Validation of Dynamic Aspartate-to–Alanine Aminotransferase Ratio for Predicting Liver Disease Mortality

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The dynamic aspartate-to–alanine aminotransferase ratio (dAAR) was developed recently to predict the risk of incident chronic liver disease among the Nordic adult population; however, the dAAR has not been externally validated in other ethnic cohorts. Therefore, we aimed to examine the predictive ability of dAAR for liver disease mortality in the South Korean adult population. As a population-based cohort study, we used the National Health Screening Cohort database, which included adult individuals who underwent standardized medical examinations between 2002 and 2003 in South Korea. The primary endpoint was liver disease mortality, defined as death due to liver disease. Liver disease mortality was evaluated between 2004 and 2015 (12 years). Analysis of data from 512,749 adults showed that 4,052 (0.8%) individuals died due to liver disease. On receiver operating characteristic (ROC) analyses, the area under curve for alanine aminotransferase (ALT), aspartate-to-ALT ratio (AAR), and dAAR for liver disease mortality were 0.74, 0.55, and 0.81, respectively. The cutoff point of dAAR was determined to be 0.72 on ROC analysis, using the Youden index method. On competing risk analysis using the Fine and Gray model, the dAAR > 0.72 group demonstrated a 4.43-fold higher rate of liver disease mortality (subdistribution hazard ratio: 4.43, 95% confidence interval: 4.11, 4.77; $P < 0.001$) after adjustment for covariates. *Conclusion*: The performance of dAAR in predicting liver disease mortality was better than that of AAR or ALT in South Korea. Our study suggests that dAAR scores can potentially be used for screening and predicting liver disease mortality among the general Korean population. (*Hepatology Communications* 2022;6:740-749).

The performance of dAAR in predicting liver disease mortality was better than that of AAR or ALT in South Korea. Our study suggests that dAAR scores can potentially be used for screening and predicting liver disease mortality among the general Korean population.

Approximately 2 million global deaths per year are attributed to liver diseases such as liver cirrhosis, viral hepatitis, and hepatocellular carcinoma.[1] In the United States, the increase in the aging population has led to a surge of inpatient chronic liver disease, concomitant with comorbidities.[2] As mortality due to liver diseases is an important global health issue,[1,3] attempts have been made to predict mortality due to liver disease using tools based on the results of laboratory tests.[4-6]

Abbreviations: AAR, aspartate-to–alanine aminotransferase ratio; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CCI, Charlson comorbidity index; CI, confidence interval; dAAR, dynamic AAR; HR, hazard ratio; ICD-10, International Statistical Classification of Diseases 10th Revision; NHIS, National Health Insurance Service; NHIS-HEALS, NHIS-National Health Screening Cohort; ROC, receiver operating characteristic; sHR, subdistribution HR.

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Traditionally, transaminases, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) are the most common liver function tests that reflect hepatocellular damage.[7] However, recent guidelines have concluded that elevated ALT or AST levels cannot accurately predict liver disease,[8] because elevated transaminases are common in approximately 10% of the general population.[9] The AST-to-ALT ratio (AAR) has been known to correlate with the severity of liver cirrhosis,[10] even when AST or ALT values are within normal range.[11] While AAR has also been used to predict liver fibrosis stage in patients with alcohol-associated liver disease,[12] chronic hepatitis,[13] and nonalcoholic fatty liver disease,[14] it has some limitations. The ability of AAR to discern cirrhosis or advanced fibrosis is not consistent among studies.[10,15] Furthermore, a study showed that AAR > 1 was common in clearly healthy adult individuals without any signs of liver disease; this may have been influenced by alcohol intake and weight.[16]

In 2021, Åberg et al. developed a new tool, the dynamic AAR (dAAR), using age, ALT, and AAR; they found that the dAAR score provided prospective predictions for liver outcomes, and by extension, the risk of chronic liver disease in the general population.[17] Although this effective approach has advanced the clinical detection of advanced liver diseases including fibrosis/cirrhosis, the authors validated their results in the Nordic population and in two independent cohorts from Boston; they suggested that further external validation was required in diverse ethnic populations.[17]

Therefore, we aimed to examine the predictive ability of dAAR for liver disease mortality in the South Korean adult population, using the national database of standard health examinations.

Patients and Methods

STUDY DESIGN AND ETHICAL ISSUES

As a population-based cohort study, we followed the guidelines of the Strengthening the Reporting of Observational Studies in Epidemiology, recommended for cohort studies.[18] The institutional review board (IRB) of the Seoul National University Bundang Hospital exempted approval of the study protocol (X-1911-579-902), and the National Health Insurance Service (NHIS) approved data sharing after approval of the study protocol (NHIS-2020-2-067). The requirement for informed consent was waived by the IRB, because the data were extracted and analyzed retrospectively, using anonymous data from the NHIS database.

NHIS–NATIONAL HEALTH SCREENING COHORT DATABASE AND STUDY POPULATION

We used the NHIS–National Health Screening Cohort (NHIS-HEALS) database for this study. The NHIS-HEALS consists of 514,795 adult individuals who underwent standardized medical examinations between 2002 and 2003 in South Korea. Usually, subscribers of the NHIS aged ≥ 40 years are recommended to undergo a standardized medical examination every 2 years for health check-ups.[19] The NHIS-HEALS contained the results of standardized medical examinations performed during 2002-2003, which were followed up until December 31, 2015. The database included all disease diagnoses using the International Statistical Classification of Diseases 10th Revision

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(ICD-10) codes and prescription information regarding procedures and/or drugs. As this is the sole public health insurance system in South Korea, all disease diagnoses and prescription information of drugs and/or procedures should be registered in the NHIS database for receipt of financial support from the government; this suggests that the data from the NHIS database are sufficiently reliable. We included individuals who underwent a standardized medical examination between 2002 and 2003. Individuals who died between 2002 and 2003 or had missing liver enzyme data during this period were excluded from the analysis.

DYNAMIC AST/ALT RATIO

AST and ALT levels were measured from venous blood samples during standardized medical examinations during 2002 and 2003. Based on another recent report by Åberg et al.,[17] the dAAR scores were calculated using age, AST, and ALT following the formula found in Supporting Table S1. If AST or ALT levels were measured twice during 2002 and 2003, the latest data of the 2 years were selected to calculate the dAAR. Among the formulas, we used R software (version 4.0.3) for applicable calculations in this study. The mean value of dAAR was −0.04 (SD: 1.24); the median value was −0.18 (interquartile range: −0.98, 0.79), ranging from −6.16 to 6.49. A higher dAAR level implies poor liver function.

STUDY ENDPOINT: LIVER DISEASE MORTALITY

NHIS-HEALS reports the primary cause of death, in addition to the date of death. Among the causes of death, liver disease–related deaths were defined as liver disease mortality. It included alcohol-associated liver disease (K70), toxic liver disease (K71), hepatic failure (K72), chronic hepatitis (K73), liver cirrhosis (K74), other inflammatory liver diseases (K75), other liver diseases (K76), liver cancer (C22), and viral hepatitis (B15-19) according to ICD-10 codes. Liver disease mortality was evaluated between January 1, 2004, and December 31, 2015 (12 years).

COVARIATES

Data regarding numerous variables were collected as covariates in this study. Age, sex, and body mass index (BMI) were collected as physical variables. As the NHIS-HEALS database did not have records of the waist circumference, the BMI was used to reflect the metabolic risk of the study population. The BMI was divided into four groups: 18.5-24.9, below 18.5, 25.0-29.9, and above 30.0 kg/m^2. The national annual income levels of all subscribers are registered in the NHIS database; they were divided into five groups using quintile ratios (first: 0%-20% [lowest], second: 20%-40%, third: 40%-60%, fourth: 60%-80%, and fifth 80% [highest]). In South Korea, the underlying disability should be registered in the NHIS database for receipt of various benefits from the social welfare system.

Disabilities were categorized into six levels based on severity. The first (most severe) to third levels of disability were included in the severe disability group, whereas the fourth to sixth (mildest) levels were considered as mild-to-moderate disability. In addition, smoking and alcohol consumption status were collected as covariates. Smoking status was classified into four groups: (1) nonsmoker, (2) previous smoker, (3) current smoker, and (4) unknown (no-response group). Alcohol consumption was also classified into four groups: (1) nondrinker, (2) mild drinker, (3) heavy drinker, and (4) unknown (no-response group). The mild drinker group was defined by alcohol consumption ≤ 210 g per week in men and ≤ 140 g per week in women, while the heavy drinker group was defined by alcohol consumption > 210 g per week in men and > 140 g per week in women. Exercise frequency was divided into six groups (no exercise, 1-2 times per week, 3-4 times per week, 5-6 times per week, exercise almost every day, and unknown [no-response group]).

To reflect the comorbid status of the study population, Charlson comorbidity index (CCI) scores were calculated using ICD-10 codes between 2002 and 2003, as provided in Supporting Table S2.[20] In addition, data pertaining to 10 liver diseases including alcohol-associated liver disease (K70), toxic liver disease (K71), hepatic failure (K72), chronic hepatitis (K73), liver cirrhosis (K74), other inflammatory liver diseases (K75), other liver diseases (K76), liver cancer (C22), chronic viral hepatitis (B18), and carrier status of viral hepatitis (Z22.5) were obtained from the NHIS database for the period between 2002 and 2003.

STATISTICAL ANALYSIS

The clinicopathological characteristics of the study participants were presented as mean values

with SD for continuous variables, and numbers with percentages for categorical variables. First, we performed receiver operating characteristic (ROC) analyses to examine the predictive ability for liver disease mortality according to ALT, AAR among the total cohort population, and dAAR. In this ROC curve, the optimal cutoff value of dAAR was calculated using the Youden index method.[21] The results of ROC analyses have been presented as areas under the curve (AUCs) with 95% confidence intervals (CIs); the Delong's test was used to compare the statistical differences between AUCs.[22] Second, we performed the ROC analyses for liver disease mortality in 13 subgroups, namely, alcohol-associated liver disease, toxic liver disease, hepatic failure, chronic hepatitis, liver cirrhosis, other inflammatory liver disease, other liver disease, liver cancer, chronic viral hepatitis, carriers of viral hepatitis, male, female, and diabetes mellitus cohorts. Third, we examined certain covariate-specific AUCs using ROC regression modeling.[23] Continuous variables such as age, CCI, BMI, and alcohol consumption per week were used to examine the covariate-specific AUCs. Fourth, we performed competing risk analysis using the Fine and Gray method to examine liver disease mortality and non-liver disease–related mortality.[24] All covariates were included in the Fine and Gray model for adjustment, and results were presented as subdistribution hazard ratios (sHRs) with 95% CIs.

For liver disease mortality, four separate multivariable models were constructed to avoid multicollinearity among ALT, AAR, and dAAR as continuous variables, and dAAR as a categorical variable using the cutoff value from the ROC curve. In addition, Schoenfeld-type residuals are used to assess the proportional subdistribution hazard assumption of the Fine and Gray models; no multicollinearity was identified between the included variables with a variance inflation factor of < 2.0. Finally, Aalen-Johansen plots were constructed for liver mortality and non-liver mortality in the dAAR score risk groups, based on the cutoff value from ROC analysis. All statistical analyses were performed using R software (version 4.0.3; R Project for Statistical Computing, Vienna, Austria). Statistical significance was set at $P < 0.05$.

Results

STUDY POPULATION

As per the NHIS-HEALS, 514,795 adults underwent standardized medical examinations between 2002 and 2003 in South Korea. After excluding 1,320 individuals who died between 2002 and 2003, and 729 individuals who had missing data pertaining to liver enzymes, 512,749 adults were finally eligible for the analysis. Among them, 4,052 (0.8%) and 41,985 individuals died due to liver and non-liver disease, respectively, between January 1, 2004 and December 31, 2015 (Fig. 1). The clinicopathological characteristics of the study participants are given in Table 1; 54.2% (277,758) were male, and the mean age of the study participants was 53.6 years (SD: 9.6).

ROC ANALYSIS FOR LIVER DISEASE MORTALITY

Table 2 and Fig. 2 show the results of the ROC analysis for liver disease mortality. In the total cohort, the AUC of ALT, AAR, and dAAR for liver disease mortality were 0.74 (95% CI: 0.73, 0.75), 0.55 (95% CI: 0.54, 0.56), and 0.81 (95% CI: 0.81, 0.82), respectively. These trends were similar in the other 13 subgroups, as in the alcohol-associated liver disease, toxic liver disease, hepatic failure, chronic hepatitis, liver cirrhosis, other inflammatory liver disease, other diseases of liver, liver cancer, chronic viral hepatitis, carrier of viral hepatitis, male, female, and diabetes mellitus cohorts. The AUCs of dAAR for liver disease mortality among the 14 groups (total cohort and the 13 subgroups) were not significantly different based on the results of the Delong's test (all $P > 0.05$). The cutoff point of dAAR was determined to be 0.72 on ROC analysis, using the Youden index method. Fig. 3 shows the results of the age (year) (A), CCI (point) (B), BMI (kg/m^2) (C), and alcohol consumption (g) per week (D) specific AUCs, respectively.

SURVIVAL ANALYSIS

Table 3 lists the results of competing risk analysis using the Fine and Gray method to examine liver

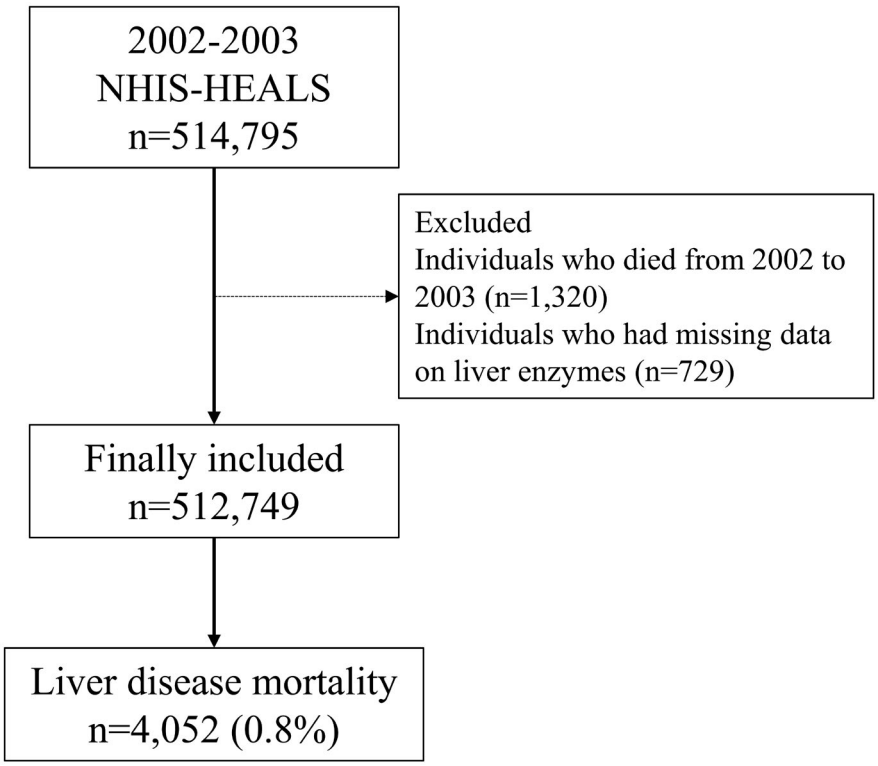

FIG. 1. Flow chart depicting individual selection process.

disease mortality and non-liver disease mortality. The data showed that an increase in the ALT, AAR, and dAAR led to a 1.01-fold (sHR: 1.01, 95% CI: 1.01, 1.01; $P < 0.001$; model 1), 1.02-fold (sHR: 1.02, 95% CI: 1.01, 1.02; $P < 0.001$; model 2), and 1.15-fold (sHR: 1.15, 95% CI: 1.15, 1.16; $P < 0.001$; model 3) increase in the rate of liver disease mortality, respectively. When dAAR was divided into two groups as categorical variables (≤ 0.72 and > 0.72), compared with the ≤ 0.72 group, the > 0.72 dAAR group was associated with a 4.43-fold higher rate of liver disease mortality (sHR: 4.43, 95% CI: 4.11, 4.77; $P < 0.001$). All other covariates used for adjustment in the Fine and Gray model 1 are presented in Supporting Table S3. Fig. 4 shows the Aalen-Johansen plots for liver mortality (A) and non-liver mortality (B) in the dAAR score risk groups based on the cutoff value (0.72) from ROC analysis. The > 0.72 dAAR group shows higher cumulative incidence of both liver disease mortality (A) and non-liver disease mortality (B) than in the ≤ 0.72-dAAR group ($P < 0.001$).

Discussion

In this population-based cohort study from South Korea, we showed that dAAR has a better predictive ability for liver disease mortality than ALT or AAR. In addition, dAAR has a strong ability of predicting liver disease mortality among adults with chronic liver disease. We also provided the cutoff value of dAAR using ROC analysis (0.72 in our cohort) for predicting liver disease mortality. The results suggest that dAAR values higher than 0.72 may be related to a higher risk of death due to liver disease in the long term. Åberg et al.[17] developed and validated the dAAR in the Nordic population; we demonstrated the clinical usefulness of dAAR in the South Korean population in this study.

Although a recent cohort study by Åberg et al.[17] focused on the performance of dAAR in predicting the risk of incident severe liver disease such as liver cirrhosis, we analyzed the predictive ability of dAAR for liver disease mortality in this study. Mortality due to chronic liver diseases such as hepatitis and

TABLE 1. CLINICOPATHOLOGICAL CHARACTERISTICS OF THE STUDY PARTICIPANTS (N = 512,746)

Variable	Number (%)	Mean (SD)
Age, year		53.6 (9.6)
Sex, male	277,758 (54.2)	
Residence at diagnosis		
Seoul (capital city)	87,993 (17.2)	
Other metropolitan city	140,239 (27.4)	
Other area	284,514 (55.5)	
BMI, kg/m^2		
18.5-24.9 (normal)	320,852 (62.6)	
Below 18.5 (underweight)	11,860 (2.3)	
25.0-29.9 (overweight)	164,840 (32.1)	
Above 30.0 (obese)	14,717 (2.9)	
Unknown	477 (0.1)	
Annual income level		
0%-20% (lowest)	80,547 (15.7)	
20%-40%	69,896 (13.6)	
40%-60%	80,940 (15.8)	
60%-80%	107,981 (21.1)	
80%-100% (highest)	173,382 (33.8)	
Underlying disability		
Mild to moderate	2,052 (0.4)	
Severe	1,245 (0.2)	
Smoking status		
Never smoker	331,264 (64.6)	
Previous smoker	43,501 (8.5)	
Current smoker	117,291 (22.9)	
Unknown	20,690 (4.0)	
Alcohol consumption		
No drink	285,927 (55.8)	
Mild drink group	188,598 (36.8)	
Heavy drink group	26,398 (5.1)	
Unknown	11,823 (2.3)	
Exercise frequency		
No exercise	285,668 (55.7)	
1-2 times per a week	118,117 (23.0)	
3-4 times per a week	47,073 (9.2)	
5-6 times per a week	13,170 (2.6)	
Almost every day	34,690 (6.8)	
Unknown	14,028 (2.7)	
CCI		1.3 (1.6)
Alcohol-associated liver disease	17,806 (3.5)	
Toxic liver disease	5,983 (1.2)	
Hepatic failure	2,252 (0.4)	
Chronic hepatitis	26,720 (5.2)	
Liver cirrhosis	4,458 (0.9)	
Other inflammatory liver diseases	7,134 (1.4)	
Other diseases of liver	54,128 (10.6)	
Liver cancer	26,720 (5.2)	
Chronic viral hepatitis	7,512 (1.5)	
Carrier of viral hepatitis	734 (0.1)	
Family history of liver disease	15,459 (3.0)	
AST		26.9 (17.7)
ALT		25.9 (21.0)
AAR		1.2 (0.9)
dAAR*		–0.04 (1.24)

*dAAR: median value (–0.18, interquartile range: –0.98, 0.79, range: –6.16, 6.49).

alcohol-associated liver disease has been an important issue in the United States[25] in addition to mortality due to liver cirrhosis.[3] Furthermore, prediction of survival in patients with hepatocellular carcinoma has been a significant health issue,[26] and we included mortality due to hepatocellular carcinoma in the category of liver disease mortality. The AUC values in this study (Table 2) were better than those in some of the external validation data sets in the previous publication by Åberg et al.[17] This is because we set more severe primary endpoints such as liver disease mortality; in contrast, the study by Åberg et al.[17] considered incident severe liver disease including liver cirrhosis as the endpoint. The findings suggest that the performance of the dAAR score may have been better in this study, when considering the severest outcomes including liver disease mortality. The incidence of severe liver disease can be influenced by external factors such as accessibility to outpatient clinics or the socioeconomic status of patients; however, mortality due to liver disease may be a more objective and accurate outcome than incident severe liver disease.

Interestingly, the AUC of AAR for liver disease mortality was very low at 0.55 (95% CI: 0.54-0.56), whereas the AUC of ALT alone for liver disease mortality was 0.74 (95% CI: 0.73-0.75). This shows that the performance of AAR in predicting liver disease mortality depends on the ALT level. Åberg et al.[17] also reported that the predictive performance for liver-related outcomes of AAR levels depends on the absolute ALT level. Therefore, our results and those of the study by Åberg et al. suggest that elevated AAR cannot be recommended for predicting

TABLE 2. ROC ANALYSIS FOR LIVER DISEASE MORTALITY

Variable	ROC Analysis AUC (95% CI)
Total cohort	
ALT	0.74 (0.73, 0.75)
AAR	0.55 (0.54, 0.56)
dAAR	0.81 (0.81, 0.82)
Alcohol-associated liver disease cohort	
ALT	0.67 (0.64, 0.69)
AAR	0.70 (0.68, 0.72)
dAAR	0.81 (0.80, 0.83)
Toxic liver disease cohort	
ALT	0.73 (0.69, 0.77)
AAR	0.57 (0.52, 0.62)
dAAR	0.82 (0.79, 0.86)
Hepatic failure cohort	
ALT	0.71 (0.67, 0.75)
AAR	0.69 (0.65, 0.73)
dAAR	0.84 (0.80, 0.87)
Chronic hepatitis cohort	
ALT	0.71 (0.69, 0.73)
AAR	0.62 (0.60, 0.64)
dAAR	0.82 (0.81, 0.84)
Liver cirrhosis cohort	
ALT	0.63 (0.60, 0.65)
AAR	0.63 (0.61, 0.65)
dAAR	0.74 (0.73, 0.76)
Other inflammatory liver diseases cohort	
ALT	0.68 (0.64, 0.72)
AAR	0.63 (0.58, 0.67)
dAAR	0.80 (0.76, 0.84)
Other diseases liver cohort	
ALT	0.72 (0.70, 0.74)
AAR	0.60 (0.58, 0.63)
dAAR	0.82 (0.80, 0.84)
Liver cancer cohort	
ALT	0.70 (0.68, 0.72)
AAR	0.61 (0.59, 0.64)
dAAR	0.81 (0.79, 0.83)
Chronic viral hepatitis cohort	
ALT	0.72 (0.69, 0.75)
AAR	0.58 (0.55, 0.62)
dAAR	0.82 (0.80, 0.85)
Carrier of viral hepatitis cohort	
ALT	0.71 (0.61, 0.80)
AAR	0.53 (0.43, 0.64)
dAAR	0.77 (0.68, 0.87)
Male cohort	
ALT	0.70 (0.69, 0.71)
AAR	0.60 (0.59, 0.61)
dAAR	0.80 (0.80, 0.81)
Female cohort	
ALT	0.74 (0.72, 0.76)
AAR	0.52 (0.49, 0.54)
dAAR	0.80 (0.79, 0.81)
Diabetes mellitus cohort	
ALT	0.69 (0.66, 0.71)
AAR	0.61 (0.59, 0.63)
dAAR	0.78 (0.76, 0.80)

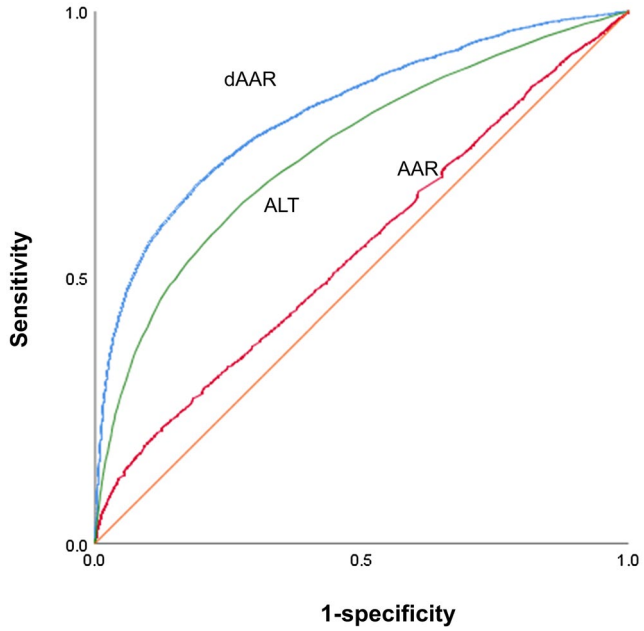

FIG. 2. ROC curves for liver disease mortality according to AAR, ALT, and dAAR.

both the risk of incidence pertaining liver disease and liver disease mortality among the adult population.

In the subgroup analyses, according to the comorbidity status of chronic liver diseases, none of the subgroups showed significant differences in AUC compared with that of the total cohort. This suggests that the efficacy of dAAR as a predictive tool in detecting liver disease mortality is not compromised relative to comorbidity status, including alcohol-associated liver disease,

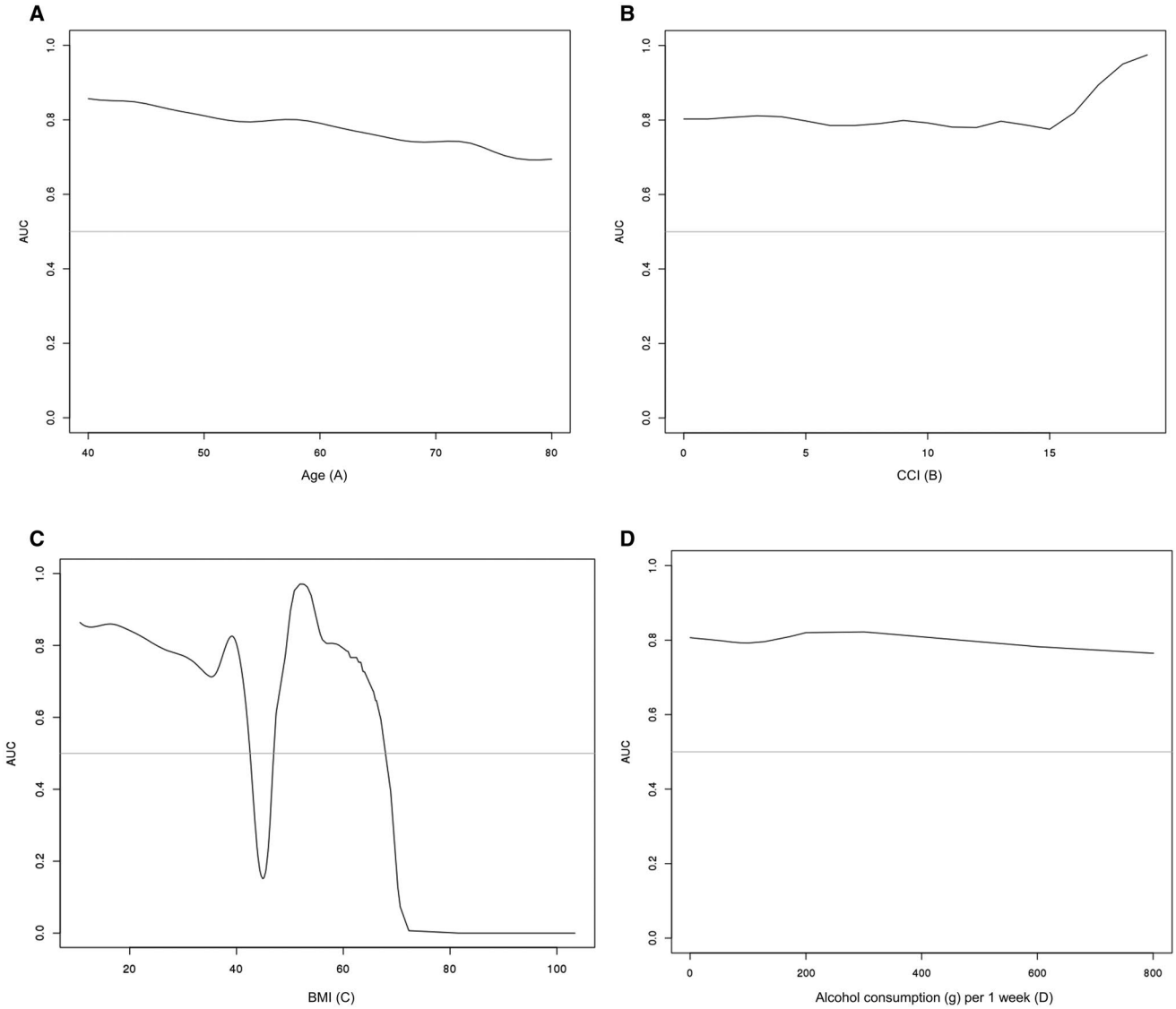

FIG. 3. Age (A), CCI (B), BMI (C), and alcohol consumption per week (D) specific AUC.

TABLE 3. FINE AND GRAY MODELS FOR LIVER DISEASE AND NON-LIVER DISEASE MORTALITY AMONG THE ENTIRE COHORT

	Liver Disease Mortality		Non-liver Disease Mortality	
Variable	HR (95% CI)	*P*-Value	HR (95% CI)	*P* Value
ALT (model 1)	1.01 (1.01, 1.01)	<0.001	1.00 (1.01, 1.00)	<0.001
AAR (model 2)	1.02 (1.01, 1.02)	<0.001	1.01 (1.01, 1.02)	<0.001
dAAR, 1 increase (model 3)	1.15 (1.15, 1.16)	<0.001	1.10 (1.07, 1.13)	<0.001
dAAR using cutoff point (model 4)				
≤0.72 (n = 376,099)	1		1	
> 0.72 (n = 136,647)	4.43 (4.11, 4.77)	<0.001	1.16 (1.14, 1.18)	<0.001

Note: Age, sex, residence, BMI, annual income level, underlying disability, smoking status, alcohol consumption, exercise frequency, CCI, chronic liver disease, and family history of liver disease were included for adjustment shown in Supporting Table S3.

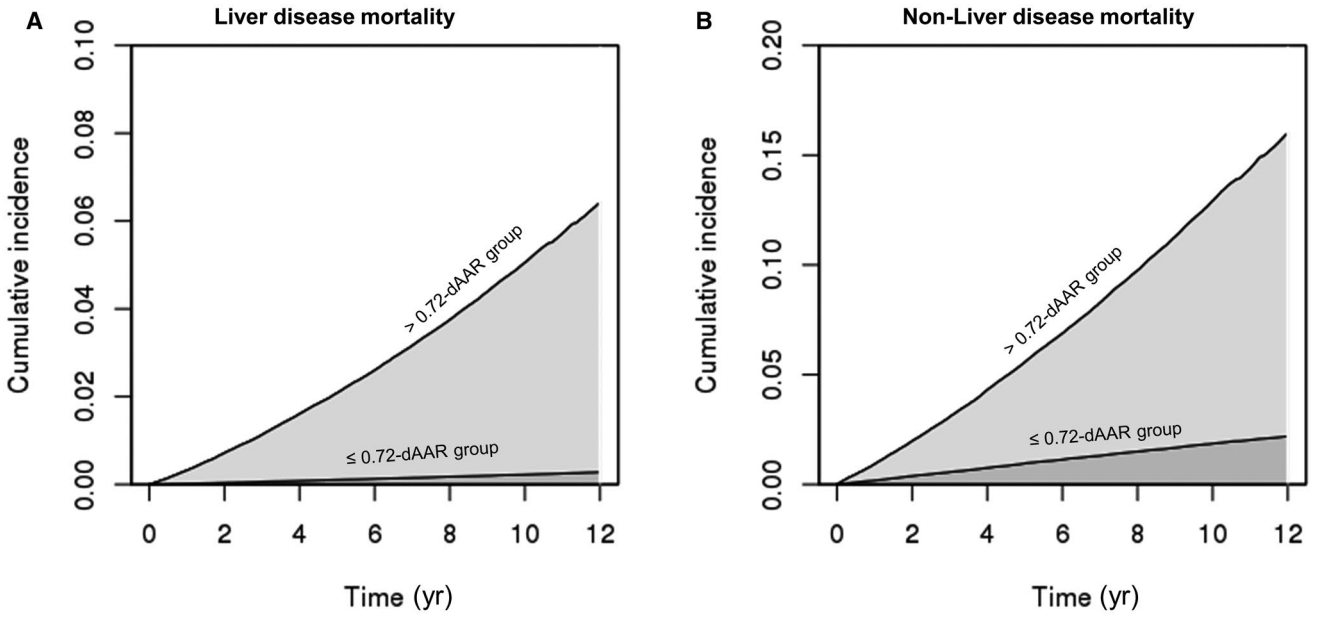

FIG. 4. Aalen-Johansen plots for liver mortality (A) and non-liver mortality (B) in the dAAR score risk groups based on the cutoff value (0.72) from ROC analysis.

hepatitis failure, chronic hepatitis, liver cirrhosis, or liver cancer. Furthermore, subclinical liver disease in the adult population may be related to the performance of dAAR in predicting liver disease mortality. Therefore, our results show that dAAR can be used to screen high-risk populations for liver disease mortality in the general adult population without chronic liver disease, in addition to adults diagnosed with chronic liver disease.

The strength of our study lies in the consistent follow-up of the occurrence of liver disease mortality over 12 years (2004-2015) in a large cohort. Moreover, we validated the performance of dAAR in the Asian population, in addition to findings from the Nordic population.[17] The C-index for liver-related outcomes according to dAAR was 0.81 in the Nordic population[17]; the AUC value of dAAR was the same (0.81) for liver disease mortality in the South Korean population. Both studies showed that the performance of dAAR in predicting liver disease–related outcomes is excellent, because AUC values of 0.8-0.9 are considered to be excellent among diagnostic tools in general.[27]

Our study has certain limitations. First, we did not compare the performance of dAAR with those of other important scoring systems such as the AST-to–platelet ratio index or Fibrosis-4 score, because the NHIS database did not contain serum platelet count levels. Therefore, further validation of dAAR is needed when comparing such data. Second, we used the registered ICD-10 codes to define any comorbidities in this study; however, these may differ from actual underlying diseases. For example, poor accessibility to outpatient clinics may affect the disease diagnosis of some individuals, and there may have been missing cases using registered ICD-10 codes. Finally, there may have been unmeasured and residual confounders during multivariable Cox regression modeling, which may have affected the results of this study.

In conclusion, in this population-based cohort study performed in South Korea, the performance of dAAR in predicting liver disease mortality was better than that of AAR and ALT. Moreover, the performance of dAAR did not significantly differ based on the comorbidity status of chronic liver disease. Our study suggests that dAAR scores can potentially be used for screening and predicting liver disease mortality among the unselected general population.

DATA AVAILABILITY STATEMENT

The data sets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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