Evaluation of Abdominal Ultrasonography Mass Screening for Hepatocellular Carcinoma in Taiwan

Yen-Po Yeh,1 Tsung-Hui Hu,2 Po-Yuan Cho,3 Hsiu-Hsi Chen,4 Amy Ming-Fang Yen,5 Sam Li-Sheng Chen,5 Sherry Yueh-Hsia Chiu,6 Jean Ching-Yuan Fann,7 Wei-Wen Su,8 Yi-Jen Fang,9 Shih-Tien Chen,10 Hsiao-Ching San,1 Hung-Pin Chen,11 and Chao-Sheng Liao,12,13 Changhua Community-Based Abdominal Ultrasonography Screening Group

Mass screening with abdominal ultrasonography (AUS) has been suggested as a tool to control adult hepatocellular carcinoma (HCC) in individuals, but its efficacy in reducing HCC mortality has never been demonstrated. This study aimed to assess the effectiveness of reducing HCC mortality by mass AUS screening for HCC based on a program designed and implemented in the Changhua Community-based Integrated Screening (CHCIS) program with an efficient invitation scheme guided by the risk score. We invited 11,114 (27.0%) of 41,219 eligible Taiwanese subjects between 45 and 69 years of age who resided in an HCC high-incidence area to attend a risk score-guided mass AUS screening between 2008 and 2010. The efficacy of reducing HCC mortality was estimated. Of the 8,962 AUS screening attendees (with an 80.6% attendance rate), a total of 16 confirmed HCC cases were identified through community-based ultrasonography screening. Among the 16 screen-detected HCC cases, only two died from HCC, indicating a favorable survival. The cumulative mortality due to HCC (per 100,000) was considerably lower in the invited AUS group (17.26) compared with the uninvited AUS group (42.87) and the historical control group (47.51), yielding age- and gender-adjusted relative mortality rates of 0.69 (95% confidence interval [CI]: 0.56-0.84) and 0.63 (95% CI: 0.52-0.77), respectively. Conclusion: The residents invited to community-based AUS screening for HCC, compared with those who were not invited, showed a reduction in HCC mortality by ~31% among subjects aged 45-69 years who had not been included in the nationwide vaccination program against hepatitis B virus infection. (HEPATOLOGY 2014;59:1840-1849)

Hepatocellular carcinoma (HCC) is still one of the leading causes of death worldwide, and HCC prevention is a major public health issue. Hepatitis B (HBV) and C virus (HCV) infections are believed to be the most important risk factors for HCC. Despite a nationwide HBV vaccination program, which has existed in Taiwan since 1984 and has already shown a reduction in HBV infection and the incidence of pediatric liver cancer,1 subjects aged 40 years or older who were born before the nationwide vaccination program are not protected by earlier vaccination. Secondary prevention by screening is thus considered an alternative approach to controlling HCC mortality. This is particularly important because the...
early detection and treatment of HCC improves the chances of survival.2,3

In the 1990s, a two-stage screening program for HCC was adopted in Taiwan. Attendees were given serological examinations as an initial screening step. Those positive for hepatitis B surface antigen (HBsAg) or anti-HCV antibodies, alpha-fetoprotein (AFP) \(\geq 20\) ng/mL, aspartate transaminase (AST) \(\geq 40\) IU/L, alanine transaminase (ALT) \(\geq 45\) IU/L, and a family history of HCC were identified as high risk and referred for ultrasonography. In the group identified as high risk, there was a 41% mortality reduction among those attending ultrasonography screenings compared with nonattendees.4 Later, to enhance the attendance rate, a two-stage screening program was integrated with screens for other neoplastic and nonneoplastic diseases.5 However, a proportion of patients with HCC do not express the five markers listed above. For example, patients with type 2 diabetes5,6 or low platelet counts7 have an increased risk for HCC compared with those in the normal range.

To control HCC on a population scale, rather than focusing on high-risk individuals, abdominal ultrasonography (AUS) of the general population may be useful. However, applying universal ultrasonography screening to the general population may not be efficient because detecting HCC is highly dependent on the extent of an individual’s risk for HCC. Attendees who participate in the early population-based screening service often belong to a low-risk group, and the screening results are thus heavily biased in a favorable direction in the early phase. To design an efficient population-based AUS screening program, it is important to consider a risk score-based approach for inviting eligible community residents.

The current study was designed and implemented to assess the effectiveness of reducing HCC mortality using risk score-guided mass ultrasonography screening for HCC based on a program designed and implemented in Changhua County, Taiwan, in October 2008.

**Materials and Methods**

**Study Population.** A community-based mass screening for AUS was designed and targeted at community residents aged 45-69 years in the Changhua County of central Taiwan, a county with a high incidence of HCC. Before the mass HCC screening with AUS, this county had conducted a community-based integrated screening program, the Changhua Community-based Integrated Screening (CHCIS) program, since 2005. The CHCIS program is similar to the Keelung Community-based Integrated Screening (KCIS) program in northern Taiwan, which screens for liver cancer and other neoplastic diseases (breast cancer, colorectal cancer, oral cancer, and cervical cancer) and nonneoplastic diseases (hyperlipidemia, hypertension, and hyperglycemia).5,8 We had adopted a two-stage screening program for HCC that was previously used in the CHCIS program prior to October 2008, when mass screening with AUS was conducted. The details of the two-stage approach have been fully described elsewhere.4 Briefly, subjects who were positive for the HBsAg or anti-HCV antibody or who had high alpha-fetoprotein (\(\geq 20\) ng/mL), AST (\(\geq 45\) IU/L), and ALT (\(\geq 45\) IU/L) levels were referred for ultrasonography performed by gastroenterologists in hospitals or clinics. Note that the information on these five biomarkers (generated from the two-stage approach) together with low platelet counts and type 2 diabetes, which are also regarded as significant risk factors for HCC6,7 and were obtained from diabetes screening and routine biochemical tests in the CHCIS program, were used to derive the risk score that enabled us to invite eligible candidates to attend the mass screening for HCC AUS; the invitation scheme was prioritized by individual HCC risk score.

Figure 1 shows a total of 41,412 community residents aged 45-69 years who had been invited and attended the CHCIS program between 2005 and September 2008. An outreach service screening for HCC has been initiated and provided for 41,412 eligible residents aged 45-69 years since October 2008 by inviting them to the local health center to undergo AUS delivered by board-certified gastroenterologists.

The eligible population invited to undergo AUS comprised 41,219 community residents after excluding deaths and those individuals who were diagnosed with...
HCC prior to being invited to undergo AUS among the 41,412 residents participating in the CHCIS program.

**Study Design for Mass Screening.** A total of 11,114 (out of 41,219) residents were invited to undergo AUS through the end of 2010. This group was called "the invited AUS group," which consisted of 8,962 attendees receiving AUS (the AUS group) and 2,152 nonattendees who did not receive AUS (the non-AUS group) (Fig. 1). There were two comparison groups for the invited AUS group in the subsequent analysis of the efficacy of the AUS. A total of 329,301 community residents aged 45-69 had not attended the CHCIS program and were not invited to undergo AUS but resided in Changhua during the same period as the invited AUS group; they were categorized as the first comparison group: "the uninvited AUS group." The other comparison group was obtained from 2003, the year before the introduction of the CHCIS program, and was defined as "the historical control group." All participants provided written informed consent. The Ethics Committee / Institutional Review Board of Shin Kong Wu Ho-Su Memorial Hospital approved the study (No. 97E-044).

**Derivation and Validation of the Risk Score for Predicting HCC.** For efficient completion of the AUS screening, we gave priority to inviting community residents in accordance with the HCC risk score for each screened subject. The derivation of the risk score for predicting HCC was based on participants in the KCIS program between 1999 and 2002, which targeted residents aged 20 years and older in Keelung City, Taiwan. As previously mentioned, a two-stage
biomarker-ultrasound method was adopted for HCC screening in the KCIS program. Predictors used in deriving the risk score and the outcome of HCC ascertained after follow-up of the entire cohort were collected. A total of 99 patients with HCC were identified out of 44,125 participants in the KCIS program with full information on predictors. These empirical data were used for training the clinical weight of each attribute (trained dataset). The data used were baseline covariates taken from participant attendance in the first screen. Internal validation with the trained dataset from the KCIS program was performed by comparing the observed numbers with the expected ones using the Hosmer and Lemeshow (H&L) goodness-of-fit test and the area under the curve (AUC) of the receiver operating characteristic (ROC) curve. To further validate the adequacy of the proposed model, we also performed external validation with the validated dataset based on the current CHCIS cohort. A total of 40,620 subjects between the ages of 45 and 69 were the target population, from whom 28 HCCs were diagnosed with the two-stage screening program; 16 additional confirmatory HCCs were identified with the ultrasonography mass screen.

**Risk Score-Guided Invitation.** Based on the risk score assigned to each participant, we invited eligible subjects with a referred risk score, which were divided into four groups. Because positive HBsAg and anti-HCV are two dominant risk factors for HCC, we classified the eligible subjects into two groups: subjects positive for HBsAg or anti-HCV (Group A) and subjects free of these hepatitis virus infections (Group B). The risk scores were therefore stratified into these two groups. In each group we computed the risk score using information on age, gender, biochemical test results, and diabetes mellitus, collected from the CHCIS program. For time-dependent biomarkers such as AST, ALT, AFP, and platelets, the most recent results were used. The risk scores for the two groups were calculated as follows:

For Group A:
\[
\text{Risk score for Group A} = \alpha_1 + \beta_1 \times \text{Age} + \beta_2 \times (\text{Male}) \\
+ \beta_3 \times (\text{AFP} \geq 20 \text{ng/mL}) + \beta_4 \times (\text{AST} \geq 45 \text{IU/L}) \\
+ \beta_5 \times (\text{Platelet count} < 150 \times 10^3)
\]

For Group B:
\[
\text{Risk score for Group B} = \alpha_2 + \beta_1 \times \text{Age} + \beta_2 \times (\text{Male}) \\
+ \beta_3 \times (\text{Type 2 diabetes}) + \beta_4 \times (\text{ALT} \geq 45 \text{IU/L}) \\
+ \beta_5 \times (\text{Platelet count} < 150 \times 10^3)
\]

where each beta represents the clinical weight (regression coefficient) for each predictor.

Given the risk scores, the priority for an invitation to undergo AUS was taken by four groups. Subjects in Group A were divided into extremely high-risk and high-risk groups based on whether their scores were above or equal to and below the median risk score in Group A, respectively. The risks in Group B were classified as intermediate- and low-risk based on scores above or equal to and below the third quartile of the risk score, respectively. Note that the classification of risk groups based on the risk score was tailored for the priority of invitation with efficiency and not for HCC screening. The cutoff was simply used to set priority for the invitation groups. Therefore, the selection of the median for Group A and the third quantile for Group B was arbitrary to enable feasibility of invitation priority.

**Invitation Scheme.** We invited the subjects to have an AUS performed by prioritizing invitations based on the risk score calculated above with a phased-in approach. In the first period (Oct. 2008 to about Jan. 2009), the eligible population was derived from those residents attending the CHCIS between 2005 and 2007. Among 26 townships, the invited subjects in each town consisted of 60 patients with the highest score selected from those who were screened within an interval of 2-4 weeks between October 2008 and January 2009. During the second period (Feb. 2009 to about Mar. 2009), the eligible population was generated from CHCIS attendees in 2008. Each town was given the list of the 40 highest scores and the 41-90 highest scores between February and March. In the third phase (Apr. 2009 to about Dec. 2010), invitations targeted Group A because Group B had a lower incidence of HCC cases.

**Clinical Surveillance and Confirmatory Diagnosis of HCC.** After the scheduled on-site ultrasonography screening, suspected HCC cases and subjects with abnormal findings, as judged by the gastroenterologists, were referred to medical centers or regional hospitals in Changhua County to confirm HCC. All confirmatory HCCs were confirmed with biopsies or dynamic imaging studies with computerized tomography (CT) or magnetic resonance imaging (MRI). HCC diagnoses were made in accordance with the American Association for the Study of Liver Diseases (AASLD) practice guidelines. Hepatic hemangiomas were recognized with typical echogenicity in ultrasonography and characteristic dynamic enhancement CT or MRI images. The focal liver lesions with undetermined diagnosis were classified as liver nodules and scheduled surveillance was assigned to patients with these lesions. All medical records of patients with abnormal ultrasonography findings (cirrhosis, liver parenchyma disease, focal liver lesions) were reviewed by clinical committees in the Changhua County Public
Health Bureau. The standard of care and clinical surveillance for people with abnormal findings were also evaluated by clinical committees. The surveillance data were reviewed and monitored at 3- to 6-month intervals after the initial screening. Case managers (public health nurses) were informed to enhance adherence to the clinical surveillance plan when necessary. All referred cases were recommended to undergo clinical surveillance with the different intervals determined by gastroenterologists in medical centers or clinical committees in the Changhua County Public Health Bureau. The protocol and flow chart for the Changhua County ultrasonography screening program are shown in Figs. 1 and 2, respectively.

**Operator Reliability.** To assess the reliability of the AUS operators, we selected 35 attendees distributed across two sessions of ultrasonography screenings. In each setting, every participant was independently screened by two gastroenterologists; one was the routine operator for the current project, and the other was a senior gastroenterologist who was also a member of the clinical committee (gold standard) in the Changhua County Public Health Bureau. Among 35 examinees, the kappa coefficients for HCC and liver cirrhosis were both 1.00, which may have been due to chance, resulting from only two sparse cases. When we included nodules, hemangiomas, liver parenchymal disease, and hepatic cysts, the kappa value was reduced to 0.47 (95% confidence interval [CI]: 0.18-0.76), which was still within the acceptable range.

**Statistical Analysis.** The coverage rate percentages for the ultrasonography screening of the eligible population and the attendance rate for those invited by groups were determined. The detection rates by different findings are presented as the number of cases detected per 1,000 attendees.

To estimate the efficacy of abdominal screening without being subject to selection bias, the HCC cumulative mortality of the invited AUS group was compared with that of the uninvited AUS group, and
the corresponding comparison of the HCC cumulative mortality between the invited AUS group and the historical control group was also performed. The detailed methodology, which takes into account different risk groups, is provided in the Supporting Material (eAppendix). The HCC cumulative mortality was compared between the attendees (the AUS group) and nonattendees (the non-AUS group) to reflect the efficacy of the actual AUS screening versus nonscreening. Because the latest information in the National Mortality Registry was available only through the end of 2009, ~15 months after the inception of our ultrasonography screening, we plotted three curves for the 15-month cumulative mortality by comparing the CHCIS intervention group (including the AUS and non-AUS group from Oct. 2008 to Dec. 2009) with the two comparison groups, including the non-AUS group (from Oct. 2008 to Dec. 2009) and the historical control group (subjects selected before CHCIS; from Oct. 2003 to Dec. 2004). We also plotted two curves for the 15-month cumulative mortality by comparing the AUS (attendees) and non-AUS groups (nonattendees) to determine the benefit of actual screening. All statistical analyses were performed using SAS software (v. 9.2; SAS Institute, Cary, NC).

Results

Clinical Weights for the HCC Risk Score. We used a multivariable logistic regression to train the clinical weights (regression coefficients) for the HCC risk score with the trained dataset based on the KCIS cohort. As mentioned in the Materials and Methods section, the computation for the risk score was stratified into two groups: Group A with subjects positive for either HBsAg or anti-HCV and Group B with subjects free of the two hepatitis virus infections. Initially, we included age, gender, type 2 diabetes, AST, ALT, and platelet count in the models to estimate the adjusted odds ratio for each risk factor in both groups. However, AST ($P = 0.1404$) and type 2 diabetes ($P = 0.4900$) were not statistically significant in the full model for Group A, and age ($P = 0.0996$) and ALT ($P = 0.4067$) were not statistically significant for Group B. Therefore, we excluded AST and type 2 diabetes for Group A and ALT for Group B but retained age, given that the incidence of HCC increases with age to derive the risk score for HCC. The results of the estimated clinical weights based on the trained dataset are given in Table 1. The formula for the HCC risk score for Groups A and B are shown in the footnote of Table 1.

Validation of the HCC Risk Score. The goodness-of-fit results show the lack of a discrepancy between the observed and expected cells in the trained data (KCIS) ($P = 0.2399$ for Group A, and $P = 0.2593$ for Group B) and the validation data (CHCIS) ($P = 0.5017$ for Group A, and $P = 0.5937$ for Group B) (see the eAppendix Table A2). Figure 3 also shows the ROC curves for internal and external validation. Because the AUC values were 0.961 (95% CI: 0.939-0.983) for the trained dataset (KCIS) and 0.960 (95% CI: 0.932-0.988) for the validated dataset (CHCIS), the predictive validity of our proposed model was adequate.

Invitation and Attendance. A total of 41,412 subjects aged 45-69 years who attended the CHCIS program between 2005 and September 2008 were included as the eligible population. After excluding 193 subjects who died or were diagnosed with HCC before AUS screening, 41,219 subjects were eligible for the study. The risk frequency among the eligible screening participants was 9.1% (3,754/41,219) for the extremely high-risk group, 8.9% (3,674/41,219) for the high-risk group, 21.8% (8,975/41,219) for the intermediate-risk group, and 60.2% (24,816/41,219) for the low-risk group. The number of eligible subjects increased with age among the extremely high-risk and intermediate-risk groups, and it decreased among the high-risk and low-risk groups.

Of the 41,219 potential participants, one-quarter of the eligible population ($n = 11,114$) was invited for AUS screening between October 2008 and December 2010 based on the invitation scheme described above because of the limited clinical capacity of ultrasonography. Because the high-risk groups were our first priority, the coverage rate was highest among the extremely high-risk (95.0% = 3,568/3,674) and high-risk groups (92.3% = 3,391/3,674), compared with a lower proportion for the intermediate-risk group (39.4% = 3,535/8,975) and a much lower proportion for the low-risk group (2.5% = 620/24,816).

A total of 8,962 participants underwent AUS. Table 2 shows the overall attendance rate, 80.6%. The attendance rates increased from the low-risk group (68.7%) to the extremely high-risk group (83.8%).

Findings From Screening. Table 3 shows the results of the ultrasonography findings among those residents attending the outreach-scheduled screening program. A total of 16 confirmed HCC cases were identified with this community-based ultrasonography screening. The detection rate (per 1,000) was 5.0 for the extremely high-risk group, 0 for the high-risk group, and 0.3 for the combined intermediate- and
low-risk groups. Similar findings were noted for the
detection of liver nodules, liver hemangiomas, and
liver parenchymal disease. Liver cirrhosis was prevalent
in the extremely high-risk group, as indicated by the
35.1 (per 1,000) detection rate; the detection rate was
similar for the high-risk and combined intermediate-
and low-risk groups. Note that the screening findings
for other liver-related lesions shown in Table 3 are not
exclusive, which indicates that some non-HCC nodule
cases out of 136 may have been indicative of hemangi-
oma and additional nodules.

**Efficacy of AUS.** Figure 4A shows three curves for
the cumulative HCC mortality (per 100,000) in the
invited AUS, uninvited AUS, and historical control
groups (the subjects before the CHCIS program). The
HCC cumulative mortality rate (per 100,000) in the
invited AUS group was 17.26, which was lower than
the two corresponding figures in the absence of
abdominal ultrasound screening, including 47.51 for
the historical control group (subjects before the
CHCIS screening) and 42.87 for the uninvited AUS
group in the corresponding period. After adjusting for
age and gender, the relative mortality rate was 0.63
(95% CI: 0.52-0.77) for the invited AUS group versus
the historical control group (the subjects before the
CHCIS program) and 0.69 (95% CI: 0.56-0.84) for
the invited AUS group versus the uninvited AUS
group. The number needed to screen to avoid one
HCC death was 12,886 and 9,763 when comparing
the invited AUS group with the uninvited AUS and
historical control groups, respectively.

Of those individuals in the invited AUS group, the
HCC risk was considerably higher in nonattendees
(non-AUS group) than in attendees (AUS-group), 148
versus 26.45, yielding a relative mortality rate of 0.18
\( (P<0.05) \), as shown in Fig. 4B. The reason for pro-
ducing such a striking result is that only two out of 16
HCC cases died from HCC.

**Discussion**

This study demonstrated a 31% reduction in HCC
mortality with the provision of AUS in a population-
based screening program in Changhua County, an area
with high HCC incidence and mortality, between
2008 and 2010. Among 16 screen-detected HCC
cases, only two died from HCC. Such a favorable sur-

![Fig. 3. The ROC curves for KCIS used to train the risk score and the external validation dataset with CHCIS.](image)

| Variables | Group A* | | Group B† |
|-----------|----------|-----------------|----------|
|           | Reg coef | SE              | P Value  | Reg coef | SE              | P Value  |
| Age       | 0.0474   | 0.0099          | <0.0001  | 0.0358   | 0.0223          | 0.1079   |
| Gender (Male vs Female) | 1.2878 | 0.2634          | <0.0001  | 1.3580   | 0.6638          | 0.0407   |
| Type 2 diabetes | 1.3872 | 0.2946          | <0.0001  | 1.3430   | 0.5757          | 0.0128   |
| AFP (≥20 vs <20 ng/mL) | 2.8922 | 0.2746          | <0.0001  | 2.0298   | 0.5962          | 0.0007   |
| AST (≥45 vs <45 IU/L) | 1.1934 | 0.2701          | <0.0001  | 1.3124   | 0.6219          | 0.0348   |
| ALT (≥45 vs <45 IU/L) | 1.3033 | 0.2644          | <0.0001  | 2.0298   | 0.5962          | 0.0007   |

Table 1. Estimated Regression Coefficients (Clinical Weights) for Deriving the HCC Risk Score by
Using the Trained Dataset From the KCIS Program

*Risk score for Group A = \(-9.1940 + 0.0474 \times \text{Age} + 1.2878 \times \text{(Male)} + 2.8922 \times \text{(AFP} \geq 20 \text{ng/mL}) + 1.1934 \times \text{(AST} \geq 45 \text{IU/L}) + 1.3033 \times \text{(Platelet count} \leq 150 \times 10^3)\).†Risk score for Group B = \(-11.7821 + 0.0358 \times \text{Age} + 1.3580 \times \text{(Male)} + 1.3124 \times \text{(type 2 diabetes)} + 2.0298 \times \text{(Platelet count} \leq 150 \times 10^3)\).
the cancer presents) in subjects with a high potential for developing HCC is highly recommended. Mass screening for HCC with ultrasonography can also confer other benefits for the early detection of HCC in the absence of hepatitis B and C virus infection, as supported by recent studies of the association between type 2 diabetes or metabolic syndrome-related disease and HCC.

However, the implementation of mass screening for HCC using AUS poses a practical challenge. The unique characteristic of this community-based screening for HCC was that eligible residents were incrementally invited using a risk score-guided approach. Patients with higher risk scores had higher priority for screening eligibility. As a result, a high rate of early HCC was efficiently detected. In our study, the detection rates for HCC were 5.0 per 1,000 for the extremely high-risk group and 0.3 per 1,000 for the combined intermediate- and low-risk groups. In addition to high yields in the high-risk individuals who were positive for HBsAg or anti-HCV antibodies, one cannot ignore the importance of the possibility of detecting HCC in the combined intermediate- and low-risk group, although a small number of cases were predicted. Additionally, the incidence of liver cirrhosis detection, an early indicator of HCC, in the combined intermediate- and low-risk group provides another rationale for performing AUS.

The elevated coverage rate of the high-risk group (95%, 3,568 out of 3,754) in the early phase may account for our effectiveness in reducing mortality by AUS. This finding was close to the corresponding 40% mortality reduction found using a two-stage screening program conducted in a high-risk HCC area after adjusting for other risk factors in a previous study. Nonetheless, our results were lower than the 56% reduction in mortality after 3 years of follow-up found in the surveillance study reported by Yu et al., who compared those individuals receiving routine ultrasonography screening (surveillance group) with a nonsurveillance group (opportunistic group or symptomatic group) using a case-control study with medical chart review to retrieve clinically relevant parameters. The fact that the study by Yu et al. was a hospital-based case-control study with a self-selection bias may account for the higher benefit of AUS in their study.

As previously mentioned, our results underscore the necessity of screening healthcare to subjects who are negative for HBV and HCV and are vulnerable to HCC. For example, a low platelet count and diabetes are associated with a higher risk for HCC. In addition, metabolic syndrome, a common chronic condition, has been shown to be associated with
nonalcoholic fatty liver disease (NAFLD) or alcoholic steatohepatitis (NASH), which leads to an elevated risk for liver cirrhosis.

There are some limitations and concerns for our study. First, we evaluated the efficacy of AUS mass screenings based on a short follow-up period. There may have been length bias for early detection because screen-detected HCCs are usually small, as observed in our study, and excellent survival would be expected. However, HCC is a rapidly progressing disease, and treatment for early detected cases is essential, and concern about length bias would not be as serious in HCC screening as in other cancer screening programs. Nevertheless, longer follow-up is required to further corroborate our reported effectiveness for mortality reduction. Second, our screening program was an outreach service program, which might compensate for an uneven geographic distribution of gastroenterological specialist services. The attendance rates for ultrasonography screening were increased from less than 50% to 80.6% in our study. However, quality concerns have been raised. Quality was ensured with respect to the structure, process, and outcome of the study. With regard to the study structure, our program provided lists of invitations under the control of the local Health Bureau to ensure that the eligible population was covered. We also recruited board-certificated gastroenterologists to conduct the abdominal ultrasonographies. With respect to the process, a clinical committee organized by the local Health Bureau of Changhua County was convened monthly to review the medical charts of the positive cases from AUS. A central database containing information on the eligible CHCIS population screening invitations, ultrasonography screening, and clinical confirmations was built to assure the availability of essential information. Third, because our study was not a randomized controlled trial, whether the baseline characteristics between the two comparison groups were similar when the comparison of the effectiveness of reducing mortality from HCC was performed is a concern. However, this concern is reduced by the study design and expedient analysis. With respect to the study design, the baseline characteristics were not expected to be dissimilar between the AUS and non-AUS groups because the invitation was based on the classification of risk score in both groups. For the comparison between the invited AUS group (the AUS group and the non-AUS group combined) and the uninvited AUS group, because the CHCIS program targets adult residents in Changhua and provides screening services for multiple

| Ultrasonography Findings and Confirmatory Diagnosis | Group A | | Group B | | Total |
|---|---|---|---|---|---|
| | E-H | H | | | |
| Total screened | 2,989 | 2,730 | 3,243 | 8,962 |
| Confirmatory HCC | 15 | 5.0 | 0 | 0.0 | 1 | 0.3 | 16 | 1.8 |
| Liver cirrhosis | 105 | 35.1 | 10 | 3.7 | 13 | 4.0 | 128 | 14.3 |
| Liver nodule | 60 | 20.1 | 37 | 13.6 | 39 | 12.0 | 136 | 15.2 |
| Liver hemangiomata | 81 | 27.1 | 60 | 22.0 | 56 | 17.3 | 197 | 22.0 |
| Liver parenchymal disease | 887 | 296.8 | 607 | 222.3 | 260 | 80.2 | 1,754 | 195.7 |

*Two cases with HCC had died. DR: detection rate per 1,000 cases; HCC: hepatocellular carcinoma; E-H: extremely high-risk group; H: high-risk group.

Fig. 4. Cumulative mortality comparisons of the invited AUS group, the uninvited AUS group, and the historical control group (before the CHCIS program) in Changhua County.
neoplasms and chronic diseases, we believe that the invited and uninvited AUS groups were not different in terms of the baseline risk for HCC. With respect to the analysis, to make a fair comparison and avoid selection bias, we combined the AUS and non-AUS groups (defined as the invited AUS group) because both groups had been invited to receive an AUS. We compared the effectiveness of the invited AUS group with that of the uninvited AUS group and the historical control group. Such a comparison is similar but not exactly identical to the intention-to-treat principle used in the analysis of the data from the randomized controlled trial. As similar results were noted regardless of the comparator using the uninvited group or the historical control, we believe a concern over selection bias would be minor.

In conclusion, our study demonstrated a 31% reduction in HCC mortality by comparing those individuals invited to a community-based AUS screening with an uninvited group using a risk score-guided invitation scheme in Changhua County during 2 years of follow-up since 2008. This finding suggests the feasibility of mass screening for HCC with AUS that targets subjects not covered by the nationwide vaccination program against hepatitis B virus infection.

Acknowledgment: Steering committee for design and analysis: Changhua County Public Health Bureau (Yen-Po Yeh and Hsiao-Ching San); Graduate Institute of Epidemiology and Preventive Medicine, College of Public Health, National Taiwan University (Hsiu-Hsi Chen); School of Oral Hygiene, College of Oral Medicine, Taipei Medical University (Amy Ming-Fang Yen and Sam Li-Sheng Chen); Department and Graduate Institute of Health Care Management, Chang Gung University (Sherry Yueh-Hsia Chiu); Department of Health Industry Management, Kainan University (Jean Ching-Yuan Fann); Division of Gastroenterology, Department of Internal Medicine, Shin-Kong Wu Ho-Su Memorial Hospital (Chao-Sheng Liao); and Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine (Tsung-Hui Hu). Clinical committee for ultrasonography screen, case referral and care: Changhua Medical Association (Ming-Chung Tsai), Changhua Christian Hospital (Wei-Wen Su, Chia-Wei Yang, Hsu-Heng Yen, Kun-Ching Chou, Pei-Yuan Su, Kai-Lun Shin, and Yu-Chung Hsu), Lutheran Christian Hospital (Jun-Hung Lai), Changhua Christian Hospital Lukang Branch (Ay-Jiun Wang and Chih-Ta Yao), Show Chwan Memorial Hospital (Yi-Jen Fang, Yung-Hsiang Yeh, Chi-Chieh Yang, Chien-Hua Chen, Ping-Hung Chan, Chih-Sheng Wu, Tai-Tien Chung, and Yu-Tsai Liu), Chang Bing Show Chwan Memorial Hospital (Sheng-Lei Yan, Tsung-Hsun Yang, Chao-Lei Mai, and Chung-Hung Chen), Changhua County, Ministry of Health and Welfare (Shih-Tien Chen), and Changhua local clinics (Chih-Min Lin, Chang-Hao Wang, Chia-Li Lin, Tien-En Lu, Shen-Jyh Chen, Shin-Jung Su, Ju-Ching Chu, Hung-Jung Hsu, Teng-Hsin Yeh, Shun-Yu Wu, and Chien-Lung Wang). Implementation committee: Changhua County (Po-Yuan Cho); Health Promotion Section (Wen-Shiow Chao, Shiu-Ann-Shiou Liou), Laboratory Section (Su-Yin Lin, Bao-Bin Fang), and Planning Information Management Section (Mei-Tzu Huang), Changhua County Public Health Bureau; and Changhua County Ershuei Township Health Center (Hung-Pin Chen).

References

1. Chang MH, Chen CJ, Lai MS, Hsu HM, Wu TC, Kong MS, et al. Universal hepatitis B vaccination in Taiwan and the incidence of hepatocellular carcinoma in children. Taiwan Childhood Hepatoma Study Group. N Engl J Med 1997;336:1855-1859.
2. Shihia S, Tateishi R, Arano T, Uchino K, Enokou K, Nakagawa H, et al. Radiofrequency ablation for hepatocellular carcinoma: 10-year outcome and prognostic factors. Am J Gastroenterol 2012;107:569-577.
3. Tseng PL, Wang JH, Tung HD, Hung CH, Kee KM, Chen CH, et al. Optimal treatment increased survival of hepatocellular carcinoma patients detected with community-based screening. J Gastroenterol Hepatol 2010;25:1426-1434.
4. Chen TH, Chen CJ, Yen MF, Lu SN, Sun CA, Huang GT, et al. Ultrasound screening and risk factors for death from hepatocellular carcinoma in a high risk group in Taiwan. Int J Cancer 2002;98:257-261.
5. Chen TH, Chiu YH, Luh DL, Yen MF, Wu HM, Chen LS, et al. Taiwan Community-Based Integrated Screening Group. Community-based multiple screening model: design, implementation, and analysis of 42,387 participants. Cancer 2004;100:1734-1743.
6. Lai MS, Hsieh MS, Chiu YH, Chen TH. Type 2 diabetes and hepatocellular carcinoma: a cohort study in high prevalence area of hepatitis virus infection. Hepatology 2006;43:1295-1302.
7. Lu SN, Wang JH, Liu SL, Hung CH, Chen CH, Tung HD, et al. Thrombocytopenia as a surrogate for cirrhosis and a marker for the identification of patients at high-risk for hepatocellular carcinoma. Cancer 2006;107:2212-2222.
8. Chiu YH, Chen LS, Chan CC, Liu DM, Wu SC, Kuo HS, et al. Health information system for community-based multiple screening in Keelung, Taiwan (Keelung Community-Based Integrated Screening No. 3). Int J Med Inform 2006;75:369-383.
9. Bruis J, Shersha M. Management of hepatocellular carcinoma: an update. HEPATOLOGY 2010;53:1020-1022.
10. Yu EW, Chie WC, Chen TTH. Does screening or surveillance for primary hepatocellular carcinoma with ultrasonography improve the prognosis of patients? Cancer J 2004;10:317-325.
11. Fan JG, Zhu J, Li XL, Chen L, Lu YS, Li L, et al. Fatty liver and the metabolic syndrome among Shanghai adults. J Gastroenterol Hepatol 2005;20:1825-1832.
12. Angulo P. Nonalcoholic fatty liver disease. N Engl J Med 2002;16:1221-1231.