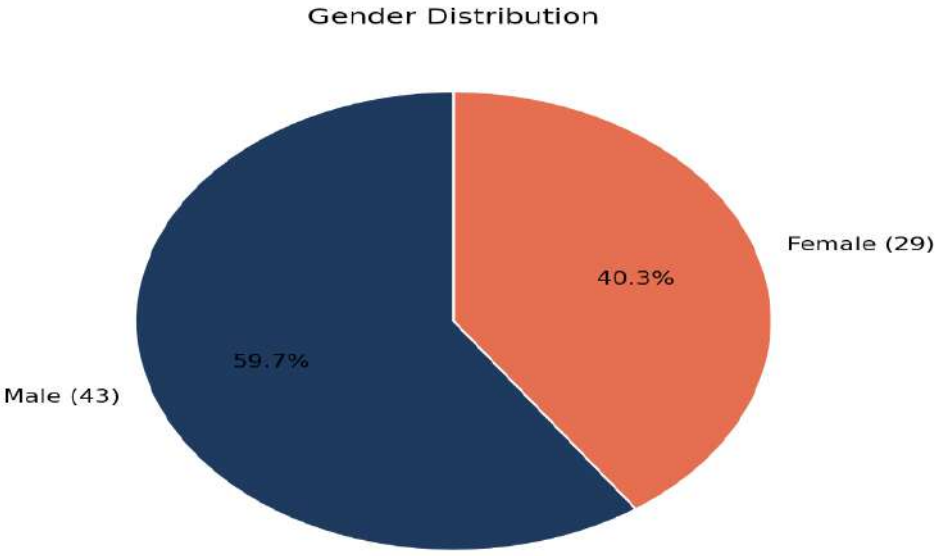


Figure 4.2 Gender distribution.

The gender representation of the 72 participants involved in the experiment is shown through the pie chart above. Majority of the patients involved in the experiment were males, 43 (59.7%) of the total number of participants while 29 (40.3%) were females.

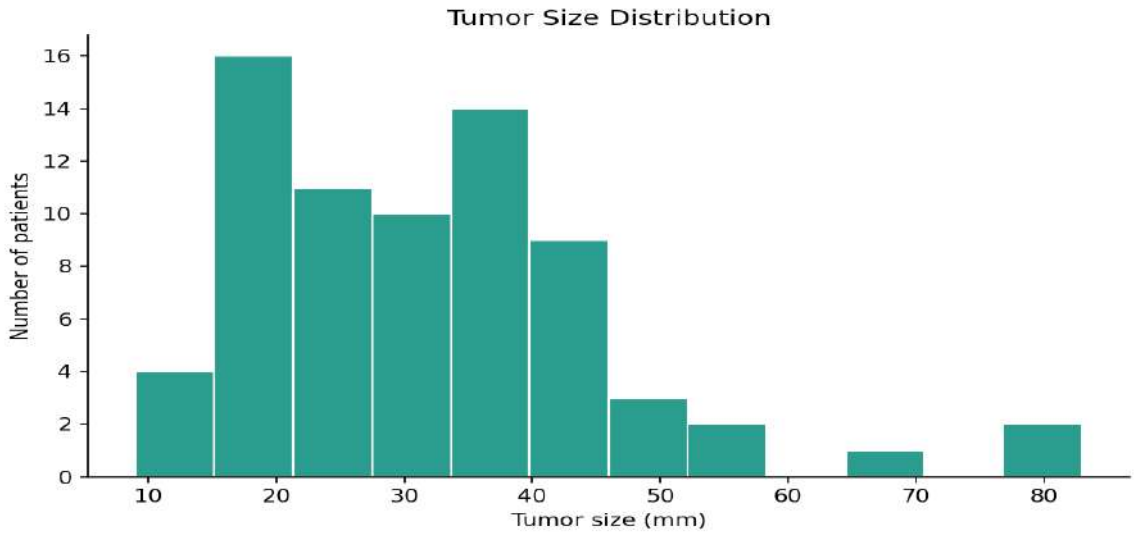


Figure 4.3 Tumor size distribution.

The distribution of the tumor size for the 72 patients is shown on the histogram, and their sizes vary from approximately 10 mm to 82 mm. Most of the tumors tend to have small and moderate size between 15 mm and 40 mm. large tumors are fairly uncommon because only a few patients had tumor size more than 50 mm, making the distribution slightly right-skewed.

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Figure 4.4 Distribution of lesions by liver segment (Couinaud).

The distribution of lesions in different liver parts is depicted in the bar chart. Segment VIII had the highest number of lesions (20), followed by Segments VII (16) and VI (15). Segments II and III displayed somewhat lower frequencies, while Segments IV and V had the fewest lesions, each with three occurrences. Overall, the results show that the right hepatic lobe (Segments VI–VIII) included the majority of liver lesions.

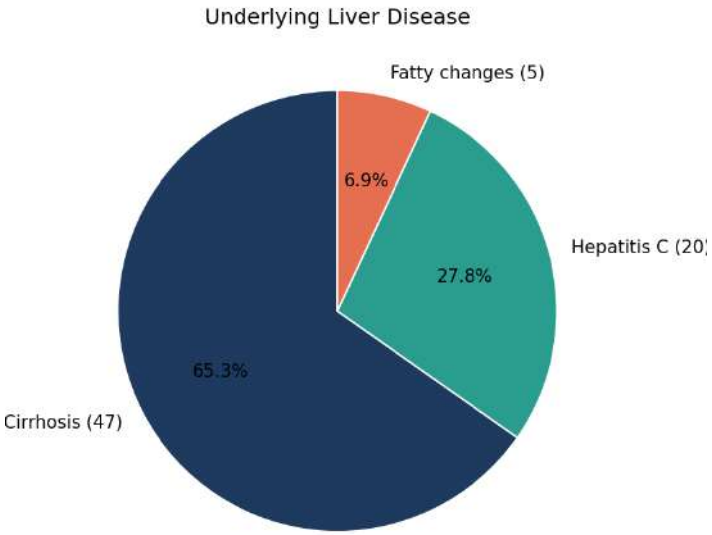


Figure 4.5 Underlying liver disease.

The distribution of underlying liver diseases among the 72 study participants is depicted in the pie chart. The most prevalent underlying condition was cirrhosis, which affected 47 patients (65.3%), followed by hepatitis C in 20 patients (27.8%). Five patients (6.9%) had fatty liver changes, which were the least frequent. These findings indicate that cirrhosis was the predominant underlying liver disease in the study population.

3. Residual Tumor Detection by CT Phase

Residual tumor after ablation was flagged separately on the arterial phase and the portal venous phase of biphasic CT.

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Table 4.2: Residual Tumor Detection by CT Phase

CT Phase	Residual tumor detected	No residual tumor	Detection rate
Arterial phase	13	59	18.1%
Portal venous phase	1	71	1.4%
Combined (either phase positive)	13	59	18.1%

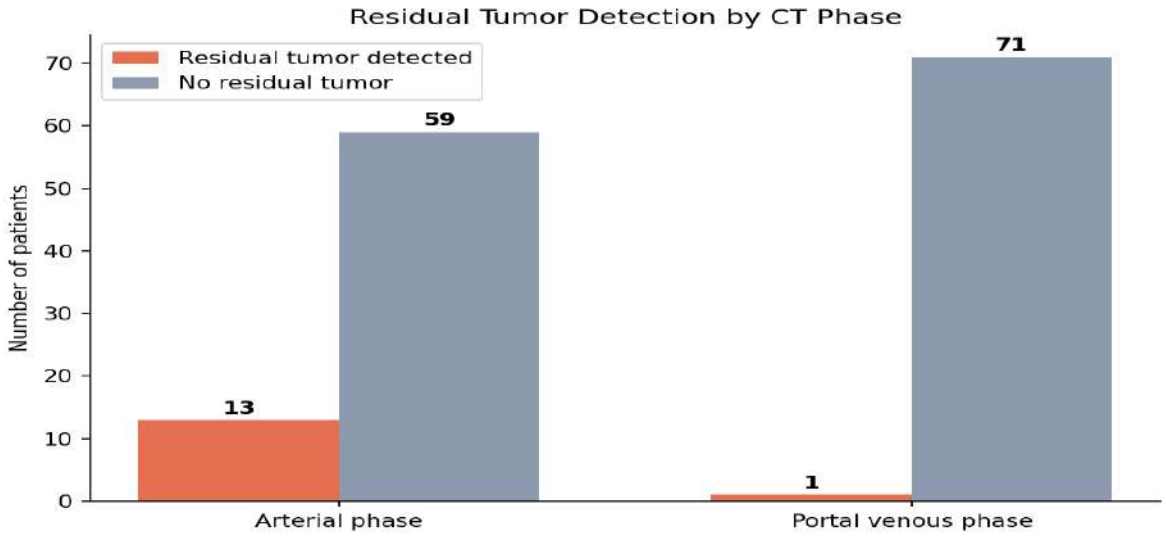


Figure 4.6 Residual tumor detection by CT phase.

Out of 72 patients, there were 13 (18.1%) patients in which residual tumor is identified in the arterial phase, and 1 (1.4%) in the portal venous phase. This indicates that residual tumors were more commonly identified in the arterial phase than in the portal venous phase. The 1 patient who was found to have a positive result in the portal venous phase was also positive in the arterial phase.

4. Tumor Marker Trends: Pre- vs Post-Ablation

AFP and PIVKA-II were measured before and after ablation for all 72 patients. A Wilcoxon signed-rank test (paired, non-parametric, appropriate given the highly skewed marker distributions) was used to test whether levels changed significantly after treatment.

Table 4.3: Tumor Marker Trends: Pre- vs Post-Ablation

Marker	Pre-ablation median (range)	Post-ablation median (range)	Wilcoxon p-value
AFP (ng/mL)	10.6 (1.9–27,295)	6.6 (1.0–12,455)	0.003
PIVKA-II (mAU/mL)	85.3 (3.8–6,263)	44.3 (16.0–3,964)	0.005

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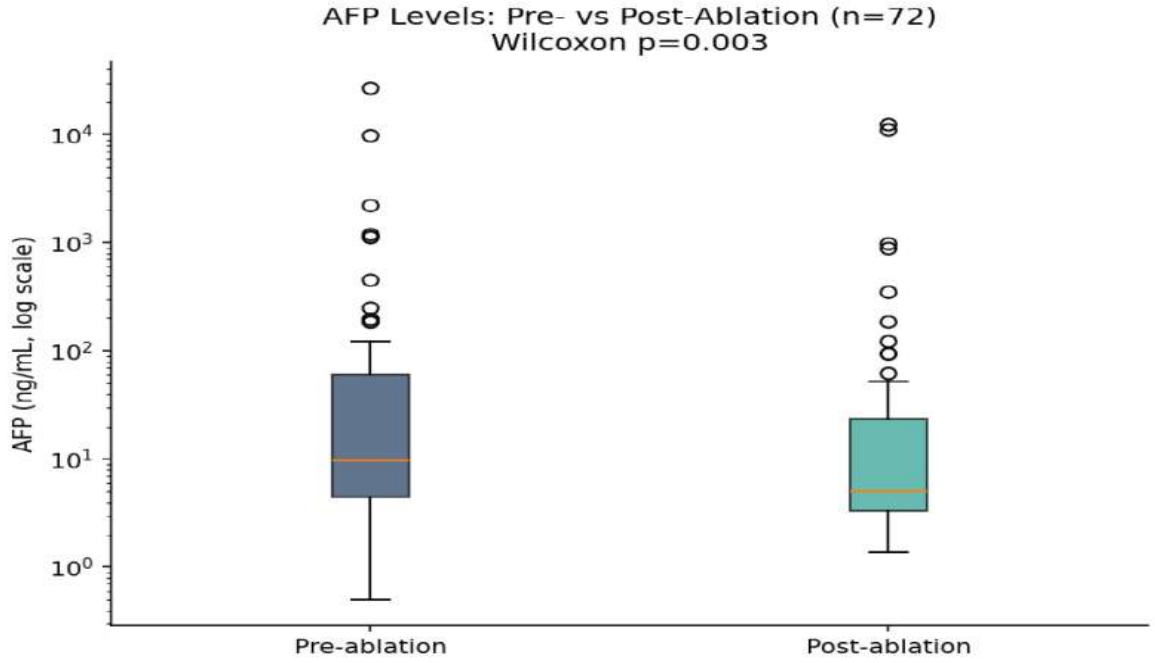


Figure 4.7 AFP levels before and after ablation (log scale).

The box plot uses a logarithmic scale to compare 72 patients' serum AFP (alpha-fetoprotein) levels prior to and following ablation. The AFP level was found to be reduced after the procedure compared to that before the ablation process. The total decline was statistically significant (Wilcoxon test, p = 0.003), despite the fact that some patients still had high AFP readings. These results imply that a notable improvement in AFP levels was linked to ablation.

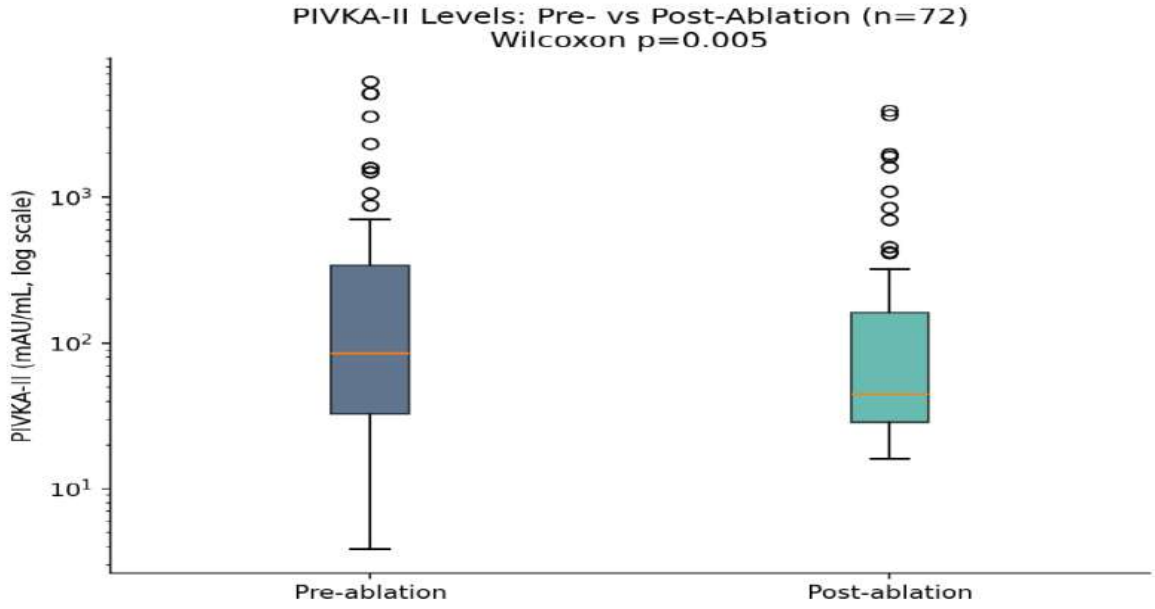


Figure 4.8 PIVKA-II levels before and after ablation (log scale).

In the box plot, logarithmic scaling is used to analyze the PIVKA-II values in 72 patients pre- and post-ablation. The PIVKA-II values were found to be lower after ablation compared to pre-ablation, indicating a positive biochemical response to treatment. The overall decrease was statistically significant (Wilcoxon test, p = 0.005), despite the fact that some patients still

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had abnormal PIVKA-II readings following ablation. According to these results, ablation was linked to a notable drop in PIVKA-II levels, indicating a better response to treatment.

5. Do Marker Changes Track with Residual Disease?

Patients were split into two groups using the combined CT result: residual tumor detected (n=13) vs. no residual tumor (n=59). Marker behavior was compared between groups.

Table 4.4: Marker Changes Track with Residual Disease

Measure	Residual tumor (n=13)	No residual tumor (n=59)	Test statistic / p-value
Median AFP % change	−2.7%	−26.7%	Mann-Whitney U, p=0.32
Median PIVKA-II % change	−32.1%	−19.4%	Mann-Whitney U, p=0.62
AFP did not decline (%)	46.2%	32.2%	Fisher's exact, p=0.35
PIVKA-II did not decline (%)	38.5%	40.7%	Fisher's exact, p=1.00

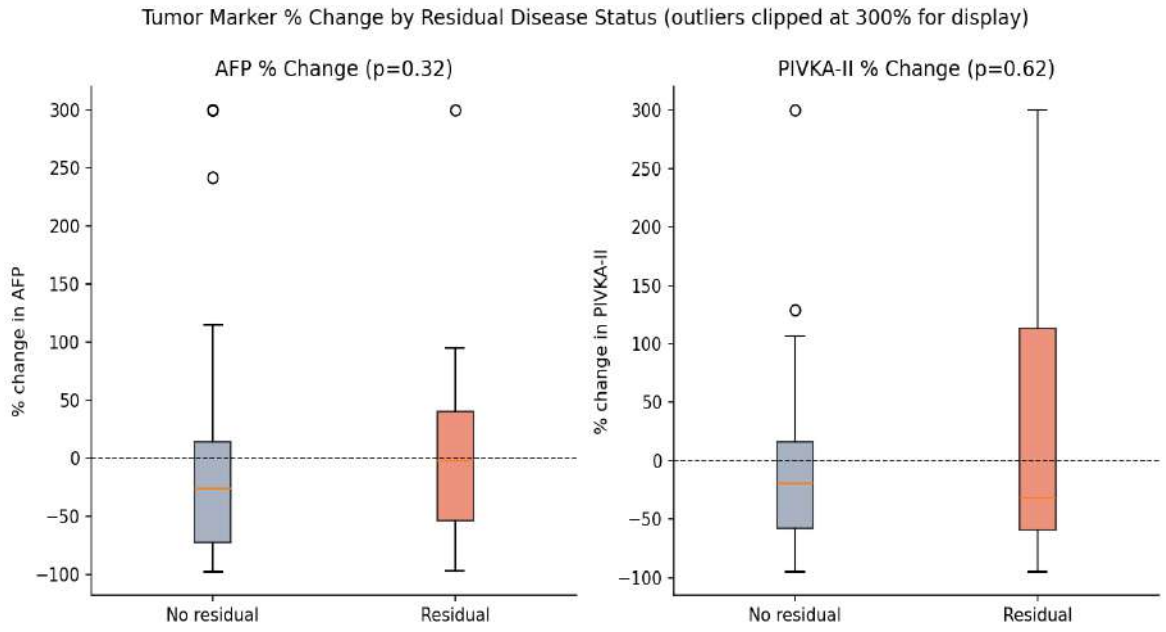


Figure 4.9 Marker % change by residual-disease status

The percentage change in AFP and PIVKA-II levels between patients with and without residual disease following ablation is shown in box plots. Tumor marker levels were typically lower in both groups, while there was a lot of variation and a few outliers. The percentage change of AFP (p = 0.32) and PIVKA-II (p = 0.62) did not differ statistically significantly between individuals with and without residual illness. These results imply that residual disease status in this study was not substantially correlated with changes in tumor marker levels alone.

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6. Tumor Size and Age vs Residual Disease

Table 4.5: Tumor Size by Residual-Disease Status

Variable	Residual tumor (n=13)	No residual tumor (n=59)	Test / p-value
Tumor size, mean ± SD (mm)	37.5 ± 17.1	30.2 ± 13.6	
Tumor size, median (IQR) (mm)	36.0 (28.0–40.0)	28.0 (20.0–38.0)	Mann-Whitney U, p=0.139
Age, mean ± SD (years)	66.2 ± 9.5	66.6 ± 7.1	
Age, median (IQR) (years)	67.0 (55.0–73.0)	67.0 (61.5–71.0)	not tested

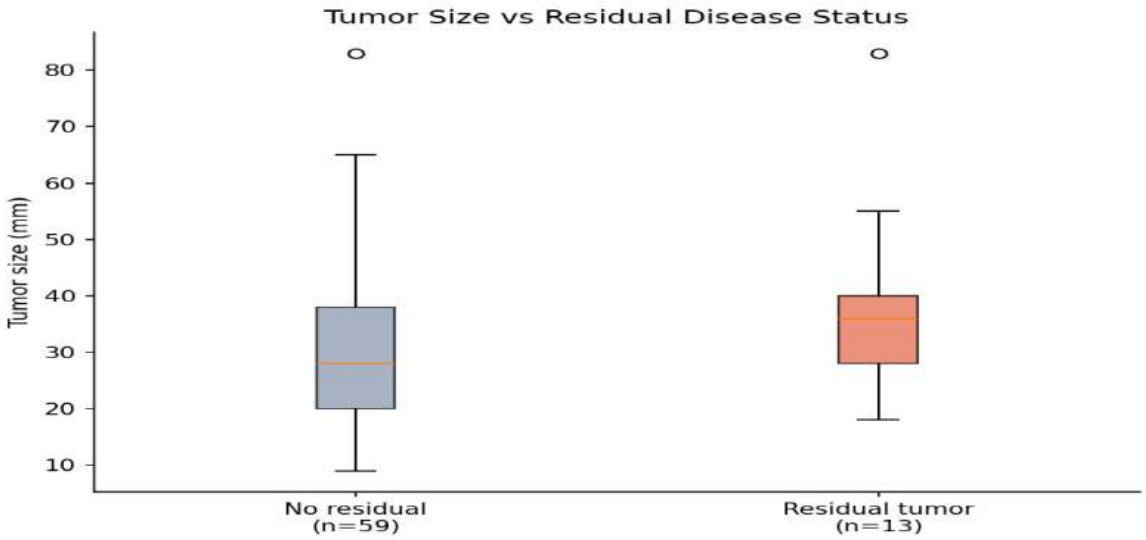


Figure 4.10 Tumor size by residual-disease status.

The sizes of the tumor are analyzed through a box plot among patients who have a remaining tumor and those that do not after ablation. As opposed to patients who do not have a tumor (n=59), the patients who have a tumor (n=13) normally have larger tumor sizes and higher medians. Even though the patients with the tumor have larger tumor sizes, the difference is not significant (p=0.139).

7. AFP and PIVKA-II Decline vs Residual HCC

Table 4.6: AFP and PIVKA-II Decline vs Residual HCC

Measure	AFP did not decline	PIVKA-II did not decline
True positive/false negative	6/7	5/8
False positive/ true negative	19/40	24/35
Sensitivity, % (95% CI)	46.2 (23.2-70.9)	38.5 (17.7-64.5)
Specificity, % (95% CI)	67.8 (55.1-78.3)	59.3 (46.6-70.9)
PPV, % (95% CI)	24.0 (11.5-43.3)	17.2 (7.6-34.5)
NPV, % (95% CI)	85.1 (72.3-92.6)	81.4 (67.4-90.3)
Accuracy, % (95% CI)	63.9 (52.4-74.0)	55.6 (44.1-66.5)

Residual HCC was detected predominantly during the arterial phase. Reference: Residual tumor on CT (13 out of 72 cases; prevalence 18.1%). CI, confidence interval (Wilson method); PPV, positive predictive value; NPV, negative predictive value. Using residual tumor on CT as reference standard, inability to decrease AFP or PIVKA-II levels had low sensitivity and low PPV. NPVs (85.1% and 81.4%) were not far from 81.9% obtained from prevalence alone. This suggested that neither marker could detect residual tumor reliably.

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These values represent concordance with residual tumor on CT, not the actual accuracy, since there was no independent reference standard.

DISCUSSION

This investigation assessed the diagnostic utility of biphasic CT and serum markers (AFP and protein induced by vitamin K absence or antagonist-II [PIVKA-II]) in revealing residual HCC following microwave ablation therapy. From the results obtained, it can be seen that the arterial phase of contrast-enhanced CT is the most effective in diagnosing residual tumors, while the portal venous phase adds only little information to diagnosis in this population. Despite the significant reduction in serum AFP and PIVKA-II levels after MWA therapy, these changes were not associated with the residual disease statistically. In other words, it seems that arterial phase CT remains the main method of patient examination after ablation procedures, while serum markers serve more as a complement to CT [11].

These parameters were consistent with previous data on epidemiology by Balogh et al., 2016, which indicate that high incidence rates of HCC in elderly men can be attributed to chronic liver diseases, hepatitis, and alcohol-induced liver disorders in men. The most common liver disease among the subjects was cirrhosis, observed in more than 60% of the subjects, collaborating its well-established role as the main risk factor for the development of HCC because of the carcinogenic environment associated with it [12].

The tumor locations were consistent to those previously described in literature, where the majority of the tumors were located in the right hepatic lobe, especially in Couinaud's segments VI, VII, and VIII. These locations may be due to the fact that the right lobe is bigger and has a higher portal blood supply. This is an important consideration for clinical practice [13].

Another key finding is that the residual hepatocellular carcinoma is found in the arterial phase. Residual tumors had enhancement during the arterial phase whereas the portal venous phase did not identify any further tumors apart from what was seen during the arterial phase. This is in agreement with the fact that the biological behavior of HCC involves arterial blood flow for most of its blood supply, and hence arterial phase hyperenhancement was an important criterion for diagnosis of viable HCC. The results agreed with the study done by Granata et al., 2021 and Meloni et al., 2001[14]. Although the portal venous phase did not play much role in this study, this phase is essential and cannot be overlooked. Previous literature suggested that this phase assists in detecting portal vein invasion, hypovascular lesions, and complications after procedure. Hence, even if the arterial phase is the most sensitive one to detect the remaining tumor, a biphasic scan must be performed [15].

There was a significant decrease in serum concentrations of AFP and PIVKA-II post-MWA, which was indicative of successful destruction of tumor cells and hence showed biochemical efficacy of the modality. This is in accordance with the study conducted by Zhou et al., 2021, where it has been found that a decrease in tumor markers is often associated with ablation success [16].

However, neither of the markers could successfully differentiate between cases with residual tumors and those without. Even though patients who had residual tumors generally demonstrated a lower decreases in the amount of AFP, this finding was not found to be statistically significant. It should be noted that there was a greater decrease in PIVKA-II for the cases of residual tumors; however, this is surprising and even further undermines the credibility of the biomarker change alone. Possible reasons for this could include liver inflammation, cirrhosis, regeneration, and personal physiology [17].

Statistical insignificance can also be attributed to the relatively low number of residual disease patients in the study, amounting to 13 only. This makes the study less capable of detecting significant differences. Conducting larger multicenter studies would yield better results regarding the predictive value of these biomarkers [18].

The size of the tumor seemed to impact the outcomes, as those patients that still had remaining disease had larger baseline tumors. Although there was no statistically significant relationship, it is in line with previous studies conducted by Shi et al. in 2019 and Zhang et al. in 2015, which stated that increased tumor size

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was associated with higher recurrence rates and made the process of complete ablation more difficult to conduct. The bigger the tumor size, the harder it is to produce adequate ablation margins [19].

The above findings highlight the importance of incorporating various imaging techniques along with laboratory data and clinical assessment, and not relying on one specific parameter alone. Although CT during the arterial phase showed evidence of residual tumor consistently, the response to various biomarkers was highly variable among different patients. This further supports existing guidelines that the best diagnostic accuracy is achieved through a multimodal approach [20].

The results carry significance in Pakistan where HCC is emerging as an increasingly significant health burden owing to chronic viral hepatitis and cirrhosis. The results of the study further confirm the ongoing validity of using biphasic contrast enhanced CT as the standard imaging technique after MWA therapy. Although AFP and PIVKA-II are significant in assessing trends in the disease, they cannot be a replacement of imaging in terms of assessing the success of therapy [21].

In conclusion, imaging during the arterial phase on biphasic CT proves to be very efficient in assessing the presence of residual HCC following microwave ablation therapy. Although AFP and PIVKA-II levels decrease greatly in patients undergoing successful ablation therapy, it is not enough to identify the residual disease based only on these factors. The optimal method of assessment would include a combination of contrast enhanced CT, tumor markers, and clinical assessment.

CONCLUSION

CT scan during the arterial phase was better at diagnosing residual HCC after microwave ablation than CT scan during the portal venous phase. Both the AFP and PIVKA-II levels were significantly lowered by the treatment, but there was no significant relationship between these markers and the residual tumors. They were of low sensitivity and predictive power in the detection of residual tumors. Therefore, the tumor markers should be used only as supportive tools.

Conflict of Interest
None

Funding
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