# Mailed Outreach Invitations Significantly Improve <FC>HCC</FC> Surveillance Rates in Patients With Cirrhosis: A Randomized Clinical Trial

**Amit G. Singal,[1-4] Jasmin A. Tiro,[3,4] Caitlin C. Murphy,[3,4] Jorge A. Marrero,[1] Katharine McCallister,[3] Hannah Fullington,[3] Caroline Mejias,[3] Akbar K. Waljee,[5-7] Wendy Pechero Bishop,[3,4] Noel O. Santini,[1,2] and Ethan A. Halm[1-4]**

*<FTNX>Abbreviations: AASLD, American Association for the Study of Liver Diseases; APRI, AST to platelet ratio index; BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; CRC, colorectal cancer; CT, computed tomography; EMR, electronic medical record; HCC, hepatocellular carcinoma; ICD-9, International Classification of Diseases, Ninth Revision; MRI, magnetic resonance imaging; PTC, proportion time covered.*

*Received April 7, 2018; accepted May 31, 2018.*

*Additional Supporting Information may be found at http://onlinelibrary.wiley.com/doi/10.1002/hep.xxxxx/suppinfo.*

*Supported by the <GS>Center for Patient-Centered Outcomes Research</GS> and the <GS>Agency for Healthcare Research and Quality</GS> (<GN>R24 HS022418</GN>, <GN>NIH RO1 CA212008</GN>), <GS>Cancer Prevention Research Institute of Texas</GS> (<GN>RP150587</GN>), and <GS>NIH/NCI Cancer Center Support</GS> (<GN>P30 CA142543</GN>).*

*ClinicalTrials.gov identifier: NCT02312817.*

*View this article at online at wileyonlinelibrary.com.*

*Potential conflicts of interest: Nothing to report.*

**ARTICLE INFORMATION:**<zaq;1>

From the [1]Department of Internal Medicine, The University of Texas Southwestern Medical Center, Dallas, Texas; [2]Parkland Health & Hospital System, Dallas, Texas; [3]Department of

Clinical Sciences, The University of Texas Southwestern Medical Center, Dallas, Texas; [4]Harold C. Simmons Cancer Center, The University of Texas Southwestern Medical Center, Dallas, Texas; [5]Department of Internal Medicine, University of Michigan, Ann Arbor, Michigan; [6]Veterans Affairs Center for Clinical Management Research, Ann Arbor, Michigan; and [7]Institute for Healthcare Policy and Innovation, University of Michigan, Ann Arbor, Michigan.

**ADDRESS CORRESPONDENCE AND REPRINT REQUESTS TO:**

Amit G. Singal, M.D., M.S.

Division of Digestive and Liver Diseases, The University of Texas Southwestern Medical Center

5959 Harry Hines Blvd., POB 1, Suite 420

Dallas, TX 75390-8887

E-mail: amit.singal@utsouthwestern.edu

Tel: +1-214-645-6111

Fax: +1-214-645-6114</FTNX>

Hepatocellular carcinoma (HCC) surveillance is associated with early tumor detection and improved survival in patients with cirrhosis; however, effectiveness is limited by underuse. We compared the effectiveness of mailed outreach and patient navigation strategies to increase HCC surveillance in a racially diverse cohort of patients with cirrhosis. We conducted a pragmatic randomized clinical trial comparing mailed outreach for screening ultrasound (n = 600), mailed outreach plus patient navigation (n = 600), or usual care with visit-based screening (n = 600) among 1800 patients with cirrhosis at a large safety-net health system from December 2014 to March 2017. Patients who did not respond to outreach invitations within 2 weeks received reminder telephone calls. Patient navigation included an assessment of barriers to surveillance and encouragement of surveillance participation. The primary outcome was HCC surveillance (abdominal imaging every 6 months) over an 18-month period. All 1800 patients were included in intention-to-screen analyses. HCC surveillance was performed in 23.3% of outreach/navigation patients, 17.8% of outreach-alone patients, and 7.3% of usual care patients. HCC surveillance was 16.0% (95% confidence interval [CI]: 12.0%-

20.0%) and 10.5% (95% CI: 6.8%-14.2%) higher in outreach groups than usual care (*P* < 0.001 for both) and 5.5% (95% CI: 0.9%-10.1%) higher for outreach/navigation than outreach alone (*P* = 0.02). Both interventions increased HCC surveillance across predefined patient subgroups. The proportion of HCC patients detected at an early stage did not differ between groups; however, a higher proportion of patients with screen-detected HCC across groups had early-stage tumors than those with HCC detected incidentally or symptomatically (83.3% versus 30.8%, *P* = 0.003). *Conclusion:* Mailed outreach invitations and navigation significantly increased HCC surveillance versus usual care in patients with cirrhosis. (H<SC>EPATOLOGY</SC> 2018;XX:XXXX.)

Hepatocellular carcinoma (HCC) is the third-leading cause of cancer-related death worldwide.[1] HCC incidence in the United States and Europe has doubled over the past 2 decades, and HCC is the leading cause of death in patients with cirrhosis.[2]

Tumor stage is the strongest prognostic indicator in HCC patients, with curative treatments only available for patients with early-stage HCC. Ultrasound-based surveillance is associated with improvements in early detection and overall survival in at-risk patients, including those with cirrhosis, and is recommended by professional societies including the National Comprehensive Cancer Network, European Association for the Study of the Liver, and American Association for Study of Liver Diseases (AASLD).[3] A randomized clinical trial with more than 18,000 hepatitis B–infected persons demonstrated that HCC surveillance significantly lowered mortality by 37%.[4] Similarly, several cohort studies have shown that cirrhosis patients receiving HCC surveillance have higher odds of early detection and improved survival, after adjusting for lead-time bias, than those not receiving surveillance.[5-7]

As with breast and colorectal cancer screening, HCC surveillance is typically only offered opportunistically during face-to-face clinic encounters.[8] Only a minority of cirrhosis patients undergo any HCC screening, and less than 5% undergo repeat semi-annual surveillance.[9,10] Population outreach programs that systematically invite patients for screening and patient navigation interventions have effectively increased screening participation for other cancers including breast and colon cancer.[11-14] For

HCC, a mailed outreach strategy increased one-time screening participation in cirrhosis patients despite unique challenges surrounding patient identification, higher burden of medical illness, and patient access barriers to preventive care.[15] However, there are few data evaluating patient navigation strategies in cirrhosis patients, and the effectiveness of either intervention strategy to promote HCC surveillance over longer periods of time remains unknown.

This study reports the primary outcome of completing HCC surveillance every 6 months over an 18-month period from a pragmatic, randomized clinical trial comparing a mailed outreach strategy, mailed outreach plus patient navigation, and usual care in patients with cirrhosis.

<H1>**Methods**</H1>

<H2>**STUDY POPULATION**</H2>

The trial was conducted at Parkland Health and Hospital System (Parkland) from December 2014 to March 2017. Parkland is a publicly funded integrated safety-net health system that includes a 900-bed hospital, 12 community-based primary care clinics, specialty hepatology and oncology clinics, and radiology suites. Parkland offers a sliding fee scale program, which provides access to primary and subspecialty medical care, including HCC surveillance, at low cost for uninsured Dallas County residents.

The study was approved by the University of Texas (UT) Southwestern's internal review board (IRB). The UT Southwestern IRB determined that a waiver of consent was ethical because (1) the study posed minimal risk, as HCC surveillance is standard of care and available for at-risk patients (including those with cirrhosis) through usual care; (2) waiver of consent would not adversely affect rights or welfare of participants; and (3) requiring consent would introduce volunteer bias threatening generalizability and validity as a population health strategy.

The trial protocol (ClinicalTrials.gov #NCT01710215) is available in the Supporting Information. As previously described,[15] we used Parkland's electronic medical record (EMR) to identify adult patients with documented or suspected cirrhosis and at least one outpatient clinic visit in the year preceding randomization. We included patients with suspected cirrhosis given many HCC patients fail to undergo screening

due to unrecognized cirrhosis.[16] "Documented cirrhosis" was defined using International Classification of Diseases, Ninth Revision (ICD-9) codes for cirrhosis or cirrhosis-related complications, which have high accuracy for identifying cirrhosis.[17] "Suspected cirrhosis" was initially defined as AST to platelet ratio index (APRI) greater than or equal to 1.0 in the presence of liver disease; however, the cut-off was increased to 1.5 in January 2015 to increase its positive predictive value for cirrhosis.[18] Patients with HCC or significant comorbid conditions, including Child C cirrhosis, were excluded given the limited benefit of HCC surveillance in those subgroups.[19] We also excluded patients with no address or phone number on file or language other than English or Spanish.

<H2>**RANDOMIZATION AND BLINDING**</H2>

Eligible persons were randomly assigned to receive usual care (group 1), mailed outreach invitations for abdominal ultrasound (group 2), or mailed outreach invitations plus patient navigation (group 3), allocated in a 1:1:1 ratio using a computer-generated randomization sequence. Randomization was stratified by documented versus suspected cirrhosis. Research staff conducted all mailings and reminder telephone calls; thus, participants and clinicians were blinded to the presence of other intervention groups. Although clinicians may have been aware of the trial, they did not have knowledge of group assignments.

<H2>**HCC SCREENING INTERVENTION COMPONENTS**</H2>

Usual care (all groups) included visit-based HCC surveillance as ordered by clinicians during any outpatient visit. Parkland clinics do not have HCC surveillance reminders or provider-level audit and feedback for performance. The Radiology department makes automated reminder calls to persons scheduled for ultrasounds 3 days preceding the appointment. Radiology uses an EMR alert to inform clinicians of findings suspicious for HCC; however, use of this system is at the discretion of the interpreting radiologist.[20]) Patients in the intervention groups were eligible for visit-based surveillance as recommended through usual care.

Mailed outreach (groups 2 and 3) was initiated for each 6-month period with one-page low-literacy letters in English and Spanish, providing basic information about HCC risk and recommending surveillance. Trained bilingual research staff conducted telephone calls using standardized scripts for persons who did not respond to mailed invitations within 2 weeks. Telephone calls were stopped for persons with nonworking phone numbers and those not reached after three attempts. Patients who did not complete screening were mailed a repeat letter recommending HCC surveillance 6 months later. Patients with normal imaging received a letter informing them of the results and inviting them for repeat surveillance during the next 6-month period. Patients with an abnormal result were contacted by research staff and referred for diagnostic contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI).

Patient navigation (group 3) included standardized phone scripts for research staff to explore barriers and encourage participation for those who declined surveillance during telephone calls. Research staff also called patients 5 to 7 days prior to ultrasound appointments to remind them of the appointment, address any concerns, and reschedule the appointment if needed.

<H2>**PRIMARY AND SECONDARY OUTCOMES**</H2>

The primary outcome was receipt of HCC surveillance, defined as completion of abdominal imaging (ultrasound, CT, or MRI) during each 6-month interval over the 18-month study. Patient follow-up was censored at death or HCC diagnosis. For example, patients who completed surveillance every 6 months prior to death or HCC diagnosis were defined as meeting the primary outcome. For persons randomized to intervention groups, we included tests completed through outreach or usual care. To ascertain surveillance participation for all persons, research staff who did not deliver interventions and were blinded to intervention status queried the EMR for completed ultrasounds, contrast-enhanced CT, or contrast-enhanced MRI. Although professional societies do not recommend CT or MRI for screening, their completion satisfies the need for liver imaging and precludes the need for screening ultrasound. Alpha fetoprotein was not required because it was removed from AASLD guidelines during the study period. Subgroup analyses were planned *a priori* to examine effect modification by

race/ethnicity, documented versus suspected cirrhosis, Child-Pugh class, and receipt of hepatology care preceding randomization.

A secondary outcome, defined *a priori*, was the proportion of patients with early-stage HCC. HCC cases were adjudicated to confirm that they met AASLD diagnostic criteria (i.e., presence of a typical vascular pattern on imaging [arterial enhancement and delayed washout] or histology).[3] The Barcelona Clinic Liver Cancer (BCLC) system was used for tumor staging, with early stage defined as BCLC stage 0 or A.

Three *post hoc* secondary analyses were performed using more liberal definitions of surveillance completion. First, we compared the effectiveness of the interventions to promote HCC surveillance every 7 months over a 21-month period. Second, we compared receipt of one-time abdominal imaging during the 18-month study period among groups. Finally, we compared the proportion time covered (PTC) as the number of days patients were up-to-date with HCC surveillance, with each ultrasound providing 6 months (180 days) of time covered, divided by the number of days of follow-up (from randomization to date of HCC diagnosis, death, or study end).

<H2>**STATISTICAL ANALYSIS**</H2>

We used intent-to-screen principles to guide the analyses. The Pearson chi-square test was used to compare primary and secondary outcomes among groups. Our primary comparisons of interest were (1) outreach alone versus usual care and (2) outreach plus navigation versus outreach alone. Participants without outpatient visits after randomization were considered as lost to follow-up but retained in analyses. Univariate logistic regression analyses were conducted to evaluate for effect modification across patient subgroups. We performed a per-protocol analysis excluding patients who died or were diagnosed with HCC after randomization but prior to cohort entry. Missing data were rare and reported as unknown.

Sample-size calculations were determined *a priori* to compare HCC surveillance across groups. With 600 persons randomly assigned to each group, we had 90% power to detect a difference of at least 7.1% in surveillance completion among groups, assuming surveillance completion of 10% in usual care at a prespecified two-sided

significance level of 0.025 (= 0.05/2 accounting for Bonferroni correction). Analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary, NC).

<H1>**Results**</H1>

<H2>**STUDY POPULATION**</H2>

Of the 1800 persons (mean age 55.3 years; 59.4% men), 600 were randomly assigned to mailed outreach and patient navigation, 600 to mailed outreach, and 600 to usual care (Fig. 1, Table 1). Participants were racially/ethnically diverse with 37.8% Hispanic, 32.1% black, and 28.3% white. Most (79.6%) patients had documented cirrhosis, and 20.4% had suspected cirrhosis. Most patients had compensated cirrhosis, with only 28.2% having ascites and 12.7% having hepatic encephalopathy. Although more than 90% of patients had one or more primary care visits in the year preceding randomization (median of four visits), only 25.7% had one or more hepatology clinic visits. One-third (31.1%) of patients received abdominal imaging within 6 months preceding randomization.

<H2>**PRIMARY OUTCOME: SURVEILLANCE COMPLETION**</H2>

HCC surveillance was performed in 23.3% (95% confidence interval [CI] 20.0%-26.9%) of outreach/navigation patients, 17.8% (95% CI: 14.9%-21.1%) of outreach-alone patients, and 7.3% (95% CI: 5.4%-9.7%) of usual care patients (Table 2). Compared with usual care, surveillance completion was significantly higher in outreach alone (+10.5%; 95% CI: 6.8%-14.2%) and outreach/navigation (+16.0%; 95% CI: 12.0%-20.0%) groups ($P < 0.001$ for both). Adding navigation to outreach increased surveillance completion by 5.5% (95% CI: 0.9%-10.1%; $P = 0.02$) (Fig. 2). There was no appreciable change in direction or magnitude of results in a per-protocol analysis excluding persons who died (n = 4) or were diagnosed with HCC (n = 3) after randomization but prior to cohort entry. In this analysis, surveillance completion was significantly higher in both intervention groups compared with usual care ($P < 0.001$ for

both) and adding navigation increased surveillance completion compared with outreach alone ($P = 0.02$).

There was no evidence of effect modification for either outreach alone or outreach/navigation interventions, compared with usual care, by race/ethnicity (white versus nonwhite) or presence of documented cirrhosis (documented versus suspected diagnosis); however, the magnitude of intervention effect varied by receipt of hepatology care in the year prior to randomization and Child-Pugh class (Supporting Figure S1A,B). Although CIs overlapped, the interventions (outreach alone and outreach/navigation versus usual care) had a stronger effect among patients with Child B cirrhosis and those who did not have hepatology care in the year preceding randomization. Among all predefined subgroups, patient navigation increased surveillance completion compared with outreach alone (Supporting Fig. S1C).

<H2>**SECONDARY OUTCOMES**</H2>

Secondary outcomes did not differ significantly among intervention groups. HCC was diagnosed in 1.8% (95% CI: 0.9%-3.3%) of outreach/navigation patients, 1.0% (95% CI: 0.4%-2.2%) of outreach-alone patients, and 2.3% (95% CI: 1.3%-3.9%) of usual care patients (Table 3). Similarly, the proportion of HCC patients detected at an early stage did not differ among study groups ($P = 1.0$), with 63.6% (95% CI: 30.8%-89.1%) of outreach/navigation HCC patients, 66.7% (95% CI: 22.3%-95.7%) of outreach-alone HCC patients, and 57.1% (95% CI: 28.9%-82.3%) of usual care HCC patients diagnosed at an early stage. Cholangiocarcinoma was diagnosed in 1 patient in the outreach/navigation group. Of note, 8 (57.1%) HCC patients in the usual care group were screen-detected; conversely, 7 (41.2%) HCC patients in the intervention groups presented incidentally or symptomatically. Overall, screen-detected patients had a higher proportion of early stage tumors than those detected incidentally or symptomatically (83.3% versus 30.8%, $P = 0.003$) (Supporting Table S1).

In a *post hoc* analysis evaluating a more liberal definition of HCC surveillance every 7 months over a 21-month period, 28.2% (95% CI: 24.6%-31.8%) of outreach/navigation patients, 20.8% (95% CI: 17.6%-24.1%) of outreach-alone patients,

and 9.5% (95% CI: 5.4%-9.7%) of usual care patients completed surveillance. HCC surveillance was 18.7% (95% CI: 14.4%-23.0%) and 11.3% (95% CI: 7.3%-15.3%) higher in outreach groups than usual care ($P < 0.001$ for both) and 7.4% (95% CI: 2.5%-12.2%) higher for outreach/navigation than outreach alone ($P = 0.003$) (Supporting Table S2). Similarly, receipt of any abdominal imaging was 22.4% (95% CI: 16.9%-27.8%) and 19.7% (95% CI: 14.2%-25.2%) higher in outreach/navigation and outreach-alone groups than usual care ($P < 0.001$ for both), respectively (difference between outreach groups: 2.7% (95% CI: 0%-8.0%; $P = 0.3$) (Supporting Table S3). Finally, PTC was 25.3% (95% CI: 22.9%-27.6%) in the usual care group, 40.9% (95% CI: 38.3%-43.6%) in the outreach-alone group, and 44.0% (95% CI: 41.2%-46.8%) in the outreach/navigation group. Both the outreach-alone and outreach/navigation groups had significantly higher PTC compared with usual care ($P < 0.0001$ for both); however, there was no significant difference between the two outreach groups ($P = 0.11$).

<H1>**Discussion**</H1>

In this pragmatic, randomized clinical trial among a large cohort of cirrhosis patients, a mailed outreach intervention significantly increased HCC surveillance every 6 months compared with usual care. Adding patient navigation further increased HCC surveillance compared with outreach alone. Both interventions were effective, independent of patient sex, race/ethnicity, receipt of hepatology care, or presence of documented versus suspected cirrhosis, although the magnitude of benefit appeared stronger in patients with Child B cirrhosis and those not engaged in hepatology care. Despite improvements in the primary outcome, HCC surveillance in both intervention groups remained below 30%, highlighting a need for more intensive interventions.

Despite literature demonstrating HCC surveillance underuse in cirrhosis patients, few studies have evaluated interventions to increase surveillance. Two small studies suggested a benefit of nursing protocols and automated reminders, but both were conducted among selected patients followed by hepatologists.[21] In clinical practice, primary care providers are often responsible for liver-related care of cirrhosis patients, particularly in rural areas where access to subspecialty care is limited.[22] Primary care

providers report several barriers to HCC surveillance, including inadequate knowledge and clinic time constraints, so it is unclear whether these interventions would be equally effective among these patients.[23] Another study suggested that EMR clinical reminders may increase HCC surveillance among cirrhosis patients followed by primary care providers, but this study relied on visit-based care and only included patients with documented cirrhosis.[24] Our study suggests that mailed outreach invitations can be an effective population health strategy to increase HCC surveillance among at-risk patients. Compared with other interventions, our mailed outreach strategy can increase surveillance participation among patients not regularly engaged in clinical care and those with suspected cirrhosis but without documented ICD-10 codes, who represent over one-third of patients failing to receive HCC surveillance.[16]

Prior intervention studies only examined one-time or intermittent HCC surveillance completion, with none evaluating semi-annual surveillance, as recommended by AASLD guidelines. Our study extends this literature by demonstrating mailed outreach strategies, and patient navigation can increase HCC surveillance over longer periods of time. This is important because cirrhosis patients have a 2% to 4% annual risk of developing HCC. HCC surveillance at regular intervals is critical to identifying incident cancer at an early stage.[25,26] Our primary outcome of HCC surveillance moves a step closer to evaluating screening process completion, which includes initial screening, repeat screening among patients with normal screen results, and diagnostic evaluation among those with abnormal screen results. This distinction is important, as studies have demonstrated failures at each step in the HCC screening process.[9,27-29] Although semi-annual HCC surveillance is a more rigorous outcome than prior studies, this still represents an imperfect surrogate for clinical outcomes including early HCC detection and improved survival. Although we found no significant differences in early HCC detection among groups, our study was not powered to detect differences in tumor stage or survival. The lack of statistical power in our study was exacerbated by a lower than anticipated HCC incidence rate. It is unclear whether this was related to a lower incidence given increased dissemination of hepatitis C antiviral therapy and shift to nonviral cirrhosis, pragmatic trial design and imperfect specificity of ICD-9 codes for presence of cirrhosis, or ascertainment bias over the relatively short 18-

month duration of the trial. An ongoing multicenter study is evaluating the effect of outreach strategies to improve outcomes such as screening process completion and early HCC detection, although this trial is years away from reporting.

We found that patient navigation increased HCC surveillance every 6 months compared with outreach alone, with the benefit being more pronounced in a secondary analysis evaluating surveillance every 7 months. Prior studies have suggested high patient acceptance of HCC surveillance, although patient barriers, including challenges with scheduling and transportation, are associated with lower surveillance participation.[30,31] Patient navigation is an effective strategy to address screening barriers for other cancer screening programs but has not been previously evaluated for HCC surveillance.[12,32] Despite demonstrated effectiveness, less than one-third of patients receiving outreach and navigation in this study underwent HCC surveillance, highlighting a need for more intensive interventions. Patient navigation in our study consisted of only barrier assessment, motivational education, and assistance with ultrasound scheduling. More extensive navigation to overcome barriers, such as transportation assistance or evening/weekend ultrasound appointments so patients do not miss work, may be effective and warrant evaluation. Alternatively, prior studies have shown receipt of subspecialty care is significantly associated with higher surveillance rates, so efforts to increase referrals may be effective for systems with sufficient hepatology capacity.

This study had the following limitations. First, our study was conducted in a safety-net health system and results may not generalize to other health systems. However, racially diverse, socioeconomically disadvantaged patients represent a difficult-to-reach population and are important to study, given lower HCC surveillance receipt and higher HCC mortality rates.[33,34] Second, patients may have received abdominal imaging at outside institutions; however, this is unlikely because many patients did not have insurance for care outside of the safety-net health system. Furthermore, we would not expect receipt of surveillance imaging at outside institutions to differ among study groups given the randomized nature of the study. Third, low-surveillance completion may be partly explained by patients no longer following at Parkland or having contraindications to screening (e.g., increased comorbidity or liver

function deterioration), which may be underrecognized given the trial's pragmatic design. Fourth, we could not differentiate imaging indication (diagnostic versus screening purposes); however, imaging for either purpose is sufficient for surveillance completion.

This study has several strengths including its large sample size with various cirrhosis etiologies, racially and socioeconomically diverse patient population, and innovation in comparing mailed outreach with and without patient navigation to promote HCC surveillance over 18 months. Our trial's pragmatic design also avoided volunteer bias, included cirrhosis patients with minimal exclusion criteria, and used processes (ultrasound scheduling, outcome ascertainment, and results notification) that could easily be adopted into clinical care.[35]

In summary, mailed outreach invitations are effective for increasing HCC surveillance among cirrhosis patients. Adding patient navigation to the outreach strategy further increased HCC surveillance. Given the pervasive nature of HCC-screening underuse among cirrhosis patients, mailed outreach with or without patient navigation can be an effective strategy for improving HCC screening delivery.

*Acknowledgments:*
The authors would like to thank Blue Faery: The Adrienne Wilson Liver Cancer Association for their help and support of this project. *Author contributions:* Dr. Singal had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design belong to Singal, Tiro, and Halm; acquisition, analysis, and interpretation of the data belong to Singal, Tiro, Murphy, Marrero, McCallister, Fullington, Mejias, Waljee, Bishop, Santini, and Halm; Singal drafted the manuscript; critical revision of the manuscript for important intellectual content was done by Singal, Tiro, Murphy, Marrero, McCallister, Fullington, Mejias, Waljee, Bishop, Santini, and Halm; Singal and Halm obtained funding; Singal and Halm provided the administrative, technical, and material support; and Singal supervised the study.

<REF>**References**</REF>

1) Bertuccio P, Turati F, Carioli G, Rodriguez T, La Vecchia C, Malvezzi M, et al. Global trends and predictions in hepatocellular carcinoma mortality. J Hepatol 2017;67:302-309.
2) El-Serag HB. Epidemiology of viral hepatitis and hepatocellular carcinoma. Gastroenterology 2012;142:1264-1273,e1261.
3) Bruix J, Sherman M. Management of hepatocellular carcinoma: an update. H<SC>epatology</SC> 2010;53:1-35.
4) Zhang BH, Yang BH, Tang ZY. Randomized controlled trial of screening for hepatocellular carcinoma. J Cancer Res Clin Oncol 2004;130:417-422.
5) Singal AG, Pillai A, Tiro J. Early detection, curative treatment, and survival rates for hepatocellular carcinoma surveillance in patients with cirrhosis: a meta-analysis. PLoS Med 2014;11:e1001624.
6) Singal AG, Mittal S, Yerokun OA, Ahn C, Marrero JA, Yopp AC, et al. Hepatocellular carcinoma screening associated with early tumor detection and improved survival among patients with cirrhosis in the US. Am J Med 2017;130:1099-1106,e1091.
7) van Meer S, de Man RA, Coenraad MJ, Sprengers D, van Nieuwkerk KM, Klümpen HJ, et al. Surveillance for hepatocellular carcinoma is associated with increased survival: results from a large cohort in the Netherlands. J Hepatol 2015;63:1156-1163.
8) Breen N, Meissner HI. Toward a system of cancer screening in the United States: trends and opportunities. Annu Rev Public Health 2005;26:561-582.
9) Singal AG, Yopp A, C SS, Packer M, Lee WM, Tiro JA. Utilization of hepatocellular carcinoma surveillance among American patients: a systematic review. J Gen Intern Med 2012;27:861-867.
10) Singal AG, Tiro J, Li X, Adams-Huet B, Chubak J. Hepatocellular carcinoma surveillance among patients with cirrhosis in a population-based integrated health care delivery system. J Clin Gastroenterol 2017;51:650-655.
11) Genoff MC, Zaballa A, Gany F, Gonzalez J, Ramirez J, Jewell ST, et al. Navigating language barriers: a systematic review of patient navigators' impact on cancer

screening for limited English proficient patients. J Gen Intern Med 2016;31:426-434.

12) Krok-Schoen JL, Oliveri JM, Paskett ED. Cancer care delivery and women's health: the role of patient navigation. Front Oncol 2016;6:2.
13) Muliira JK, D'Souza MS. Effectiveness of patient navigator interventions on uptake of colorectal cancer screening in primary care settings. Jpn J Nurs Sci 2016;13:205-219.
14) Singal AG, Gupta S, Skinner CS, Ahn C, Santini NO, Agrawal D, et al. Effect of colonoscopy outreach vs fecal immunochemical test outreach on colorectal cancer screening completion: a randomized clinical trial. JAMA 2017;318:806-815.
15) Singal AG, Tiro JA, Marrero JA, McCallister K, Mejias C, Adamson B, et al. Mailed outreach program increases ultrasound screening of patients with cirrhosis for hepatocellular carcinoma. Gastroenterology 2017;152:608-615,e604.
16) Singal AG, Yopp AC, Gupta S, Skinner CS, Halm EA, Okolo E, et al. Failure rates in the hepatocellular carcinoma surveillance process. Cancer Prev Res (Phila) 2012;5:1124-1130.
17) Nehra MS, Ma Y, Clark C, Amarasingham R, Rockey DC, Singal AG. Use of administrative claims data for identifying patients with cirrhosis. J Clin Gastroenterol 2013;47:e50-e54.
18) Abd El Rihim AY, Omar RF, Fathalah W, El Attar I, Hafez HA, Ibrahim W. Role of fibroscan and APRI in detection of liver fibrosis: a systematic review and meta-analysis. Arab J Gastroenterol 2013;14:44-50.
19) Trevisani F, De Notariis S, Rapaccini G, Farinati F, Benvegnù L, Zoli M, et al. Semiannual and annual surveillance of cirrhotic patients for hepatocellular carcinoma: effects on cancer stage and patient survival (Italian experience). Am J Gastroenterol 2002;97:734-744.
20) Mokdad A, Browning T, Mansour JC, Zhu H, Singal AG, Yopp AC. Implementation of a voice messaging system is associated with improved time-to-treatment and overall survival in patients with hepatocellular carcinoma. J Natl Compr Canc Netw 2016;14:38-46.

21) Wigg AJ, McCormick R, Wundke R, Woodman RJ. Efficacy of a chronic disease management model for patients with chronic liver failure. Clin Gastroenterol Hepatol 2013;11:850-858,e851-854.
22) Singal AG, Li X, Tiro J, Kandunoori P, Adams-Huet B, Nehra MS, et al. Racial, social, and clinical determinants of hepatocellular carcinoma surveillance. Am J Med 2015;128:e1-7.
23) Dalton-Fitzgerald E, Tiro J, Kandunoori P, Halm EA, Yopp A, Singal AG. Practice patterns and attitudes of primary care providers and barriers to surveillance of hepatocellular carcinoma in patients with cirrhosis. Clin Gastroenterol Hepatol 2015;13:791-798.
24) Beste LA, Ioannou GN, Yang Y, Chang MF, Ross D, Dominitz JA. Improved surveillance for hepatocellular carcinoma with a primary care-oriented clinical reminder. Clin Gastroenterol Hepatol 2015;13:172-179.
25) Lok AS, Seeff LB, Morgan TR, di Bisceglie AM, Sterling RK, Curto TM, et al. Incidence of hepatocellular carcinoma and associated risk factors in hepatitis C-related advanced liver disease. Gastroenterology 2009;136:138-148.
26) Ascha MS, Hanouneh IA, Lopez R, Tamimi TA, Feldstein AF, Zein NN. The incidence and risk factors of hepatocellular carcinoma in patients with nonalcoholic steatohepatitis. H<SC>epatology</SC> 2010;51:1972-1978.
27) Singal AG, Tiro JA, Gupta S. Improving hepatocellular carcinoma screening: applying lessons from colorectal cancer screening. Clin Gastroenterol Hepatol 2013;11:472-477.
28) Patel N, Yopp AC, Singal AG. Diagnostic delays are common among patients wtih hepatocellular carcinoma. J Natl Compr Canc Netw 2015;13:543-549.
29) Singal AG, Waljee AK, Patel N, Chen EY, Tiro JA, Marrero JA, et al. Therapeutic delays lead to worse survival among patients with hepatocellular carcinoma. J Natl Compr Canc Netw 2013;11:1101-1108.
30) Singal A, Volk M, Rakoski MO, Fu S, Su GL, McCurdy H, et al. Patient involvement in healthcare is associated with higher rates of surveillance for hepatocellular carcinoma. J Clin Gastroenterol. 2011;45:727-732.

31) Farvardin S, Patel J, Khambaty M, Yerokun OA, Mok H, Tiro JA, et al. Patient-reported barriers are associated with lower hepatocellular carcinoma surveillance rates in patients with cirrhosis. H<SC>epatology</SC> 2017;65:875-884.
32) Percac-Lima S, Ashburner JM, Zai AH, Chang Y, Oo SA, Guimaraes E, et al. Patient navigation for comprehensive cancer screening in high-risk patients using a population-based health information technology system: a randomized clinical trial. JAMA Intern Med 2016;176:930-937.
33) Artinyan A, Mailey B, Sanchez-Luege N, Khalili J, Sun CL, Bhatia S, et al. Race, ethnicity, and socioeconomic status influence the survival of patients with hepatocellular carcinoma in the United States. Cancer 2010;116:1367-1377.
34) Ha J, Yan M, Aguilar M, Tana M, Liu B, Frenette CT, et al. Race/ethnicity-specific disparities in hepatocellular carcinoma stage at diagnosis and its impact on receipt of curative therapies. J Clin Gastroenterol 2016;50:423-430.<zaq;2>

**FIG. 1.** Study consort diagram**.**

**FIG. 2.** HCC surveillance completion over 18-month study period by intervention group (HCC surveillance was defined as receipt of abdominal imaging during each 6-month period after randomization). Compared with usual care, HCC surveillance was significantly higher in the outreach-alone (+10.5%; 95% CI: 6.8%-14.2%) and outreach/navigation (+16.0%; 95% CI: 12.0%-20.0%) groups ($P < 0.001$ for both). Adding navigation to outreach increased the surveillance proportion by 5.5% (95% CI: 0.9%-10.1%; $P = 0.02$).

**TABLE 1 Characteristics of Cirrhosis Patients Enrolled in a Pragmatic Randomized Clinical Trial Promoting HCC Surveillance, Overall and by Study Group**

| | Usual Care (n = 600) | Outreach Alone (n = 600) | Outreach/ Navigation (n = 600) | Total (n = 1800) |
|---|---|---|---|---|
| Age (years) | | | | |
| 21-50 | 183 (30.5) | 174 (29.0) | 158 (26.3) | 515 (28.6) |
| 51-60 | 259 (43.2) | 272 (45.3) | 269 (44.8) | 800 (44.4) |
| 61-90 | 158 (26.3) | 154 (25.7) | 173 (28.8) | 485 (26.9) |
| Male sex (%) | 350 (58.3) | 361 (60.2) | 358 (59.7) | 1069 (59.4) |
| Race/ethnicity (%) | | | | |
| Non-Hispanic white | 182 (30.3) | 165 (27.5) | 163 (27.2) | 510 (28.3) |
| Hispanic white | 217 (36.2) | 230 (38.3) | 234 (39.0) | 681 (37.8) |
| Non-Hispanic black | 186 (31.0) | 197 (32.8) | 195 (32.5) | 578 (32.1) |
| Other/Unknown | 15 (2.5) | 8 (1.3) | 8 (1.3) | 31 (1.7) |
| Etiology of liver disease (%) | | | | |
| Hepatitis C | 320 (53.3) | 285 (47.5) | 313 (52.2) | 918 (51.0) |
| Alcohol-related | 98 (16.3) | 115 (19.2) | 104 (17.3) | 317 (17.6) |
| Nonalcoholic steatohepatitis | 104 (17.3) | 101 (16.8) | 94 (15.7) | 299 (16.6) |
| Hepatitis B | 21 (3.5) | 27 (4.5) | 14 (2.3) | 62 (3.4) |
| Other/unknown | 57 (9.5) | 72 (12.0) | 75 (12.5) | 204 (11.3) |
| Presence of documented cirrhosis (%)* | 472 (78.7) | 479 (79.8) | 482 (80.3) | 1433 (79.6) |
| Hepatic decompensation (%)† | 181 (30.2) | 192 (32.0) | 201 (33.5) | 574 (31.9) |
| Child-Pugh class (% Child A)‡ | 432 (72.0) | 435 (72.5) | 424 (70.7) | 1291 (71.7) |
| Charlson comorbidity index (%)† | | | | |
| 0 | 76 (12.7) | 95 (15.8) | 79 (13.2) | 250 (13.9) |
| 1 | 140 (23.3) | 143 (23.8) | 149 (24.8) | 432 (24.0) |
| 2 | 103 (17.2) | 99 (16.5) | 84 (14.0) | 286 (15.9) |
| 3+ | 281 (46.8) | 263 (43.8) | 288 (48.0) | 832 (46.2) |
| Number of primary care visits† | 4 (IQR 2-7) | 3 (IQR 2-7) | 4 (IQR 2-7) | 4 (IQR 2-7) |

| Intervention Group | Completed HCC Surveillance* (n) | Proportion Completed Surveillance (95% CI) | Difference in Proportion Completing HCC Surveillance by Intervention Group (95% CI) | |
|---|---|---|---|---|
| | | | vs. Usual Care | vs. Outreach Alone |
| Outreach/navigation (n = 600) | 140 | 23.3 (20.0-26.9) | +16.0 (12.0-20.0) | +5.5 (0.9-10.1) |

| | Usual Care (n = 600) | Outreach Alone (n = 600) | Outreach/ Navigation (n = 600) | Total (n = 1800) |
|---|---|---|---|---|
| Receipt of hepatology care† | 153 (25.5) | 153 (25.5) | 157 (26.2) | 463 (25.7) |

*Defined using ICD-9 codes for cirrhosis or cirrhosis-related complications.

†During year prior to randomization.

‡Defined using validated measure based on EMR data.[26]

Abbreviation: IQR, interquartile range.

Outre
(n = 6

Usual
(n = 6

| Intervention Group | Any-Stage HCC Diagnosis | | Early-Stage HCC Diagnosis* | |
|---|---|---|---|---|
| | n | Study Group Percentage (95% CI) | n | HCC Diagnoses in Study Group Percentage (95% CI) |
| Outreach/navigation (n = 600) | 11 | 1.8 (0.9-3.3) | 7 of 11 | 63.6 (30.8-89.1) |
| Outreach alone (n = 600) | 6 | 1.0 (0.4-2.2) | 4 of 6 | 66.7 (22.3-95.7) |
| Usual care (n = 600) | 14 | 2.3 (1.3-3.9) | 8 of 14 | 57.1 (28.9-82.3) |

**TABLE 2 HCC Surveillance Completion Over 18-Month Study Period**

*HCC surveillance was defined as receipt of abdominal imaging during each 6-month period after randomization.

**TABLE 3 Hepatocellular Carcinoma Surveillance Outcomes by Study Group**

*Early HCC was defined as BCLC stage 0 or stage A.

<H1>**Supporting Information**</H1>

Additional Supporting Information may be found in the online version of this article at http://onlinelibrary.wiley.com/doi/10.1002/hep.xxxxx/suppinfo.

AQ1: Please confirm or correct the names of the authors, the affiliations, and the correspondence footnote (include academic degrees of the correspondence author up to highest achieved).

AQ2: For all listed citations with two or more authors who share first authorship, HEPATOLOGY stipulates those authors' names to be in bold type. It is the authors' responsibility to ensure that these names appear in bold in the reference section when

submitting a manuscript. This allows giving due credit to joint first authors. Also, please include the phrase, ‘Author names in bold designate shared co-first authorship’ at the end of the references section if you have citations that have joint first authors. Please see author guidelines for further details.

**Table 1:** Characteristics of cirrhosis patients enrolled in a pragmatic randomized clinical trial promoting HCC surveillance, overall and by study group

| | **Usual Care n=600** | **Outreach Alone n=600** | **Outreach/ Navigation n=600** | **Total N=1,800** |
|---|---|---|---|---|
| Age (years) | | | | |
| 21-50 | 183 (30.5) | 174 (29.0) | 158 (26.3) | 515 (28.6) |
| 51-60 | 259 (43.2) | 272 (45.3) | 269 (44.8) | 800 (44.4) |
| 61-90 | 158 (26.3) | 154 (25.7) | 173 (28.8) | 485 (26.9) |
| Male sex (%) | 350 (58.3) | 361 (60.2) | 358 (59.7) | 1,069 (59.4) |
| Race/Ethnicity (%) | | | | |
| Non-Hispanic White | 182 (30.3) | 165 (27.5) | 163 (27.2) | 510 (28.3) |
| Hispanic White | 217 (36.2) | 230 (38.3) | 234 (39.0) | 681 (37.8) |
| Non-Hispanic Black | 186 (31.0) | 197 (32.8) | 195 (32.5) | 578 (32.1) |
| Other/Unknown | 15 (2.5) | 8 (1.3) | 8 (1.3) | 31 (1.7) |
| Etiology of Liver Disease (%) | | | | |
| Hepatitis C | 320 (53.3) | 285 (47.5) | 313 (52.2) | 918 (51.0) |
| Alcohol-related | 98 (16.3) | 115 (19.2) | 104 (17.3) | 317 (17.6) |
| Nonalcoholic steatohepatitis | 104 (17.3) | 101 (16.8) | 94 (15.7) | 299 (16.6) |
| Hepatitis B | 21 (3.5) | 27 (4.5) | 14 (2.3) | 62 (3.4) |
| Other/unknown | 57 (9.5) | 72 (12.0) | 75 (12.5) | 204 (11.3) |
| Presence of documented cirrhosis (%)[1] | 472 (78.7) | 479 (79.8) | 482 (80.3) | 1,433 (79.6) |
| Hepatic decompensation (%)[2] | 181 (30.2) | 192 (32.0) | 201 (33.5) | 574 (31.9) |
| Child Pugh Class (% Child A)[3] | 432 (72.0) | 435 (72.5) | 424 (70.7) | 1,291 (71.7) |

| Intervention Group | Completed HCC Surveillance [a] (n) | Proportion Completed Surveillance (95% CI) | Difference in Proportion Completing HCC Surveillance by Intervention Group (95% CI) |
|---|---|---|---|



| | Usual Care n=600 | Outreach Alone n=600 | Outreach/ Navigation n=600 | Total N=1,800 |
|---|---|---|---|---|
| Charlson Comorbidity Index (%)[2] | | | | |
| 0 | 76 (12.7) | 95 (15.8) | 79 (13.2) | 250 (13.9) |
| 1 | 140 (23.3) | 143 (23.8) | 149 (24.8) | 432 (24.0) |
| 2 | 103 (17.2) | 99 (16.5) | 84 (14.0) | 286 (15.9) |
| 3+ | 281 (46.8) | 263 (43.8) | 288 (48.0) | 832 (46.2) |
| Number of primary care visits[2] | 4 (IQR 2-7) | 3 (IQR 2-7) | 4 (IQR 2-7) | 4 (IQR 2-7) |
| Receipt of hepatology care[2] | 153 (25.5) | 153 (25.5) | 157 (26.2) | 463 (25.7) |

IQR – interquartile range

[1] Defined using ICD-9 codes for cirrhosis or cirrhosis-related complications

[2] During year prior to randomization

[3] Defined using validated measure based on EMR data[26]

| | vs. Usual Care | vs. Outreach Alone |
|---|---|---|

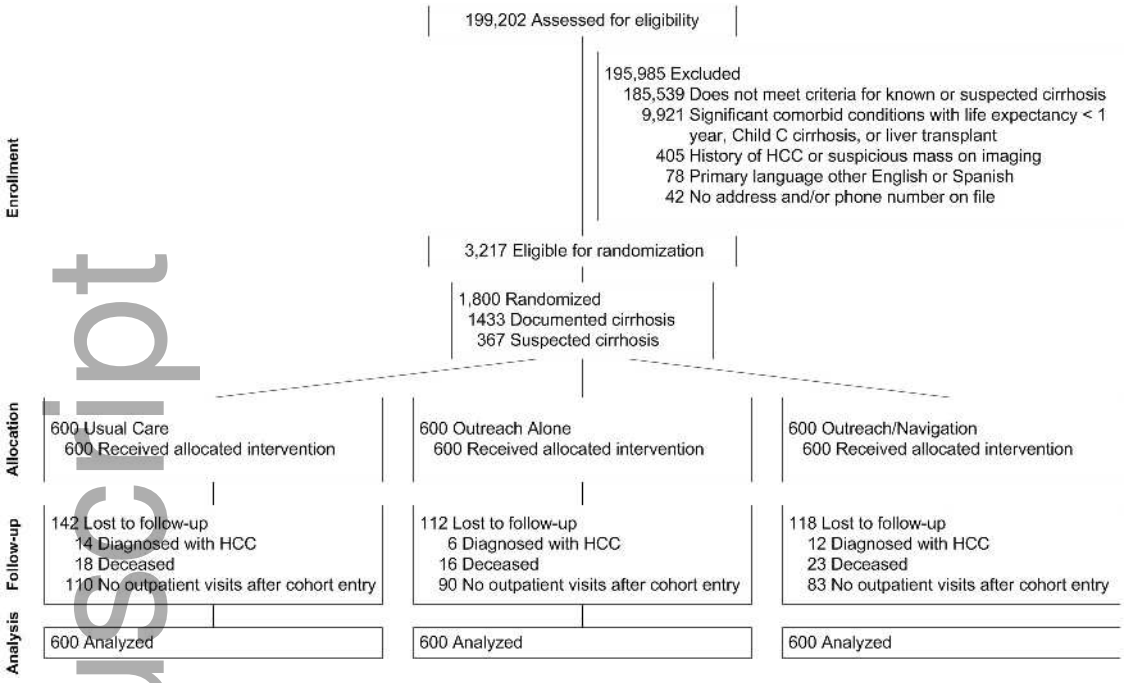
| Intervention Group | Any Stage HCC Diagnosis | | Early Stage HCC Diagnosis [a] | |
|---|---|---|---|---|
| | ***n*** | ***% of study group, (95% CI)*** | ***n*** | ***% of all HCC diagnoses in study group (95% CI)*** |
| Outreach/Navigation (n=600) | 11 | 1.8 (0.9 – 3.3) | 7 of 11 | 63.6 (30.8 – 89.1) |
| Outreach Alone (n=600) | 6 | 1.0 (0.4 – 2.2) | 4 of 6 | 66.7 (22.3 – 95.7) |
| Usual Care (n=600) | 14 | 2.3 (1.3 – 3.9) | 8 of 14 | 57.1 (28.9 – 82.3) |

**Table 2.** HCC surveillance completion over 18-month study period

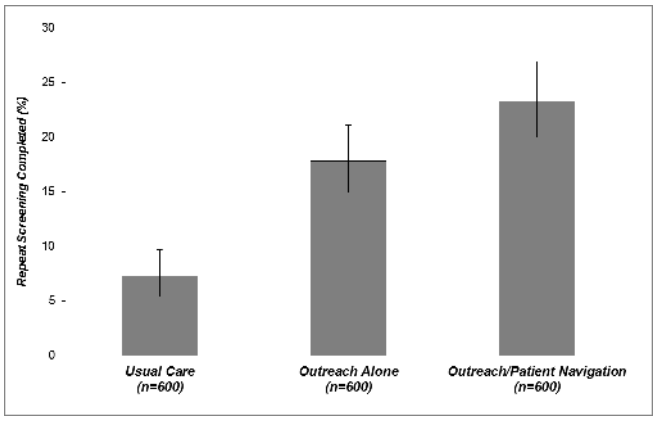
[a] HCC surveillance was defined as receipt of abdominal imaging during each 6-month period after randomization.

**Table 3.** Hepatocellular carcinoma surveillance outcomes, by study group

[a] Early HCC was defined as Barcelona Clinic Liver Cancer (BCLC) stage 0 or stage A.




hep_30129_f1.tif




hep_30129_f2.tiff