Utility contrast enhanced ultrasonography for detecting residual liver tumor early after transarterial chemoembolization: A diagnostic metanalysis

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Buleleng, 2022-10-29

Introduction

Transarterial chemoembolization (TACE) is the recommended treatment of choice for intermediate stage HCCs.[1] The underlying principle of TACE is inducing tumor tissue hypoxia with the selective delivery of embolization particles together with a chemotherapeutic drug. TACE is still considered a palliative method, although it might achieve a complete therapeutic response, small numbers of malignant cells can escape necrosis.[2] Early evaluation and detection of those residual tumor warrant a chance for immediate repeat treatment.[3–6] Thereby, the modality for early detection is paramount important. The most promising modality is the contrast-enhanced ultrasonography (CEUS). This study aimed to gather evidence for diagnostic performance of CEUS in detecting residual tumor within 24-72 hours after TACE treatment.

Methods

Literature Search

Data from literature up to September 2022 were searched from PubMed, Embase and Google schoolar. The search term were combination of following: (1) hepatocelular carcinoma, liver carcinoma, liver cancer, hepatoma and HCC; (2) transarterial chemoembolization and TACE; and (3) contrast enhanced ultrasound, contrast enhanced ultrasonography and CEUS.

Study Selection

Studies were included in the analysis if they met the following inclusion criteria: (1) all participant received TACE treatment for hepatocelular carcinoma; (2) all participant had CEUS examination within 72 hours after TACE; (3) All participant undwerwent confirmation test after 1 month with Contrast Enhanced Computed Tomography (CECT) or Magnetic Resonance Imaging (MRI) or both; (4) The study included the absolute number of true-positive, true-negative, false-positive, false-negative or the value of sensitivity, specificitty, positive predictive value and negative predictive value. The study excluded if met the following criteria: (1) the publication included a case report, reviews, or editorial; (2) the study did not report the sufficient parameter of the diagnostic performance about the index test of interest. Literature search and study selection were conducted by two authors (MVLW and KAW). Discrepancy, if any, were resolved by discussion and agreement.

Data Collection

The screened study were evaluated and the following data were collected: (1) author, publication date and study design; (2) study quality assessed by the Quality Assessment of Diagnostic Accuracy Studies (QUADAS)[7]; (2) investigators (MVLW and KAW) independently performed a quality assessment of the included studies, and disagreements were resolved by discussion; (3) the data regarding true positive, false-positive, false-negative, and true-negative results gathered or calculated from each study

Risk of Bias and Quality Assement

Risk of bias of the included study was assesed with QUADAS. Visualization for study heterogeneity, indicating for variations between studies, was presented with SROC and Cross-Hairs plots as well as calculation for I^2 statistics. if an I^2 indicate significant heterogeneity, data were pooled by random-effects model, otherwise it pooled by fixed-effects model.

Statistical Analysis

The collected data were tabulated in spreadsheet (Google Sheet) and analyzed in R statistical language (v 4.1.2)[8] through Rstudio interface (RStudio Server 2022.02.3+492 for Ubuntu Bionic).[9,10] Diagnostic metanalysis specific calculation conducted using Mada package.[11] Univariate analysis of diagnostic performance conducted using metaprop function from Meta package.[12] The main analysis was focused on the pooled diagnostic parameter of CEUS early after TACE in detecting residual tumors. The pooled sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (PLR), negative likelihood ratio (NLR) and the diagnostic odds ratio were calculated using the suitable model in respect for the between study heterogeneity. The summary of diagnostic performance were presented in SROC curve. Additional R package used include rmarkdown for reproducible data calculation and manuscript preparation,[13] googlesheet4 for data bridging from Google Sheets to R,[14] gtsummary for table generation,[15] PRISMA2022 for PRISMA chart generation,[16] and robvis for risk of bias plotting.[17]

Results

Search Results

A total of XX studies were identified by literature search. Studies were excluded after screened for title, abstract, or the entire full text. A total of four studies were suitable for the review and thus included in the metanalysis. A PRISMA flow diagram depicting the screening and review process is presented in the figure 1.[18]

Summary of the Included Studies

The included studies were mostly pubslished within the last decade, starting from 2013 to 2021. The four studies were all prospective studies. The study sample size ranging from X to Y, involved X to Y nodules, both totalling at XXXX patients and YYYY nodules. The range of patients age were X to Y. The tumor size between x to y. Two studies examined the liver after two days post TACE, other studies one day and at the third day after TACE. The main reference examination were X, x studies include A examination, x studies include B examination, and x studies include C examination. The X study followed up the patients for X month with X examination at X month. X studies also conduct CT scan accompanying the standalone CEUS. One study by X et al., include a an image fusion of CEUS and CT scan.

Table 1. Summary of the included Study.

Table 2. Summary for the Diagnostics and Treatment in the Included Studies.

```
## Descriptive summary of ceus with 4 primary studies.
## Confidence level for all calculations set to 95 %
## Using a continuity correction of 0.5 if applicable
##
## Diagnostic accuracies
##       sens  2.5% 97.5%  spec  2.5% 97.5%
## [1,] 0.682 0.511 0.814 0.905 0.803 0.957
## [2,] 0.948 0.846 0.984 0.808 0.537 0.938
## [3,] 0.900 0.660 0.977 0.635 0.444 0.791
## [4,] 0.790 0.619 0.897 0.955 0.679 0.995
##
## Test for equality of sensitivities:
```

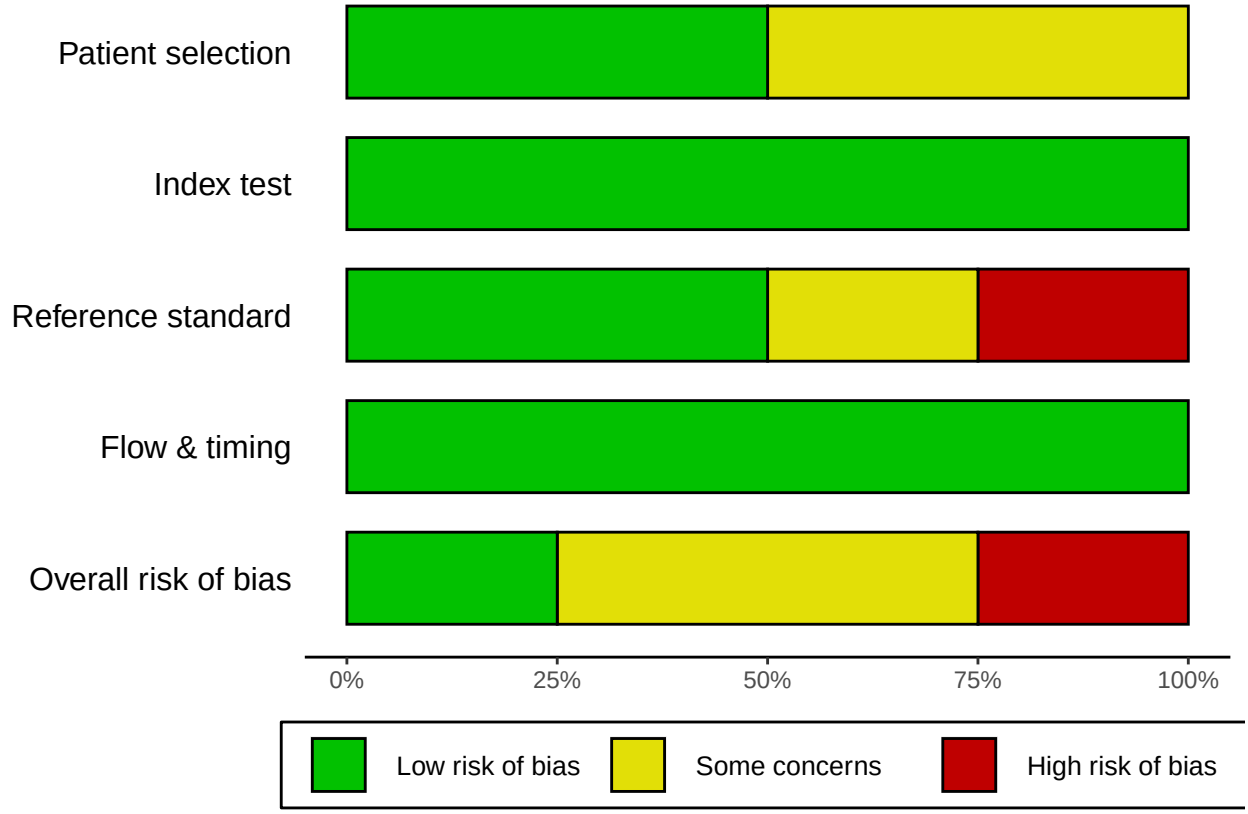
```
## X-squared = 10.9525, df = 3, p-value = 0.012
## Test for equality of specificities:
## X-squared = 10.7727, df = 3, p-value = 0.013
##
##
## Diagnostic OR and likelihood ratios
##         DOR   2.5%    97.5%  posLR  2.5%   97.5% negLR  2.5% 97.5%
## [1,] 20.455  6.517   64.198  7.190 3.140  16.466 0.352 0.212 0.583
## [2,] 76.440 11.698  499.492  4.929 1.615  15.047 0.064 0.019 0.222
## [3,] 15.632  2.418  101.038  2.463 1.444   4.201 0.158 0.034 0.739
## [4,] 79.154  4.078 1536.547 17.387 1.152 262.400 0.220 0.110 0.440
##
## Correlation of sensitivities and false positive rates:
##    rho  2.5 % 97.5 %
##  0.644 -0.832  0.991
```

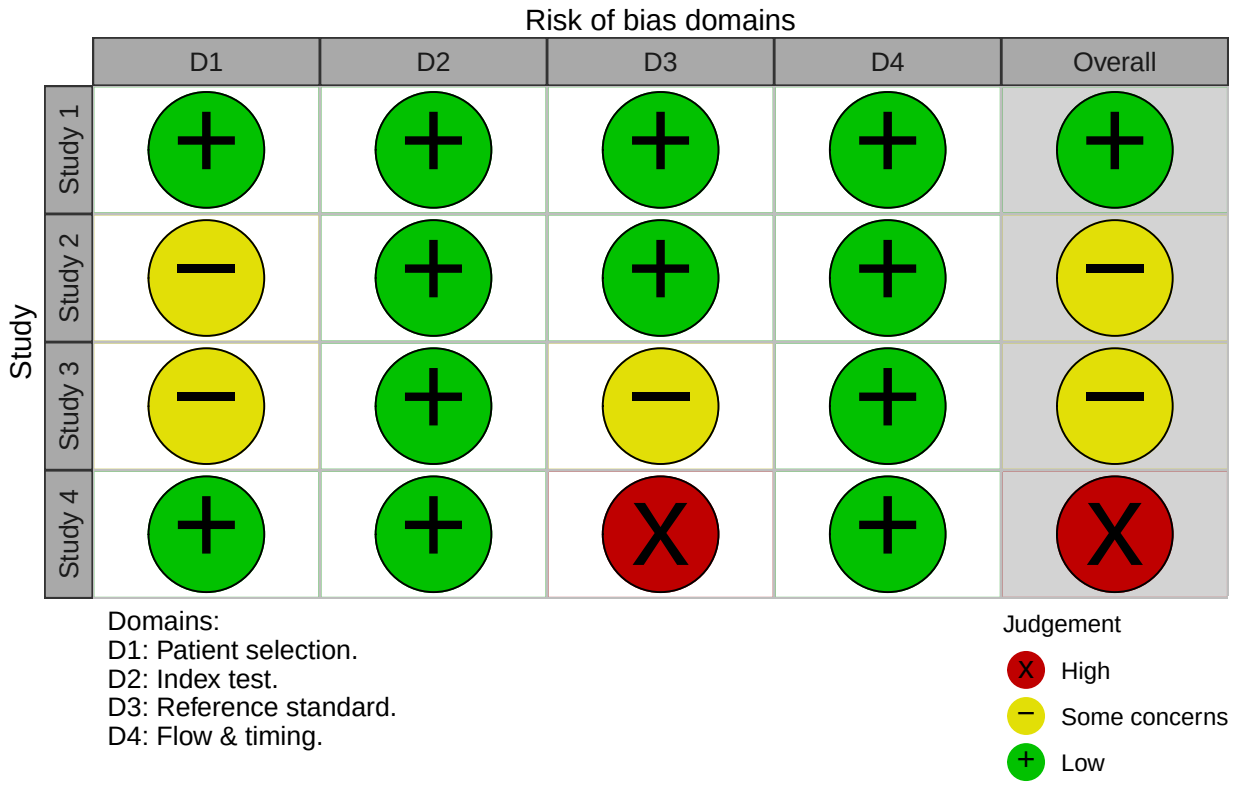
```
## Call:
## madauni(x = ceus, type = "DOR", method = "DSL")
##
##    DOR  tau^2
## 27.918  0.000
```

```
## Call:
## madauni(x = ceus, type = "posLR", method = "DSL")
##
## posLR tau^2
## 4.508 0.249
```

```
## Call:
## madauni(x = ceus, type = "negLR", method = "DSL")
##
## negLR tau^2
## 0.201 0.238
```

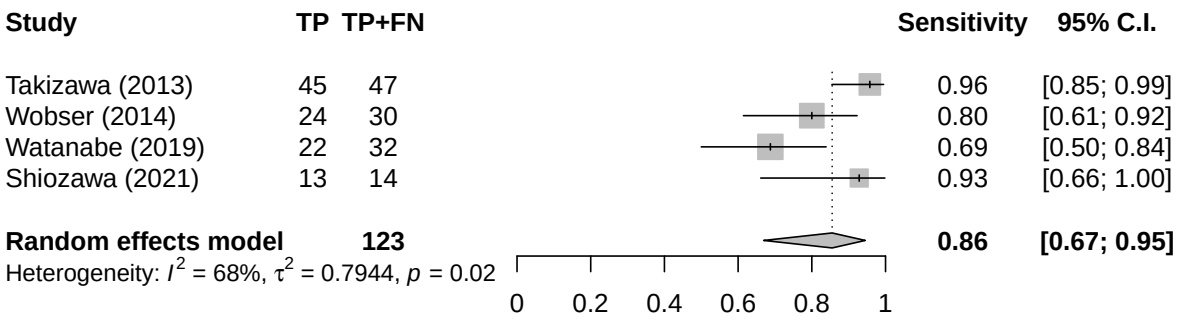
Study Heterogeneity and Publication Bias

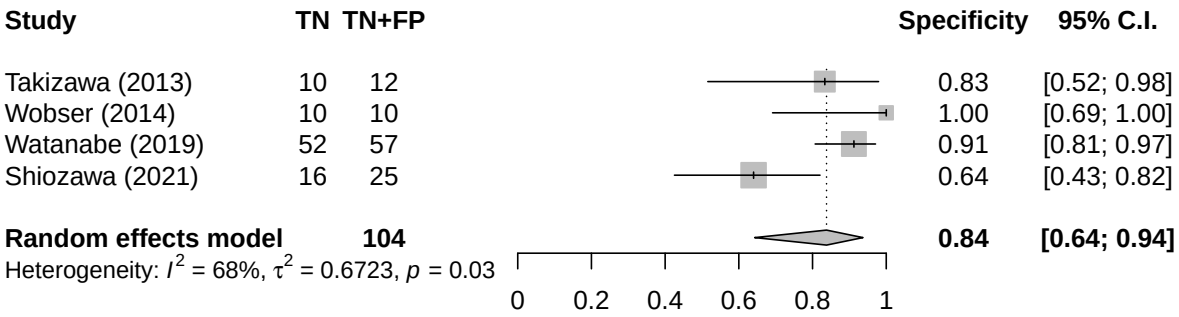


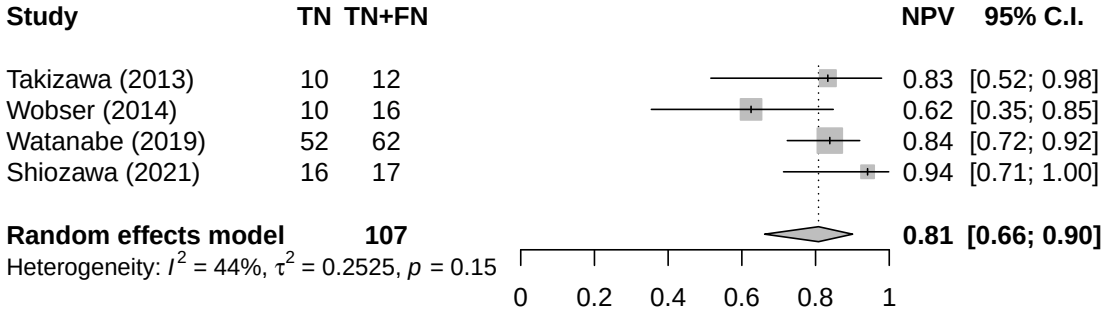


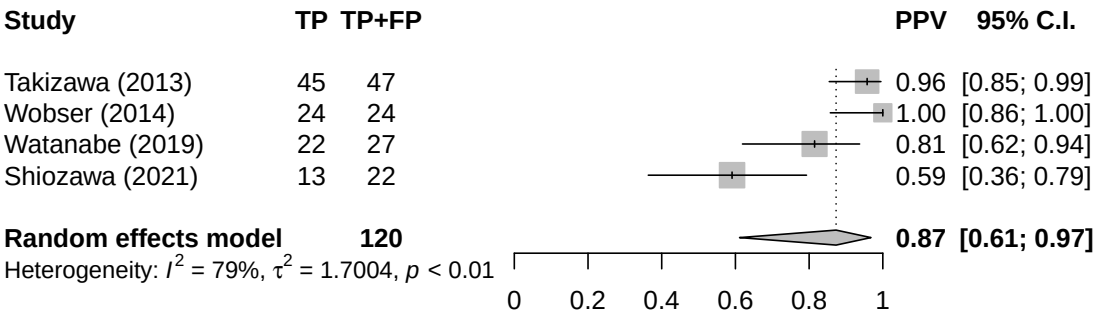
Diagnostic Accuracy of CEUS and CECT

Table 3. Individual and Pooled Diagnostic Performance of CEUS.

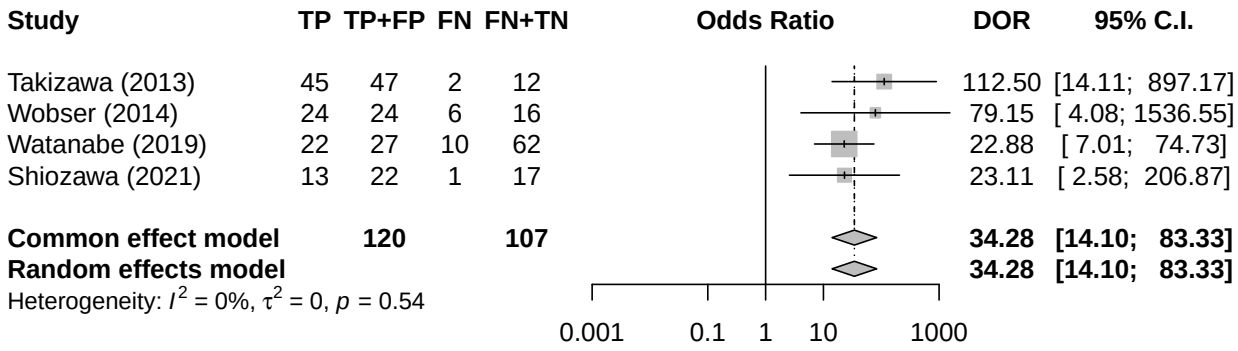


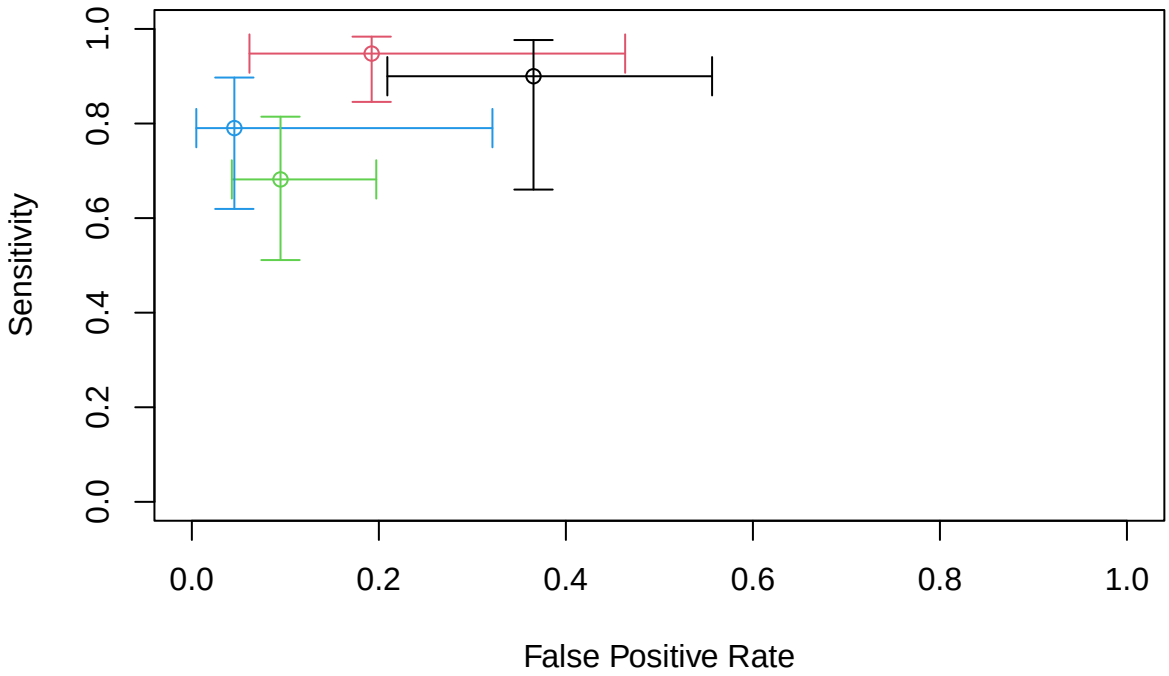

Study TN TN+FP Specificity 95% C.I.
Takizawa (2013) 10 12 0.83 [0.52; 0.98]
Wobser (2014) 10 10 1.00 [0.69; 1.00]
Watanabe (2019) 52 57 0.91 [0.81; 0.97]
Shiozawa (2021) 16 25 0.64 [0.43; 0.82]
Random effects model 104 0.84 [0.64; 0.94]
Heterogeneity: I^2 = 68%, τ^2 = 0.6723, p = 0.03
0 0.2 0.4 0.6 0.8 1

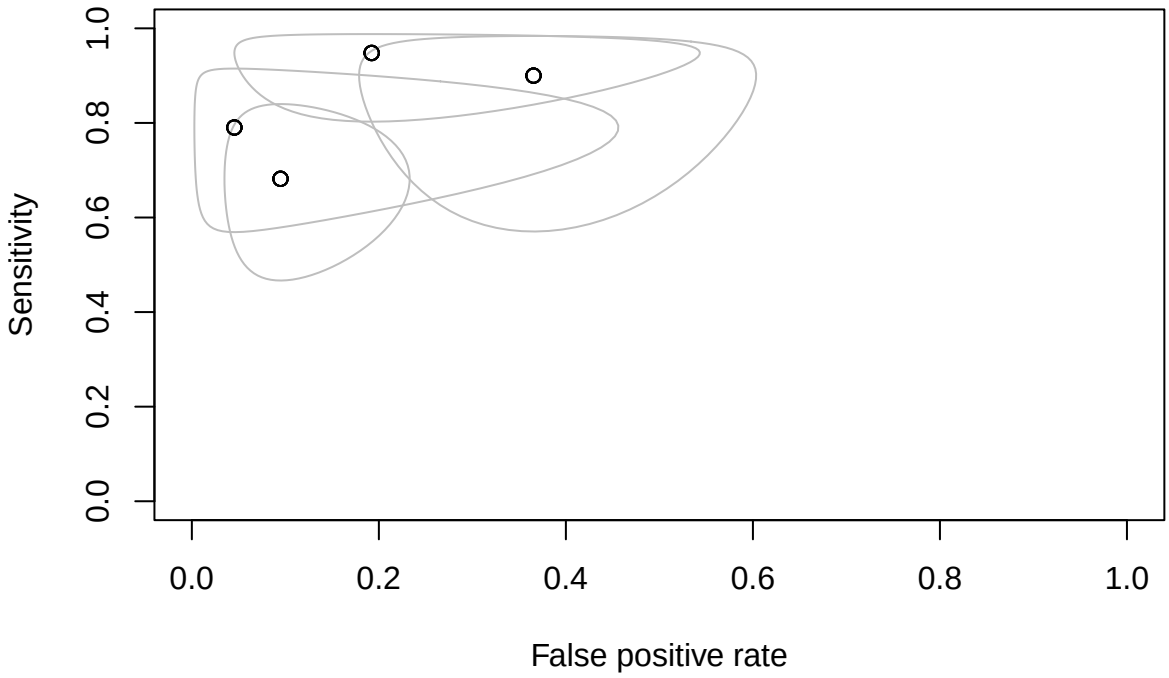

Study TN TN+FN NPV 95% C.I.
Takizawa (2013) 10 12 0.83 [0.52; 0.98]
Wobser (2014) 10 16 0.62 [0.35; 0.85]
Watanabe (2019) 52 62 0.84 [0.72; 0.92]
Shiozawa (2021) 16 17 0.94 [0.71; 1.00]
Random effects model 107 0.81 [0.66; 0.90]
Heterogeneity: I^2 = 44%, τ^2 = 0.2525, p = 0.15
0 0.2 0.4 0.6 0.8 1




```
## Number of studies combined: k = 4
## Number of observations: o = 227
## Number of events: e = 123
##
##                          OR         95%-CI    z  p-value
## Common effect model  34.28 [14.10; 83.33] 7.80 < 0.0001
## Random effects model 34.28 [14.10; 83.33] 7.80 < 0.0001
##
## Quantifying heterogeneity:
##  tau^2 = 0 [0.0000; 8.4176]; tau = 0 [0.0000; 2.9013]
##  I^2 = 0.0% [0.0%; 84.7%]; H = 1.00 [1.00; 2.56]
##
## Test of heterogeneity:
##     Q d.f. p-value
##  2.14    3  0.5445
##
## Details on meta-analytical method:
## - Inverse variance method
## - Restricted maximum-likelihood estimator for tau^2
## - Q-Profile method for confidence interval of tau^2 and tau
## - Continuity correction of 0.5 in studies with zero cell frequencies
```

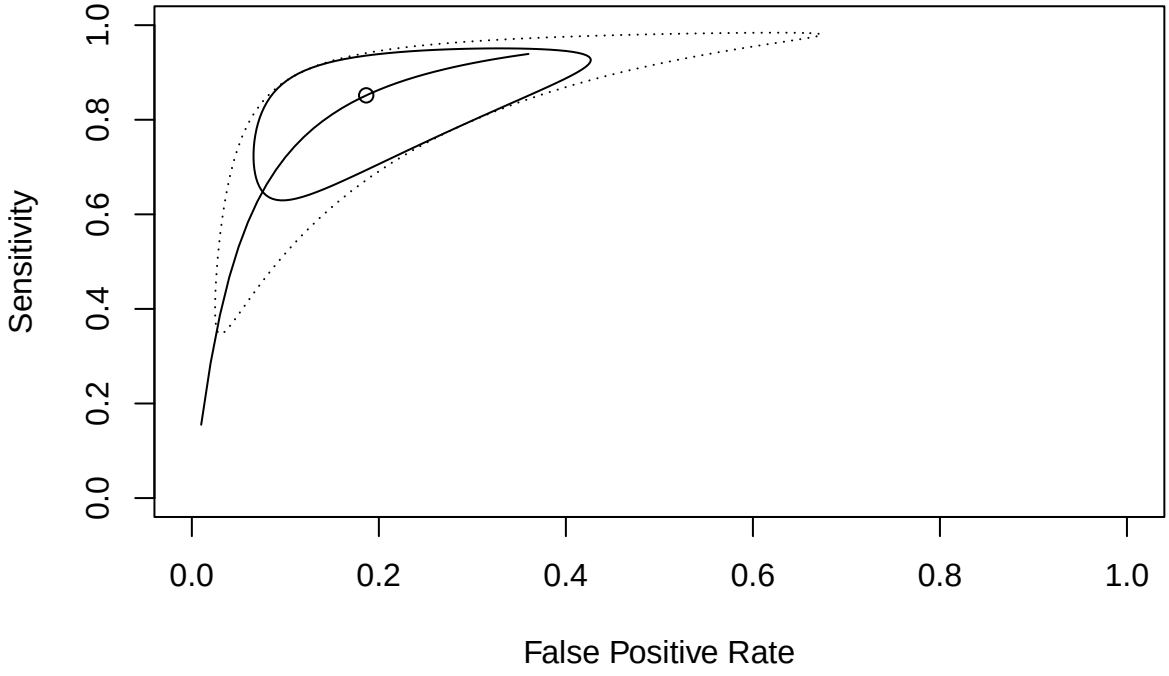

Study
TP
TP+FP
FN
FN+TN
Odds Ratio
DOR
95% C.I.
Takizawa (2013) 45 47 2 12 112.50 [14.11; 897.17]
Wobser (2014) 24 24 6 16 79.15 [4.08; 1536.55]
Watanabe (2019) 22 27 10 62 22.88 [7.01; 74.73]
Shiozawa (2021) 13 22 1 17 23.11 [2.58; 206.87]
Common effect model 120 107 34.28 [14.10; 83.33]
Random effects model 34.28 [14.10; 83.33]
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.54
0.001
0.1
1
10
1000


Sensitivity
0.0
0.2
0.4
0.6
0.8
1.0
False Positive Rate




```
## Call:  reitsma.default(data = ceus)
##
## Bivariate diagnostic random-effects meta-analysis
## Estimation method: REML
##
## Fixed-effects coefficients
##                   Estimate Std. Error      z Pr(>|z|) 95%ci.lb 95%ci.ub
## tsens.(Intercept)    1.747      0.497  3.513    0.000    0.773    2.722 ***
## tfpr.(Intercept)    -1.473      0.481 -3.062    0.002   -2.416   -0.530  **
## sensitivity          0.852          -      -        -    0.684    0.938
## false pos. rate      0.186          -      -        -    0.082    0.370
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Variance components: between-studies Std. Dev and correlation matrix
##       Std. Dev tsens  tfpr
## tsens    0.835 1.000     .
## tfpr     0.757 1.000 1.000
##
## logLik    AIC    BIC
##  8.576 -7.152 -6.755
##
## AUC:  0.899
## Partial AUC (restricted to observed FPRs and normalized):  0.771
##
## I2 estimates
```

```
## Zhou and Dendukuri approach:  0 %
## Holling sample size unadjusted approaches:  28.2 - 37.3 %
## Holling sample size adjusted approaches:  1.5 - 2 %
```



Discussion

Summary of the Results

Limitations

Applications

Conclusion

CEUS has shown a good diagnostic performace for detecting non responding tumor within 72 hours after TACE and could be utilized as a modality for early residual tumor detection.

Disclaimer

Funding

This study was not supported by third party funding

Conflict of Interest

All authors declare no conflict of interest.

Authors Contribution

Both MVLW and KAW share a proportional contribution in all phases of this study.

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Abstract

Background Transarterial chemoembolization (TACE) is the recommended treatment for intermediate stage Hepatocelular Carcinomas (HCC). TACE is local delivery of embolization and chemotherapeutic particle that might not achieve a complete therapeutic response, small numbers of malignant cells can escape necrosis. Early evaluation and detection of those residual tumor warrant a chance for immediate repeat treatment and Contrast-enhanced Ultrasonography (CEUS) is among the most promising modality for early evaluation.

Objective This study aimed to gather evidence for diagnostic performance of CEUS in detecting residual tumor within 24-72 hours after TACE treatment.

Methods Literature search regarding CEUS utilization early after TACE were conducted through PubMed, Embase and Google scholar up to September 30th, 2022 with various keywords combination. Suitable literatures were screened and evaluated for risk of bias with QUADAS-2. Diagnostic outcume data were analyzed with R programming. Pooled sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), diagnostic odd ratio (DOR) calculated with Meta package. Area under the curve (AUC) from the summary of the receiver operating characteristics (sROC) curve using Reitsma method were calculated using Mada package to get the overall diagnostic performance of CEUS.

Results A total of four selected study among XXXX screened literature including XXX patients and YYYY nodules. The analysis conclude the following values (95%CI) diagnostic parameter: (1) sensitivity 0.86 (0.67 - 0.95), (2) specificity 0.84 (0.64 - 0.94), (3) PPV 0.87 (0.61 - 0.95), (4) NPV 0.81 (0.66 - 0.90), (5) DOR 34.28 (14.10 - 83.33), (8) AUC sROC 0.89. The correlation of sensitivities and false positive rates was 0.64.

Conclusion CEUS has shown a excelent sensitivity and specificity for detecting residual tumor within 72 hours after TACE.

Keywords Contrast-enhanced ultrasonography, Diagnostics test accuracy meta-analysis, Hepatocelular carcinoma, Transarterial chemoembolization