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Original article

Original article

Vitamin D deficiency and C-reactive protein: a bidirectional Mendelian randomization study

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Background: Low vitamin D status is often associated with systemic low-grade inflammation as reflected by elevated C-reactive protein (CRP) levels. We investigated the causality and direction of the association between vitamin D status and CRP using linear and non-linear Mendelian randomization (MR) analyses.

Methods: MR analyses were conducted using data from 294 970 unrelated participants of White-British ancestry from the UK Biobank. Serum 25-hydroxyvitamin D [25(OH)D] and CRP concentrations were instrumented using 35 and 46 genome-wide significant variants, respectively.

Results: In non-linear MR analysis, genetically predicted serum 25(OH)D had an L-shaped association with serum CRP, where CRP levels decreased sharply with increasing 25(OH)D concentration for participants within the deficiency range (<25 nmol/L) and levelled off at ~50 nmol/L of 25(OH)D ($P_{non\text{-}linear}$ = 1.49E-4). Analyses using several pleiotropy-robust methods provided consistent results in stratified MR analyses, confirming the inverse association between 25(OH)D and CRP in the deficiency range (P = 1.10E-05) but not with higher concentrations. Neither linear or non-linear MR analysis supported a causal effect of serum CRP level on 25(OH)D concentration (P_{linear} = 0.32 and $P_{non\text{-}linear}$ = 0.76).

Conclusion: The observed association between 25(OH)D and CRP is likely to be caused by vitamin D deficiency. Correction of low vitamin D status may reduce chronic inflammation.

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ARTICLES | VOLUME 7, ISSUE 9, P843-850, SEPTEMBER 01, 2022

Radiation segmentectomy for curative intent of unresectable very early to early stage hepatocellular carcinoma (RASER): a single-centre, single-arm study

Prof Edward Kim, MD • Alex Sher, MD • Ghadi Abboud, MD • Prof Myron Schwartz, MD • Prof Marcelo Facciuto, MD • Parissa Tabrizian, MD • et al. Show all authors

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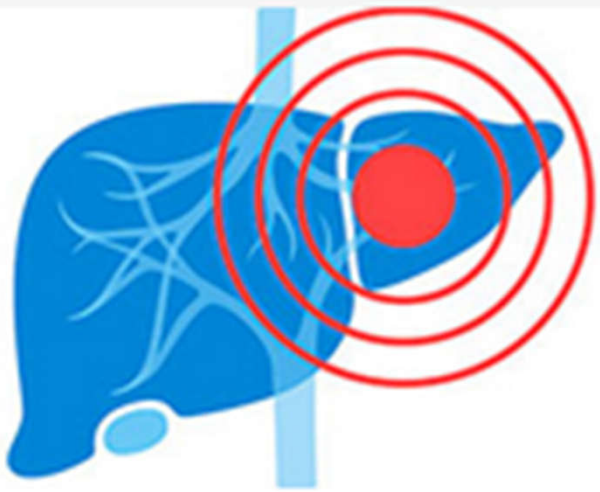

ARTICLES

Radiation segmentectomy for curative intent of unresectable very early to early stage hepatocellular carcinoma (RASER): a single-centre, single-arm study

Kim et al.

hepatocellular carcinoma deemed unfavourable for ablation.

Methods

RASER was a single-centre, single-arm study that included adults (>18 years) with solitary hepatocellular carcinoma with unfavourable location for ablation, without metastasis or macrovascular invasion. Eligibility criteria included measurable disease 3 cm or less in diameter, Child-Pugh score A–B7, an Eastern Cooperative Oncology Group score of 0, and adequate haematological and organ function. The primary endpoint was target tumour response measured by mRECIST. Patients were followed up with imaging and office visits for up to 24 months. The trial is registered with ClinicalTrials.gov (NCT03248375), and is completed.

Findings

Individuals were enrolled between Aug 3, 2016, and April 4, 2019, and the last patient follow-up occurred on March 31, 2021. Of the 44 individuals assessed for eligibility, 29 patients were included in the study. Initial target lesion complete response was observed in 24 (83%) of 29 patients, and partial response was observed in five (17%) of patients. All patients had an initial objective response and 26 (90%) individuals had a sustained complete response. Four (14%) patients had grade 3 leukopenia and two (7%) had grade 3 thrombocytopenia. There were two (7%) non-laboratory-related grade 3 adverse events (one arterial injury and one ascites). The most frequent (>10% patients) grade 1 or 2 adverse events were fatigue (nine [31%]); nausea, vomiting, or anorexia (seven [24%]); abdominal discomfort (six [21%]), leukopenia (nine [31%]), thrombocytopenia (four [14%]), increased alkaline phosphatase (four [14%]), increased alanine or aspartate aminotransferase (four [14%]), increased bilirubin (four [14%]), and decreased albumin (six [21%]). There was one death that was not treatment related.

Interpretation

Radiation segmentectomy was efficacious, with a low proportion of high-grade adverse events in patients with unresectable very early to early stage hepatocellular carcinoma with suboptimal location for ablation. These results suggest that radiation segmentectomy should be further investigated as a potential curative treatment option for well selected patients.

Funding

Journal of Clinical Or
An American Society of Clinical Oncology Journal

ORIGINAL REPORTS | Gastrointestinal Cancer

Lenvatinib Combined With Transarterial Chemoembolization as First-Line Treatment for Advanced Hepatocellular Carcinoma: A Phase III, Randomized Clinical Trial (LAUNCH)

Zhenwei Peng, MD, PhD[1,2]; Wenzhe Fan, MD[3]; Bowen Zhu, MSc[3]; Guoyir

MATERIALS AND METHODS

This was a multicenter, randomized, open-label, parallel group, phase III trial. Patients with primary treatment-naive or initial recurrent advanced HCC after surgery were randomly assigned (1:1) to receive LEN plus on-demand TACE (LEN-TACE) or LEN monotherapy. LEN was initiated within 3 days after random assignment (initial dose: 12 mg once daily for patients ≥ 60 kg; 8 mg once daily for patients < 60 kg). TACE was initiated one day after LEN initiation. The primary end point was overall survival (OS).

RESULTS

Between June 2019 and July 2021, a total of 338 patients underwent random assignment at 12 centers in China: 170 to LEN-TACE and 168 to LEN. At a prespecified event-driven interim analysis after a median follow-up of 17.0 months, the median OS was significantly longer in the LEN-TACE group (17.8 *v* 11.5 months; hazard ratio, 0.45; $P < .001$). The median progression-free survival was 10.6 months in the LEN-TACE group and 6.4 months in the LEN group (hazard ratio, 0.43; $P < .001$). Patients in the LEN-TACE group had a higher objective response rate according to the modified RECIST (54.1% *v* 25.0%, $P < .001$). Multivariable analysis revealed that portal vein tumor thrombus and treatment allocation were independent risk factors for OS.

CONCLUSION

The addition of TACE to LEN improves clinical outcomes and is a potential first-line treatment for patients with advanced HCC.

Journal of Hepatocellular Carcinoma

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ORIGINAL RESEARCH

Comparison of the Efficacy and Safety of Transarterial Chemoembolization with or without Lenvatinib for Unresectable Hepatocellular Carcinoma: A Retrospective Propensity Score–Matched Analysis

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Background: Combination of angiogenesis inhibitor may achieve better therapeutic synergistic efficacy, considering of tumor hypoxia and promoted angiogenesis after transarterial chemoembolization (TACE). This study aimed to compare the safety and efficacy of TACE plus lenvatinib (TACE-lenvatinib) with TACE alone for patients with unresectable hepatocellular carcinoma (HCC).
Methods: Between June 2019 and September 2021, a total of 215 patients diagnosed with unresectable HCC were retrospectively reviewed, including 53 patients who received TACE-lenvatinib and 162 patients who received TACE alone. The patient selection bias between the TACE-lenvatinib group and the TACE group was balanced by propensity score matching analysis at a 1:2 ratio. Progression-free survival (PFS), overall survival (OS) and tumor response were evaluated in the two groups.
Results: After propensity score matching analysis, 34 patients receiving TACE-lenvatinib and 68 patients receiving TACE alone were enrolled. The median PFS and OS times in the TACE-lenvatinib group were significantly greater than those in the TACE group (PFS: 8.3 months vs 4.6 months, $P = 0.008$; OS: 27.7 months vs 18.4 months, $P = 0.043$). The objective response rate (ORR) in the TACE-lenvatinib group was higher than that in the TACE alone group (64.1% vs 36.5%, $P = 0.002$). Univariate and multivariate analyses revealed that TACE-lenvatinib treatment was an independent favorable prognostic factor for both PFS and OS.
Conclusion: For unresectable HCC patients, the TACE-lenvatinib appeared superior to TACE alone regarding tumor control, PFS, and OS. However, considering the limitations of this study, these results should be interpreted as preliminary and warrant further confirmation.

Journal of Hepatocellular Carcinoma

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ORIGINAL RESEARCH

Transarterial Chemoebolization in Hepatocellular Carcinoma: A Binational Japanese-German Study

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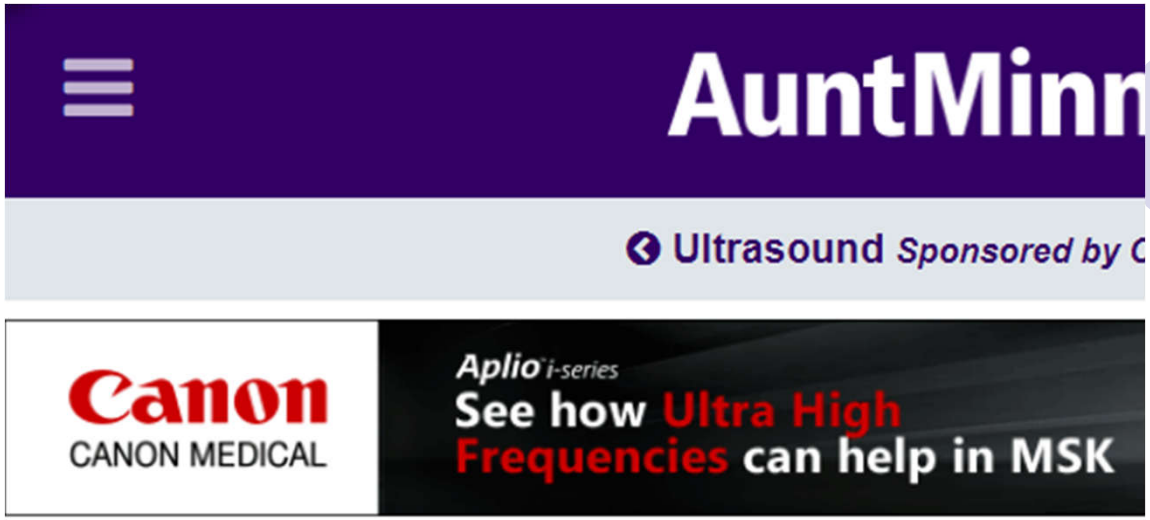
Objective: The purpose of this study was to investigate outcomes of transarterial chemoembolization (TACE) in treating hepatocellular carcinoma (HCC) comparing the different approaches used in Germany and Japan.

Methods: This binational IRB-approved retrospective dual-center study included a total of 94 HCC patients subdivided in a German and a Japanese cohort. For each patient, liver and tumor volumetry was performed using computed tomography (CT) and magnetic resonance imaging (MRI). Furthermore, a comprehensive risk profile, including body constitution and liver and kidney function was established. Primary endpoints were progression-free and overall survival (PFS/OS).

Results: PFS in the German cohort was 168 vs 224d in the Japanese cohort (p=0.640). When subdivided by BCLC stage, no significant differences were reported (p=0.160–0.429). OS was significantly longer in the Japanese cohort with 856 vs. 303d (p<0.001). OS for BCLC A was significantly longer in the Japanese cohort (1960 vs. 428d; p<0.001), while survival rates did not differ significantly in BCLC B (785 vs 330d; p=0.067) and C-stages (208 vs 302d; p=0.186). Older age (p=0.034), poorer liver/kidney function (p=0.025-0-035), and a higher liver/tumor ratio (p<0.001) were found to correlate with shorter survival. ECOG scores were significantly higher in the German cohort (p=0.002).

Conclusion: While OS is longer in TACE-treated patients in the Japanese cohort compared to the German cohort, the two approaches seem to be equally effective as PFS does not differ significantly. The different survival rates may be caused by the different clinical performance status of the selected collectives. In very early and early stage HCC, TACE in Japan seems to be an effective treatment option while in Germany for patients in those stages TACE remains a second-line option for patients not available for surgery or ablation.



CEUS-guided biopsy shows superiority in liver imaging

By Amerigo Allegretto, AuntMinnie.com staff writer

August 3, 2022 -- Biopsy guided by contrast-enhanced ultrasc
(CEUS) is effective, safe, and more accurate than convention
ultrasound-guided biopsy when it comes to diagnosing focal l
lesions, a multicenter study published August 2 in *Radiology*
found.

Radiology

ORIGINAL RESEARCH • U

A Multicenter Randomized Controlled Study of Contrast-enhanced US versus US-guided Biopsy of Focal Liver Lesions

Wei Wu, MD • Xiang Jing, MD* • Gai-qin Xue, BM • Xiao-lin Zhu, MD • Jing Wang, MM • Rui-qing Du, MD • Bin Lv, MD • Ke-feng Wang, BM • Ji-Ping Yan, MD • Zhong-yi Zhang, MD • Man-di Li, MM • Yuko Kono, MD, PhD • Kun Yan, MD*

Background: Retrospective or single-center prospective studies with relatively small samples have shown that contrast-enhanced US (CEUS) can improve the diagnostic accuracy of percutaneous biopsy, but larger prospective studies are lacking.

Purpose: To assess the diagnostic performance of CEUS-guided biopsy (CEUS-GB) of focal liver lesions (FLLs) compared with US-guided biopsy (US-GB) in a prospective multicenter study.

Materials and Methods: In this randomized controlled study conducted in nine hospitals in China between March 2016 and August 2019, adult participants with FLLs detected with US, CT, or MRI and planned for percutaneous biopsy were randomly assigned to undergo either US-GB or CEUS-GB. Lesions diagnosed as malignant at histopathologic analysis were considered true-positive findings. Benign or indeterminate lesions required further confirmation with either repeat biopsy or clinical follow-up at 6 months or later. The primary endpoint was the diagnostic accuracy rate, and comparison between groups was made using the χ^2 test.

Results: In this study, 2056 participants (1297 men, 759 women; mean age, 58 years ± 11 [SD]) were analyzed: 1030 underwent biopsy with US guidance and 1026 underwent biopsy with CEUS guidance. The overall diagnostic accuracy rate of CEUS-GB was 96% (983 of 1026) versus 93% (953 of 1030) for US-GB ($P = .002$), CEUS-GB enabled correct identification in 96% of participants (983 of 1026) compared with 92% (953 of 1030) with US-GB ($P = .002$). The negative predictive value (NPV) for both biopsy methods was moderate but significantly higher for CEUS-GB than for US-GB (74% vs 57%, $P = .001$). The difference was remarkable for lesions smaller than 2.0 cm, with CEUS-GB showing higher diagnostic accuracy (96% vs 88%, $P = .004$) and sensitivity (95% vs 87%, $P = .007$) than US-GB. Among lesions smaller than 2.0 cm, the accuracy of CEUS-GB and US-GB for detection of hepatocellular carcinoma was 93% and 80%, respectively ($P = .008$), while it was comparable for liver metastases (98% vs 95%, $P = .63$).

Conclusion: Contrast-enhanced US-guided biopsy of focal liver lesions is an effective and safe procedure with a higher diagnostic accuracy than US-guided biopsy, especially for lesions smaller than 2.0 cm and for hepatocellular carcinoma diagnosis.

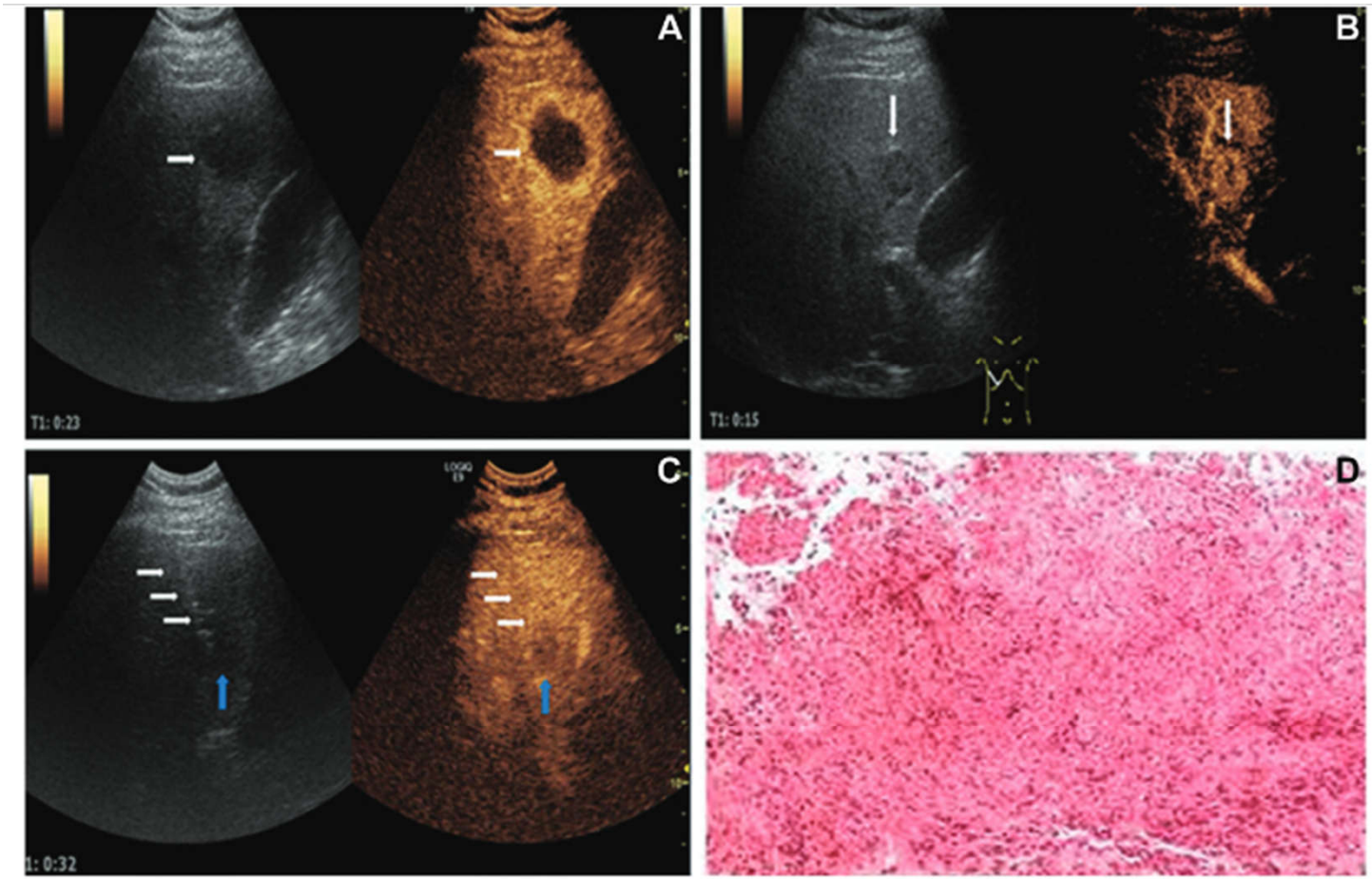
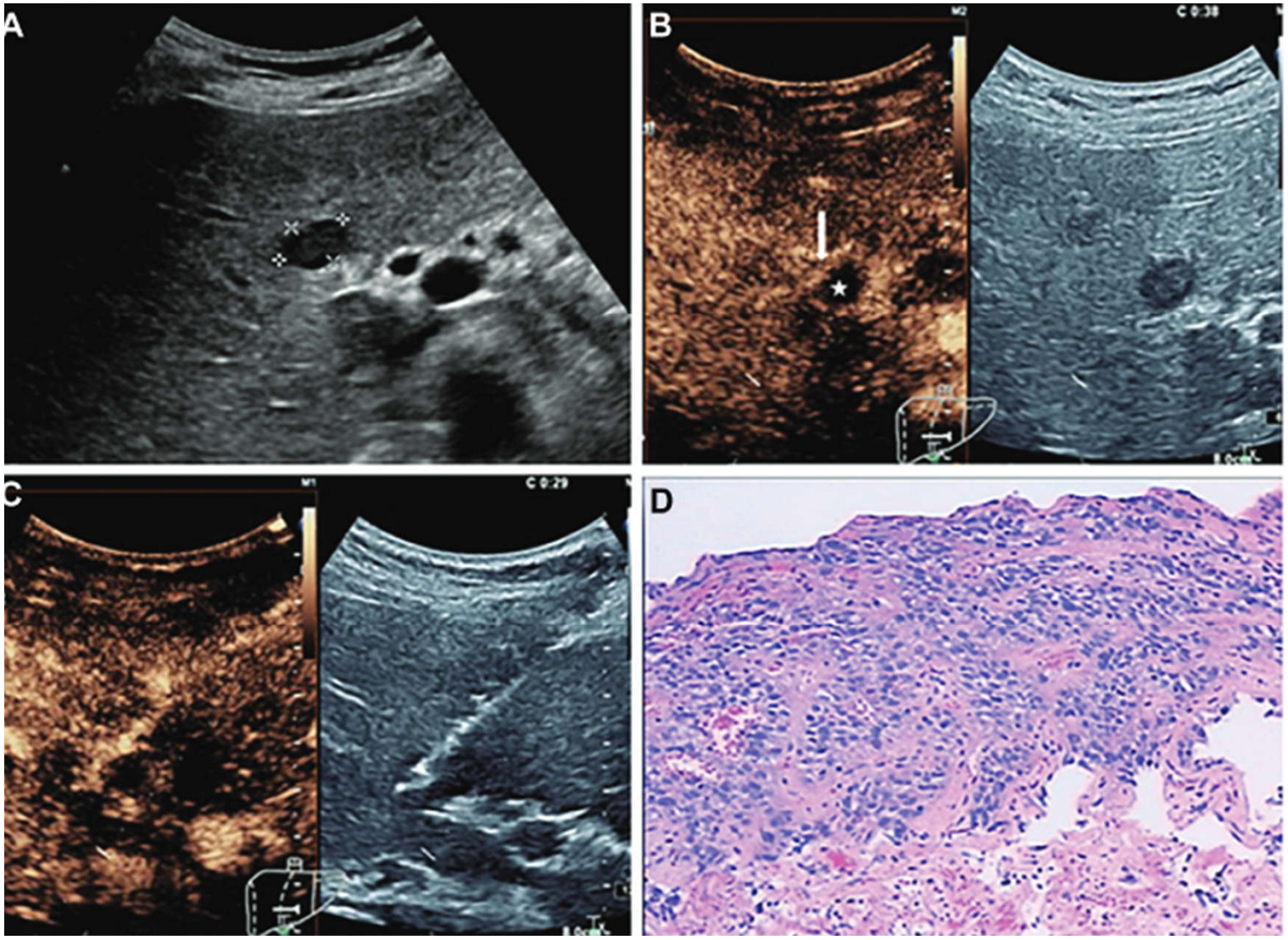


Figure 2: Representative contrast-enhanced US (CEUS) images with a change of the biopsy target lesion in a 49-year-old man with a gastrointestinal stromal tumor and focal liver lesions (FLLs) detected with US. **(A)** Hypoechoic lesion in segment V on US scans was selected as the target lesion initially. CEUS showed that the lesion (arrow) had thin ringlike enhancement, and the center was considered necrotic. **(B)** CEUS scan shows that another FLL in segment V was substantially enhanced in the arterial phase. This lesion was chosen as the target lesion after CEUS. **(C)** Biopsy was performed in this smaller enhancing lesion (blue arrow) with CEUS guidance in the portal phase (white arrow indicates puncture needle). **(D)** Pathologic analysis was performed to confirm a liver metastasis from the stromal tumor. (Hematoxylin-eosin stain; original magnification, X100.)


A
B
C
D

CEUS-guided biopsy vs. conventional ultrasound-guided biopsy for focal liver lesions

	Conventional arm	CEUS arm	p-values
Overall accuracy	93%	96%	0.002
Correct identification	92%	96%	0.002
Negative predictive value	57%	74%	0.001
Accuracy (lesions smaller than 2 cm)	88%	96%	0.004
Sensitivity (lesions smaller than 2 cm)	87%	95%	0.007

The researchers also found that the accuracy of CEUS-guided biopsy (93%) was superior to that of standard ultrasound-guided biopsy (80%) among lesions smaller than 2 cm ($p = 0.008$). However, the two methods were comparable when it came to liver metastases ($p = 0.63$).

COMMENTARY

Lack of Convincing Evidence That the Widely Used COVID-19 Vaccines Will Produce Herd Immunity

Two mRNA vaccines are in wide usage in the United States and elsewhere.[1-5] In the initial clinical trials these 2 vaccines were found to have a high level of efficacy for prevention of symptomatic infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), that is, COVID-19 infection. The efficacy of each of the 2-dose mRNA vaccines for prevention of symptomatic infection was more than 90% at approximately 2 months after the second vaccine dose.[2,3,6] Although also efficacious in preventing asymptomatic infections, the level of efficacy was lower at 63.0% (95% confidence interval: 56.6%-68.5%).[5] Asymptomatic infections are important because they can lead to transmission to others.[7] However, the efficacy declined fairly rapidly over the next few months; consequently a third dose (booster dose) is now widely used to restore a high degree of vaccine efficacy in the United States.[8] And even a fourth dose is now being used in Israel. A third vaccine not based on mRNA is also available in the United States.[8]

Coincident with the arrival of the omicron variant of

Information that would explain what is currently being widely observed is becoming available. A relevant study of COVID-19 vaccine effectiveness over time was conducted in the United States Veterans Health Administration.[9] From February to October 2021, vaccine efficacy for the 2 mRNA vaccines dropped. Specifically, in March of 2021 the mRNA vaccine efficacy rates for prevention of symptomatic COVID-19 infection was 86.9%-89.2%; by September 2021, however, the efficacy rates had declined to 43.3% to 58.0%. During the delta variant surge, however, vaccination continued to demonstrate at least moderate

One illustrative example of the remarkable potential for the spread of SARS-CoV-2 despite vaccination is as follows. In mid-December 2021 a group of 30 graduate

Funding: None

variant does not invariably cause a benign infection.

In conclusion, the efficacy of the currently available mRNA vaccines for prevention of symptomatic COVID-19 infections falls over relatively short periods of time. Efficacy is also highly dependent on the particular variant of SARS-CoV-2 that a person is exposed to. Although these vaccines have been successful in reducing hospitalization and death, the likelihood of developing herd immunity using the currently available vaccines appears to be low.

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NEWS RELEASE 8-AUG-2022

Triple therapy halved the risk of death among patients hospitalized with severe COVID-19

Peer-Reviewed Publication

RUTGERS UNIVERSITY

Hindawi
Canadian Journal of Infectious Diseases and Medical Microbiology
Volume 2022, Article ID 9209618, 8 pages
https://doi.org/10.1155/2022/9209618

Research Article

A Retrospective Study of Dexamethasone, Remdesivir, and Baricitinib in Severe COVID-19

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Purpose. RECOVERY, ACTT-1, and ACTT-2 trials have demonstrated that utilization of dexamethasone, remdesivir, or a combination of remdesivir with baricitinib leads to mortality benefit and faster time to recovery, respectively. However, no studies have investigated the benefit of triple therapy of dexamethasone, remdesivir, and baricitinib. We investigate the benefits of triple therapy compared to dual therapy of dexamethasone with remdesivir in patients with severe COVID-19 on HFNC. *Materials and Methods.* A retrospective data analysis was performed on patients with severe COVID-19 requiring HFNC and evaluated for hospital discharge status, requirement of mechanical ventilation, length of stay, and days on HFNC. *Results.* Among 191 patients with severe COVID-19, 81 patients received dexamethasone, remdesivir, and baricitinib. Patients receiving triple therapy had a significant survival benefit (HR 0.52; $P = 0.042$). Treatment with triple therapy vs. dual therapy also trended towards less requirement of mechanical ventilation (OR 0.66; $P = 0.26$). There was no significant change in length of stay (mean 13.74 vs. 13.31; $P = 0.74$) or days on HFNC (mean 8.95 vs. 7.28 days, $P = 0.16$). *Conclusions.* The use of dexamethasone, remdesivir, and baricitinib in patients with severe COVID-19 requiring HFNC was associated with a significant survival benefit in comparison to dual therapy of dexamethasone with remdesivir.

THE END