Prognostic Value of the Alcoholic Hepatitis Histologic Score in Korean Patients with Biopsy-Proven Alcoholic Hepatitis

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Background/Aims: The alcoholic hepatitis histologic score (AHHS) is a recently developed clinical model for predicting short-term mortality in Caucasian patients with alcoholic hepatitis (AH). The AHHS has not been extensively validated in other ethnic populations. This study validated the AHHS in a Korean patient cohort. Methods: We conducted a prospective cohort study of hospitalized Korean patients with AH between January 2010 and August 2017. Histopathological findings were assessed to determine the AHHS in all study subjects. Histopathological risk factors were examined by Cox regression analysis to predict overall survival (OS). Kaplan-Meier curves were plotted to assess the diagnostic performance of the AHHS. Results: We recruited a total of 107 patients with biopsy-proven AH. None of the individual AHHS components were associated with 3-month mortality. However, the bilirubinostasis type and fibrosis severity were significantly associated with AH mortality beyond 6 months (all p<0.05, except fibrosis severity for 6-month mortality) and OS (all p<0.05). The modified AHHS classification as a binary variable (<5 vs ≥5) was also associated with OS (hazard ratio, 2.88; 95% confidence interval [CI], 1.50 to 5.56; p=0.002), and had higher predictive performance for OS (concordance index [C-index], 0.634; 95% CI, 0.561 to 0.707) than the original AHHS classification (mild vs moderate vs severe: C-index, 0.577; 95% CI, 0.498 to 0.656). This difference was statistically significant (p=0.045). Conclusions: In this prospective Korean AH cohort, the modified AHHS was significantly associated with OS. Therefore, the AHHS might be a useful histological prognosticator for long-term prognosis in patients with nonsevere AH. (Gut Liver 2020;14:636-643)

Key Words: Hepatitis, alcoholic; Alcohol-related disorder; Classification; Biopsy; Prognosis

INTRODUCTION

In developed countries, alcohol-related liver disease is a major cause of advanced liver disease and is the leading cause of death among those who abuse alcohol.1,2 The most severe form of alcohol-related liver disease is alcoholic hepatitis (AH), which is clinically characterized by jaundice and liver failure.3 As patients with AH exhibit higher rates of short-term mortality, there is a need for more accurate patient characterization and more targeted therapies.4 Although AH is often suspected based on clinical and biochemical findings, histological confirmation remains the only method of confirming the diagnosis.5 As such, reliable noninvasive tests for AH are clearly needed.

In order to predict clinical outcome in patients with AH, a number of models have been proposed. The Maddrey discriminant function and the model for end-stage liver disease (MELD) score have been used to identify those patients most likely to benefit from pharmacological therapy.6,7 Other validated models include the ABIC (age, serum bilirubin, international normalized ratio, and serum creatine) score, the Lille score, and the Glasgow alcoholic hepatitis score, and the MAGIC (model for AH to
grade severity in an Asian patient cohort) score.\textsuperscript{8-11} Although biochemical data can be used to predict clinical outcome, AH is likely the only chronic liver disease that lacks a validated histological classification.

Previous studies have shown that several individual histological parameters are associated with clinical outcome in patients with AH.\textsuperscript{12-16} However, there was no attempt to develop a novel histological classification by integrating these parameters. Al-tamirano et al.\textsuperscript{17} recently proposed a new histological scoring system, named the alcoholic hepatitis histologic score (AHHS) for predicting short-term survival in patients with AH. The AHHS is based on several histological features, including degree of fibrosis, degree of neutrophil infiltration, type of bilirubinostasis, and presence or absence of megamitochondria. The AHHS is associated with disease severity and predicts the risk of death within 90 days after histological confirmation in patients with AH.\textsuperscript{17}

The aims of this study were to (1) assess the frequency of each AHHS histological feature among Korean patients with AH and (2) evaluate the prognostic value of the AHHS for predicting long-term survival as well as short-term survival in Korean patients with AH.

MATERIALS AND METHODS

1. Study cohort

The longitudinal cohort for this study was derived from an ongoing, single-center AH registry. Subjects with clinical and biochemical evidence of AH between January 2010 and August 2017 were prospectively enrolled based on inclusion criteria. The criteria for eligibility for liver biopsy were as follows: (1) ≥18 years old; (2) alcohol consumption >60 g/day for men and >40 g/day for women before admission; (3) recent onset of jaundice; (4) elevated levels of gamma-glutamyl transpeptidase; (5) elevated levels of transaminases with an aspartate aminotransferase/alanine aminotransferase ratio >1; and (6) an absence of other etiologies for chronic liver disease such as hepatitis B or C, autoimmune hepatitis, drug-induced liver injury, hemochromatosis, primary biliary cholangitis, or Wilson disease. The prospective study was conducted with those patients with histological confirmation of AH as evidenced by hepatocellular ballooning, steatosis, and neutrophil infiltration. Forty patients were not enrolled due to the presence of other causes of chronic liver disease (hepatitis C infection, n=16; concomitant hepatitis C/human immunodeficiency virus [HIV] coinfection, n=3; military tuberculosis, n=1; syphilitic hepatitis, n=1; hemochromatosis, n=1; or drug-induced liver injury, n=4) or failure to fulfill histologic criteria for AH (n=14). Based upon inclusion and exclusion criteria along with histological confirmation of AH, we enrolled a total of 107 patients in this study.

During the study, all patients received general supportive care including nutrient supplementation, enteral or parenteral nutrition if needed, and administration of B complex vitamins. Those patients that developed complications during hospitalization were treated according to current international practice guidelines.\textsuperscript{18-21} Patients with an Maddrey discriminant function score ≥32 were treated with oral prednisolone (40 mg daily) for 4 weeks, followed by a 2-week taper period. If oral dosing was not tolerated, methylprednisolone (intravenous) with equivalent efficacy (32 mg each 24 hours) was administered. The treatment response to corticosteroids was assessed at day 7 using the Lille score with a cutoff of 0.45.\textsuperscript{11} Patients with contraindications to corticosteroids were treated with pentoxifylline. We obtained written informed consent from each patient in the study cohort. This study was conducted according to the provisions in the Declaration of Helsinki for the participation of human subjects in research and was approved by the Institutional Review Board of Boramae Medical Center (IRB number: 16-2013-45). The trial was registered at clinicaltrials.gov (NCT 01943318).

2. Histological and clinical assessment

Electronic medical records were used to obtain demographic, clinical, and laboratory parameters. Liver samples were obtained between days 1 and 7 after admission, either percutaneously or via a transjugular approach depending on the presence of variceal bleeding, ascites, or coagulopathy. Samples were fixed in 4% formalin, then embedded in paraffin. All liver biopsies were assessed and reviewed by a single, experienced liver pathologist (J.M.B.). Detailed histological analyses were performed both prospectively and retrospectively and included the following observations: (1) presence or absence of hepatocellular damage or ballooning; (2) degree of polymorphonuclear leukocyte infiltration (absent, mild, moderate, or severe); (3) presence or absence of Mallory bodies; (4) degree of steatosis (absent, mild, moderate, or severe); (5) presence and location of bilirubinostasis (absent, hepatocellular bilirubinostasis, canalicular or ductular bilirubinostasis, or mixed hepatocellular plus canalicular or ductular bilirubinostasis); (6) presence or absence of megamitochondria; and (7) stage of fibrosis (no fibrosis, portal fibrosis, expansile fibrosis, bridging fibrosis, or cirrhosis).\textsuperscript{15-17} Diagnosis of AH was based on the overall pattern of histological injury including hepatocellular damage (presence of Mallory bodies and hepatocellular ballooning), inflammatory infiltrate polymorphonuclear leukocytes, and pericellular fibrosis.\textsuperscript{8-22} In order to evaluate a possible association between short-term outcomes and the AHHS score, we graded the severity of fibrosis, type of bilirubinostasis, degree of neutrophil infiltration, and presence of megamitochondria.\textsuperscript{17}

3. Endpoints and assessments

The endpoints included overall survival (OS) and mortality at 3 months, 6 months, and 1 year from the date of biopsy. OS was measured from the date of biopsy until the date of liver transplantation (LT) or death from any cause. When study par-
ticipants were lost to follow-up before LT or death, those data were censored with respect to the date of their last clinic visit. The data cutoff date was May 10, 2018. All death events were verified using mortality data from the Ministry of the Interior and Safety of South Korea. Short-term mortality was defined as death within 3 months, whereas long-term mortality was defined as death beyond 6 months.

4. Statistical analysis

Median and interquartile range (IQR) were used to describe continuous variables, while means of counts and percentages were used to describe categorical variables. Logistic regression analysis was performed to identify histological features associated with 3-month, 6-month, and 1-year mortality. Associations between histological features and OS, and between the AHHS and OS, were assessed using Cox proportional hazard models. Harrell’s concordance-index (C-index) was calculated to validate the prognosis-predictive performance of the AHHS based on the histological classification system. The “compareC” package was used to determine significance between C-indices of the anatomic and prognostic staging models. Kaplan-Meier curves were used to generate survival data; statistical significance was determined using log-rank tests. p-values <0.05 were considered significant. All statistical analyses were performed using SPSS version 20.0 (IBM Corp., Armonk, NY, USA) and the R statistical programming environment, version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

1. Characteristics of study participants

This study included 107 patients with AH as confirmed by histological confirmation. Demographic, clinical, and biochemical data for the study population are presented in Table 1. The median age was 52 years (IQR, 43 to 59 years); 85 patients (79.4%) were male. The median time interval between admission and liver biopsy was 3 days (IQR, 1 to 4 days). One patient experienced acute anemia after percutaneous liver biopsy. However, he was discharged safely after conservative management without further deterioration.

A total of 31 patients (29.0%) were treated with corticosteroids; among these, 28 patients (90.3%) responded to steroid therapy in terms of the Lille score (<0.45) and completed the scheduled treatment for 28 days. Four patients with contraindications to corticosteroids were treated with pentoxifylline as an alternative therapy. Median follow-up duration was 68 weeks (IQR, 22 to 130 weeks), and the observed overall 3-month, 6-month, and 1-year mortality rates were 12.1%, 19.6%, and 30.8%, respectively. After discharge, only 20 patients (18.7%) achieved alcohol abstinence until the last follow-up and 43 patients (40.2%) were readmitted due to alcohol recidivism within 3 months.

2. Histological factors associated with mortality

First, we assessed the relationships between histological features and 3-month mortality (Supplementary Table 1). Univariate and multivariate analyses revealed that none of the AHHS components or any other histological features at admission were significantly associated with 3-month mortality. However, bilirubinostasis type and fibrosis severity were significantly associated with long-term mortality greater than 6 months (Supplementary Table 2). Ductular and/or canalicular plus hepatocellular bilirubinostasis was associated with 6-month mortality (odds ratio, 3.88; 95% confidence interval [CI], 1.39 to 10.83; p=0.010) and 1-year mortality (adjusted odds ratio, 7.05; 95% CI, 2.34 to 21.23; p=0.001), and bridging and/or cirrhosis was significantly associated with 1-year mortality (adjusted odds ratio, 25.96; 95% CI, 3.13 to 215.00; p=0.003).

OS was significantly associated with the bilirubinostasis type (ductular and/or canalicular plus hepatocellular vs no or hepatocellular only: adjusted hazard ratio [HR], 3.37; 95% CI, 1.79 to 6.34; p<0.001) and fibrosis severity (no/portal and/or expansive vs bridging and/or cirrhosis: adjusted HR, 5.28; 95% CI, 2.04 to 13.70; p=0.001) (Table 2).

3. Prognostic assessment based on the AHHS

Fifty patients (46.7%) died and two patients (1.9%) received LT during the follow-up period. Because more than half of patients were still alive without LT during the follow-up duration, we could not estimate the median OS. Among the 50 deaths, 19 occurred in the hospital and 16 (84.2%) succumbed to liver-related events (seven for bleeding, five for hepatorenal syndrome, and four for infection). Patients classified into the mild disease group (AHHS 0–3 points) had better prognosis than those classified into the moderate (4–5 points) and severe (6–9 points) groups. These differences, however, were not statistically significant (moderate vs mild: HR, 1.57; 95% CI, 0.67 to 3.66; p=0.300; severe vs mild: HR, 2.37; 95% CI, 1.00 to 5.59; p=0.050; and severe vs moderate: HR, 1.51; 95% CI, 0.83 to 2.73; p=0.176) (Table 3). The C-index of the AHHS was 0.577 (95% CI, 0.498 to 0.656) (Table 4).

Next, we used an alternative cutoff value (c 5 vs ≥ 5) proposed by Altamirano et al. for sequential use of noninvasive scoring systems (i.e., MELD and ABIC scores) and the AHHS. Using this cutoff, the AHHS successfully defined two subgroups with different survival rates (HR, 3.16; 95% CI, 1.65 to 6.07; p=0.001). The C-index of the modified AHHS classification system (<5 vs ≥5: C-index, 0.634; 95% CI, 0.561 to 0.707) was significantly better than that of the original AHHS classification system (mild vs moderate vs severe: C-index, 0.577; 95% CI, 0.498 to 0.656; p=0.045). The log-rank test showed that the modified AHHS classification as a binary variable (p<0.001) provided better discrimination between subgroup differences than the original AHHS classification (p=0.106) (Fig. 1).

3 months. (40.2%) were readmitted due to alcohol recidivism within 6-month, and 1-year mortality rates were 12.1%, 19.6%, and 30.8%, respectively. After discharge, only 20 patients (18.7%) achieved alcohol abstinence until the last follow-up and 43 patients (40.2%) were readmitted due to alcohol recidivism within 3 months.
4. Sequential use of clinical scoring systems and the AHHS

The modified AHHS (<5 vs ≥5) was independently associated with OS after adjusting for ABIC (p<0.001) or MELD (p<0.001) score (Supplementary Table 3). Therefore, we investigated whether the sequential use of clinical and histological scores improved the prognostic performance for predicting survival in patients with AH. Since there were only six patients in the ABIC class C, the analysis for patients with ABIC class C was not conducted. The sequential use of the AHHS (<5 vs ≥5) did not improve the prognostic assessment in patients with a MELD score ≥21 (p=0.262). However, the AHHS (<5 vs ≥5) did successfully discriminate two subgroups according to the risk of death in patients with ABIC class A and B (ABIC score <9) (p=0.001) (Fig. 2A), and patients with MELD score <21 (p=0.006) (Fig. 2B).

DISCUSSION

In this prospective Korean AH cohort, we validated the prognosis-predictive value of the recently proposed AHHS by assessing OS in histologically confirmed patients. Contrary to the
previous analyses indicate that none of the integral components of the AHHS were associated with 3-month mortality. By contrast, the type of bilirubinostasis and severity of fibrosis were significantly associated with long-term survival greater than 6 months. The bilirubinostasis pattern and fibrosis stage were also significantly associated with OS. The AHHS was significantly associated with OS when a cutoff of 5 points was used. Therefore, these results suggest that long-term survival (as compared to short-term survival) may be predicted by the AHHS in patients with nonsevere AH.

Previous studies reported that the presence of bilirubinostasis is an independent predictor of short-term mortality in AH. Although bilirubinostasis was not associated with 3-month mortality in our cohort, it was significantly associated with 6-month and 1-year mortality. Since the presence of bilirubinostasis was an independent predictor of short-term mortality in AH, the absence of bilirubinostasis may be associated with a better prognosis. The AHHS was significantly associated with OS when a cutoff of 5 points was used. Therefore, these results suggest that long-term survival (as compared to short-term survival) may be predicted by the AHHS in patients with nonsevere AH.

Table 2. Univariate and Multivariate Analyses of Histological Features Associated with Overall Survival in Patients with Alcoholic Hepatitis

| Histologic features | Univariate Cox regression (events, n=52) | Multivariate Cox regression (events, n=52) | Multivariate Cox regression (events, n=52) |
|---------------------|-----------------------------------------|-------------------------------------------|------------------------------------------|
|                     | HR 95% CI p-value                       | HR 95% CI p-value                       | HR 95% CI p-value                       |
| Fibrosis            |                                         |                                           |                                           |
| No/portal and/or expansive | 1.00 Reference                        | 1.00 Reference                        | 1.00 Reference                        |
| Bridging and/or cirrhosis | 5.66 2.24–14.31 <0.001                  | 5.28 2.04–13.70 0.001                   | 5.69 2.22–14.57 <0.001                   |
| Bilirubinostasis    |                                         |                                           |                                           |
| No or hepatocellular only | 1.00 Reference                       | 1.00 Reference                       | 1.00 Reference                       |
| Ductular and/or canalicular | 4.20 1.24–14.14 0.021                 | 3.44 0.99–12.02 0.052                  | 5.31 1.49–18.88 0.010                  |
| Ductular and/or canalicular plus hepatocellular | 4.02 2.27–7.13 <0.001                 | 3.37 1.79–6.34 <0.001                  | 4.10 2.23–7.55 <0.001                  |
| PMN infiltration    |                                         |                                           |                                           |
| Mild                | 1.00 Reference                         | 1.00 Reference                         | 1.00 Reference                         |
| Moderate/severe     | 1.40 0.70–2.80 0.345                    | 0.63 0.29–1.36 0.235                    | 1.00 0.51–1.97 0.997                    |
| Megamitochondria    |                                         |                                           |                                           |
| No                  | 1.00 Reference                         | 1.00 Reference                         | 1.00 Reference                         |
| Yes                 | 1.40 0.75–2.63 0.295                    | 0.63 0.29–1.36 0.235                    | 1.00 0.51–1.97 0.997                    |
| Ballooning          |                                         |                                           |                                           |
| Occasional          | 1.00 Reference                         | 1.00 Reference                         | 1.00 Reference                         |
| Marked              | 2.60 1.50–4.51 0.001                    | 0.98 0.52–1.85 0.944                    | 1.00 0.51–1.97 0.997                    |
| Mallory bodies      |                                         |                                           |                                           |
| No                  | 1.00 Reference                         | 1.00 Reference                         | 1.00 Reference                         |
| Yes                 | 2.57 1.37–4.80 0.003                    | 1.64 0.83–3.24 0.153                    | 1.00 0.51–1.97 0.997                    |
| Steatosis, %        |                                         |                                           |                                           |
| 5–33                | 1.00 Reference                         | 1.00 Reference                         | 1.00 Reference                         |
| 33–66               | 1.63 0.80–3.32 0.177                    | 0.63 0.31–1.30 0.500                    | 1.00 0.51–1.97 0.997                    |
| >66                 | 1.02 0.52–1.99 0.954                    | 0.63 0.31–1.30 0.500                    | 1.00 0.51–1.97 0.997                    |

HR, hazard ratio; CI, confidence interval; PMN, polymorphonuclear neutrophil.

Table 3. Cox Model Results for Overall Patient Survival Based on the AHHS

| Histologic features | Cox regression (events, n=52) |
|---------------------|-----------------------------|
|                     | HR 95% CI p-value           |
| AHHS                |                             |
| Mild (0–3)          | 1.00 Reference              |
| Moderate (4–5)      | 1.57 0.67–3.66 0.300        |
| Severe (6–9)        | 2.37 1.00–5.59 0.050        |
| Moderate (4–5)      | 1.00 Reference              |
| Severe (6–9)        | 1.51 0.83–2.73 0.176        |
| AHHS <5             | 1.00 Reference              |
| AHHS ≥5             | 3.16 1.65–6.07 0.001        |

AHHS, alcoholic hepatitis histologic score; HR, hazard ratio; CI, confidence interval.

Table 4. Ranking of Classification by the C-Index

| Histologic features | C-index 95% CI p-value |
|---------------------|------------------------|
| AHHS (mild vs moderate vs severe) | 0.577 0.498–0.656 0.045 |
| AHHS <5 vs ≥5       | 0.634 0.561–0.707       |

C-index, concordance index; CI, confidence interval; AHHS, alcoholic hepatitis histologic score.
rubinostasis is a surrogate marker for impairment in hepatocellular bile transport and hepatic bile flow, it is common to find bilirubinostasis in patients with severe AH. Several studies have reported that development of bacterial infection and sepsis was associated with bilirubinostasis type. Fibrosis severity was associated with 1-year survival in these patients. This can be attributed to the fact that advanced fibrosis can lead to cirrhosis-related complications and portal hypertension. Further studies are warranted to identify key molecular drivers and optimal therapeutic targets for bilirubinostasis and fibrosis in patients with AH.

A novel histological scoring system was developed by Altimirano et al. to predict short-term mortality in patients with AH. Multiple comparison correction Mild vs moderate: p=0.338 Moderate vs severe: p=0.173

Fig. 1. Overall survival probability of patients with alcoholic hepatitis according to the original alcoholic hepatitis histologic score (AHHS) (A) and the modified AHHS with a cutoff of 5.0 (B).

Fig. 2. Overall survival probability of patients with alcoholic hepatitis (AH) and ABIC class A and B (ABIC score <9) (A) and patients with AH and a MELD score <21 (B) according to the modified AHHS with a cutoff of 5.0. ABIC, age, serum bilirubin, international normalized ratio, and serum creatinine; MELD, model for end-stage liver disease; AHHS, alcoholic hepatitis histologic score.
successfully predicted by AHHS with an area under the receiver operating characteristic curve of 0.77 (95% CI, 0.71 to 0.83). The present study reveals that the AHHS can be used to predict OS using a cutoff of 5.0 points with a C-index of 0.634 (95% CI, 0.561 to 0.707), although the prognostic performance of the AHHS in our Korean cohort was inferior to that of the original discovery cohort. We also found that the AHHS was independently associated with OS even after adjusting for some clinical scoring systems, which is consistent with the previous study.\textsuperscript{17} We used the AHHS to improve the prognostic stratification of AH patients with ABIC class A and B (ABIC score <9) showing low to moderate risk of mortality.\textsuperscript{9} The AHHS also provided a more accurate prediction of survival for AH patients with a MELD score <21, the low risk of mortality group.\textsuperscript{26} Sequential use of the noninvasive clinical scoring systems and the AHHS could help to discriminate patients with relatively high risk of death from those with low to moderate risk of death.

Our study is the first to evaluate the ability of AHHS to evaluate long-term prognosis in patients with AH. In addition, a major strength of this study is that it is the first external validation of AHHS in a Korean population with histologically confirmed AH. The impact of race and ethnicity on AH is not clear. However, this independent external validation of the AHHS in the Korean population is indispensable because of known ethnic significant differences in mitochondrial aldehyde dehydrogenase activity and obesity prevalence.\textsuperscript{27,28} The present study also is the first to clarify the association of the AHHS with OS, not restricted to liver-related mortality. Although a previous study performed survival analyses in some subgroups, it did not perform survival analyses for all patients.\textsuperscript{17} Another strength of our study lies in the fact that it affirms the usefulness of the AHHS and sequential use of noninvasive clinical scoring systems for risk stratification, demonstrating that using a cutoff of 5.0 points derived for sequential analyses was more effective and simpler for risk stratification than the original AHHS classification (mild vs moderate vs severe).

There are certain limitations that should be considered in the present study. First, the majority of patients had relatively well-preserved hepatic reserve (median MELD score, 14; median ABIC score, 7.0), and the 3-month mortality rate was much lower in the current study than in the previous discovery and validation studies.\textsuperscript{17,24} The disease severity of the observed population was different in our study than in the previous studies; therefore, the AHHS might not accurately predict 3-month mortality in our study despite the scoring system that was designed to predict short-term mortality. Second, we did not consider potential differences in interobserver variability in the present and previous studies. Significant interobserver variability among individual pathologists was found in the previous study.\textsuperscript{17} Although the majority of patients in our study exhibited mild to moderate AH, the proportion of patients with severe polymorphonuclear leukocyte infiltration, known as a favorable prognostic marker, was lower than in the previous study (13.1% vs 33%). These findings suggest that there could be significant interobserver variability among pathologists in the present and previous studies.

In summary, we observed that the AHHS accurately predicted OS and mortality beyond 6 months although the integral components of the AHHS were not significantly associated with 3-month mortality. Our results suggest that the AHHS is a useful tool to predict long-term prognosis rather than short-term mortality in Korean patients with relatively nonsevere AH.

**CONFLICTS OF INTEREST**

No potential conflict of interest relevant to this article was reported.

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**AUTHOR CONTRIBUTIONS**

Study concept and design: D.H.L., Y.I.C., W.K. Data acquisition: Y.I.C., J.M.B., S.K.J. Data analysis and interpretation: D.H.L., W.K. Drafting of the manuscript: D.H.L., Y.I.C. Critical revision of the manuscript for important intellectual content: M.S.C., Y.J.J., K.L.L. Statistical analysis: D.H.L., Y.I.C. Obtained funding: B.G.K. Study supervision: B.G.K., W.K. Final approval of the article: all authors.

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