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[Dong-Hee Ryu](#) , Eun-Young Lee , Soo-Jung Ha , [Namsoo Hong](#) *

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Article

Seroepidemiology of Hepatitis B and C in a Medically Vulnerable Area: An Experience from the Ulleung Liver Cancer Prevention and Management Project

Dong-Hee Ryu ¹, Eun-Young Lee ², Soo-Jung Ha ³ and Namsoo Hong ^{2,*}

¹ Department of Preventive Medicine, Daegu Catholic University School of Medicine, Daegu, Korea; ryudh@cu.ac.kr

² Daegu-Gyeongbuk Regional Cancer Center, Kyungpook National University Medical Center, Daegu, Korea; eunyoung0902@naver.com

³ Ulleung Public Community Health Center, Gyeongbuk, Korea; why610@naver.com

⁴ Department of Preventive Medicine, Kyungpook National University School of Medicine, Daegu, Korea; kusmac25@knu.ac.kr

* Correspondence: kusmac25@knu.ac.kr; Tel.: +82-53-420-4864

Simple Summary: Ulleung County, a medically underserved area in South Korea, shows high liver cancer incidence, prompting the Daegu-Gyeongbuk Regional Cancer Center to launch the Ulleung Liver Cancer Prevention and Management Project in 2018. This study aimed to estimate hepatitis B and C prevalence and their risk factors in Ulleung. From 2019 to 2022, 1,792 residents aged 40 and older participated. Blood tests revealed 7.19 HBsAg positivity and 1.37% anti-HCV positivity. The study suggests that while HBsAg prevalence may contribute to Ulleung's high liver cancer rates, anti-HCV prevalence does not fully explain it. Further research is needed on hepatitis and liver cancer in this vulnerable area.

Abstract: Ulleung County, one of the most medically vulnerable areas in South Korea, requires public attention because of the high incidence of liver cancer. This study was conducted as a part of the Ulleung Liver Cancer Prevention and Management Project. The purpose of this study was to estimate the community prevalence of hepatitis B and C viruses and to identify the associated risk factors. The Project's interagency workgroup established a procedure for conducting blood sampling and health behavior surveys at the Ulleung Public Community Health Center. A total of 1,792 residents aged 40 years and older voluntarily participated in the study between 2019 and 2022. The hepatitis B surface antigen (HBs Ag) and hepatitis C virus antibody (anti-HCV) positive rates in Ulleung were 7.19% and 1.37%, respectively. Low education level and lifetime smoking were associated with HBsAg positivity, whereas cupping therapy at non-medical institutions was associated with anti-HCV positivity. The odds of HBs Ag positivity were lower among those with tattoos than among those without. There was a difference in the risk factors associated with hepatitis B and C viral infection. While a high HBs Ag positivity rate alone may not fully explain the high incidence of liver cancer in Ulleung, it may be a contributing factor.

Keywords: early detection of cancer; health behavior; health risk behaviors; hepatitis B; hepatitis C; liver neoplasm; residence characteristics

1. Introduction

As of 2020, the age-standardized liver cancer mortality in South Korea was 909 per 100,000 people which was the highest in the world [1]. According to the World Health Organization, "viral hepatitis causes more than one million deaths per year worldwide, including deaths due to liver cancer caused by hepatitis infection." [2] As such, hepatitis viruses are well-known risk factors for liver cancer.

Ulleung County is one of the most medically vulnerable areas in South Korea. This small island, located in Gyeongbuk province (Figure 1) had a population of 8,996 resident (4,976 males and 4,020 females) in 5,479 households as of 2022 [3]. There are only three private medical institutions, two oriental medicine clinics, and a dental clinic in this county [4]. The Ulleung Public Community Health Center foresees general medical care, as well as public health services. This county requires public attention because of the high incidence in of liver cancer. According to the National Cancer Statistics, the age-standardized liver cancer incidence in Ulleung was 102.5 per 100,000 population during 1999-2003 and 61.5 during 2014-2018, while the national figures for the same period were 50.1 and 35.1, respectively [5]. Considering this high incidence, it is necessary to investigate the viral hepatitis prevalence in the area, but no large-scale research has been conducted so far.



Figure 1. Map of South Korea, with Ulleung shaded in red.

Considering the high incidence of liver cancer in this area, the Daegu-Gyeongbuk Regional Cancer Center launched the Ulleung Liver Cancer Prevention and Management Project in 2018. For this project, an Interagency Workgroup, comprising members from the Department of Health Policy Division of the Gyeongbuk local government, Ulleung Public Community Health Center, regional branch of the National Health Insurance Service, Liver Cancer Center of Kyungpook National University Medical Center, Department of Preventive Medicine in Kyungpook Medical School, and Regional Cancer Center, was organized, and various activities were executed to address the indicators of liver cancer incidence. The activities included prevention education and promotion

within the county, establishing partnerships with policy makers and decision-makers, analyzing the characteristics of registered liver cancer patients in the area, and conducting health behavior surveys for high-risk groups. A study summarizing the results of these activities was published in 2020 [6].

As part of the Ulleung Liver Cancer Prevention and Management Project, this study aimed to estimate the prevalence of community hepatitis B and C viruses and to identify the associated risk factors.

2. Materials and Methods

2.1. Subject Recruitment

As of 2019, the number of registered residents in Ulleung was 9,617 (5,230 males and 4,387 females), and people aged 40 years and older accounted for 70.2% (6,750) of this population [3]. The Interagency Workgroup decided to use several means to encourage community participation in the project. A promotional video was produced by the Regional Cancer Center under the supervision of medical professionals and transmitted through billboards at Ulleung Port. Simultaneously, banners stating that the Ulleung Public Community Health Center was conducting screening tests for hepatitis B and C were placed around the island. Leaflets were placed at the Ulleung Public Community Health Center to guide the users. The Ulleung Public Community Health Center established detailed procedures for conducting blood sampling and health behavior surveys.

In total, 1,792 residents aged 40 years and older voluntarily participated in this study between 2019 and 2022. Well-trained nurses explained the study's purpose and methods. All participants provided written informed consent, and the study protocol was approved by the Institutional Review Board of Kyungpook National University Medical Center (approval number: knuh2018-11-005 and approval date: November 21, 2019)

2.2. Serologic Tests

Approximately 15 mL of venous blood was drawn from all participants by a trained nurse. All the samples were subjected to hepatitis B surface antigen (HBsAg) and hepatitis C virus antibody (anti-HCV) test. HBsAg and anti-HCV screening were performed using the Cobas e801 module (Roche Diagnostic International Ltd., Rotkreuz, Switzerland), and Alinity (Abbott Diagnostics, Wiesbaden, Germany), respectively. Samples that yielded positive results for anti-HCV were subjected to additional quantitative HCV RNA screening and HCV genotyping tests using the Cobas 8800 and Cobas 4800 (C4800) modules (Roche Diagnostics International Ltd., Rotkreuz, Switzerland), respectively. The Ulleung Public Community Health Center obtained serological test results from Seoul Clinical Laboratories, the official test institution, and the test results were recorded for each study participant.

2.3. Health Behavior Survey

The health behavior survey was conducted using a previously established questionnaire [6]. The questionnaire was reviewed and approved by members of the Interagency Workgroup and an epidemiologist [6]. The items were categorized into general characteristics, general health behaviors, and risky health behaviors.

The general characteristics included sex, age (40-49, 50-59, 60-69, and ≥ 70 years), level of education (\leq elementary, junior high school, high school, and \geq college), average monthly household income (<500, 500-999, 1000-1999, 2000-2999, 3000-3999, and ≥ 4000), and duration of residence in Ulleung (<1 year, 1-9 years, and ≥ 10 years).

The general health behaviors included cigarette smoking (never, former, or current), alcohol consumption (no, moderate, or heavy), obesity (normal, overweight, or obese), and regular cancer screening. Heavy alcohol consumption was defined as seven or more drinks for men and five or more drinks for women at least twice per week. Obesity status was based on body mass index (BMI); height was measured using the BSM330 instrument (Biospace Inc., Seoul, South Korea); and body composition was measured using the InBody770 analyzer (Biospace Inc., Seoul, South Korea).

Risky health behaviors included tattooing, piercing, acupuncture, cupping therapy, transfusion, dialysis, doctor-diagnosed diabetes mellitus, and lack of knowledge of liver diseases (hepatitis B, hepatitis C, and liver cirrhosis). Regarding the items on knowledge of liver diseases, detailed information could not be obtained owing to methodological limitations; therefore, each participant was simply asked whether they knew about the diseases; the response of “yes” to the questions indicated the participant had the necessary knowledge. Acupuncture and cupping therapy can cause blood-borne infections [7-9]; hence, these therapies should be performed only at certified medical institutions, but they are sometimes illegally performed at non-medical institutions in Korea [10]. Therefore, the participants were asked whether they received acupuncture or cupping therapy at uncertified places.

2.4. Statistical Analysis

The participants with missing values for the main variables were excluded from the analysis. A total of 1,684 individuals were included in the final analysis (Table 1). We used the chi-square test or Fisher’s exact test for frequency analysis. Logistic regression analyses were performed to examine the association between HBsAg or anti-HCV positivity and health behavioral characteristics. Additional analyses were performed after adjusting for sex, age, education, monthly household income, and residential period. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA), and statistical significance was set at p-value <0.05.

Table 1. General characteristics.

Variables	n (%)
Total	1684 (100.0)
Sex	
Male	840 (49.9)
Female	844 (50.1)
Age	
40-49	417 (24.8)
50-59	531 (31.5)
60-69	726 (43.1)
≥70	10 (0.6)
Education	
≤Elementary	218 (13.0)
Junior high	331 (19.7)
High	660 (39.2)
≥College	475 (28.2)
Monthly household income (1000 KRW)	
<500	256 (15.2)
500-999	170 (10.1)
1000-1999	373 (22.2)
2000-2999	330 (19.6)
3000-3999	227 (13.5)
≥4000	328 (19.5)
Residential period in Ulleung	
<1 year	75 (4.5)
1-9 years	412 (24.5)
≥10 years	1197 (71.1)

Abbreviation: KRW, the currency of Korea (1000 KRW is approximately 1 USD).

3. Results

As per the results of the serological tests for hepatitis, 121 participants had HBsAg-positive (7.19%) and 23 had anti-HCV-positive (1.37%) status (Table 1); 67% were enrolled in the study before the coronavirus disease (COVID-19) pandemic in 2019. The participation rate decreased since 2020 owing to the spread of the COVID-19. However, there were no statistically significant differences in sex or age before and during the pandemic (sex: $p=0.184$; age: $p=0.142$; data not shown).

HBsAg positivity was high among men, those aged 60 years and older, those with education level below junior school, those with monthly household income less than KRW 2,000,000, and those residing in the county for ≥ 10 years. In addition, the BsAg positivity rate increase as age increased and as education level decreased. There was a significant association between HBsAg positivity and educational attainment. On the other hand, anti-HCV positivity was high among women, those aged 50 years and younger, those with education level below elementary school or above college degree, those with moderate monthly household incomes, and those residing in the county <10 years. There was no statistically significant association between anti-HCV positivity and any of the general characteristics analyzed (Table 2).

Table 2. Seropositivity for HBsAg and anti-HCV according to general characteristics.

Variables	HBsAg positivity			Anti-HCV positivity		
	n (%)	Crude OR (95% CI)	Adjusted OR ^a (95% CI)	n (%)	Crude OR (95% CI)	Adjusted OR ^a (95% CI)
Total	121 (7.19)	-	-	23 (1.37)	-	-
Sex						
Male	66 (7.86)	Reference	-	10 (1.19)	Reference	-
Female	55 (6.52)	0.83 (0.59, 1.18)	-	13 (1.54)	1.41 (0.62, 3.19)	-
Age						
40-49	22 (5.45)	Reference	-	5 (1.24)	Reference	-
50-59	33 (6.21)	1.15 (0.69, 1.92)	-	8 (1.51)	1.27 (0.41, 3.91)	-
60-69	62 (8.54)	1.50 (0.95, 2.38)	-	9 (1.24)	1.16 (0.39, 3.41)	-
≥ 70	4 (40.00)	13.18 (4.14, 41.94)	-	1 (10.00)	7.28 (0.79, 67.22)	-
Education						
\leq Elementary	27 (12.39)	3.31 (1.86, 5.87)	3.58 (1.79-7.15)	5 (2.29)	1.59 (0.50, 5.05)	1.07 (0.25-4.53)
Jr. high	29 (8.76)	2.34 (1.34, 4.08)	2.55 (1.35-4.81)	3 (0.91)	0.61 (0.16, 2.37)	0.46 (0.10-2.11)
High	43 (6.52)	1.79 (1.08, 2.99)	1.90 (1.12-3.21)	8 (1.21)	0.91 (0.34, 2.45)	0.78 (0.28-2.19)
\geq College	22 (4.63)	Reference	Reference	7 (1.47)	Reference	Reference
Monthly household income (1000 KRW)						
<500	22 (8.59)	1.89 (1.01, 3.53)	1.71 (0.85-3.43)	1 (0.39)	0.43 (0.04, 4.16)	0.34 (0.03-3.55)
500-999	19 (11.18)	2.24 (1.16, 4.36)	2.06 (1.01-4.21)	1 (0.59)	1.27 (0.21, 7.65)	1.04 (0.16-6.86)
1000-1999	28 (7.51)	1.65 (0.91, 2.99)	1.51 (0.81-2.82)	10 (2.68)	2.95 (0.81, 10.82)	2.47 (0.63-9.62)
2000-2999	20 (6.06)	1.43 (0.77, 2.65)	1.41 (0.75-2.64)	7 (2.12)	2.28 (0.59, 8.89)	2.22 (0.56-8.74)
3000-3999	15 (6.61)	1.44 (0.73, 2.83)	1.43 (0.73-2.81)	1 (0.44)	0.47 (0.05, 4.52)	0.47 (0.05-4.57)
≥ 4000	17 (5.18)	Reference	Reference	3 (0.91)	Reference	Reference

Residential period in Ulleung						
<1 year	4 (5.33)	0.54 (0.19, 1.49)	0.57 (0.20-1.60)	2 (2.67)	2.37 (0.53-10.61)	3.10 (0.66-14.52)
1-9 years	14 (3.40)	0.45 (0.27, 0.73)	0.48 (0.29-0.80)	8 (1.94)	1.67 (0.69-4.00)	2.00 (0.80-5.01)
≥10 years	103 (8.60)	Reference	Reference	13 (1.09)	Reference	Reference

^a Adjusted for sex and age

Abbreviations: OR, odds ratio; CI, confidence interval; KRW, the currency of Korea (1000 KRW is approximately 1 USD)

Table 3 shows the general health behaviors according to HBsAg and anti-HCV positivity. There was a positive association between cigarette smoking and HBsAg positivity but not with anti-HCV positivity. Former and current smokers showed statistically and significantly higher odds of HBsAg positivity than non-smoker even after adjusting for sex, age, level of education, monthly household income, and residential period in Ulleung (adjusted odds ratio [aOR] = 2.06 and 1.86, respectively). Alcohol consumption, obesity, and regular cancer screening did not show a significant association with HBsAg and anti-HCV positivity.

Table 3. General health behaviors according to seropositivity of HBsAg and Anti-HCV.

Variables	HBsAg positivity			Anti-HCV positivity		
	n (%)	Crude OR (95% CI)	Adjusted OR ^a (95% CI)	n (%)	Crude OR (95% CI)	Adjusted OR ^a (95% CI)
Cigarette smoking						
Never	57 (5.83)	Reference	Reference	14 (1.43)	Reference	Reference
Former	35 (10.23)	1.69 (1.11, 2.57)	2.06 (1.12, 3.80)	1 (0.29)	0.19 (0.03, 1.46)	1.70 (0.52, 5.56)
Current	29 (7.97)	1.44 (0.95, 2.20)	1.86 (1.03, 3.35)	8 (2.20)	1.40 (0.59, 3.33)	0.28 (0.03, 2.53)
Alcohol consumption						
No	54 (9.08)	Reference	Reference	11 (1.85)	Reference	Reference
Moderate	42 (5.48)	0.61 (0.42, 0.91)	0.70 (0.47, 1.06)	9 (1.17)	0.70 (0.30, 1.67)	0.74 (0.30, 1.85)
Heavy	25 (7.74)	0.78 (0.49, 1.26)	0.83 (0.48, 1.41)	3 (0.93)	0.49 (0.14, 1.76)	0.59 (0.14, 2.43)
Obesity						
Normal	39 (7.29)	Reference	Reference	7 (1.31)	Reference	Reference
Overweight	31 (7.47)	0.85 (0.53, 1.35)	0.81 (0.50, 1.31)	4 (0.96)	0.66 (0.20, 2.21)	0.69 (0.20, 2.38)
Obese	51 (6.95)	0.94 (0.64, 1.40)	0.90 (0.60, 1.35)	12 (1.63)	1.12 (0.46, 2.76)	1.31 (0.51, 3.34)
Cancer screening						
No	18 (4.93)	0.61 (0.38, 0.99)	0.63 (0.38, 1.04)	9 (2.47)	2.17 (0.94, 4.99)	2.44 (0.99, 6.04)
Yes	103 (7.81)	Reference	Reference	14 (1.06)	Reference	Reference

^a Adjusted for sex, age, education, monthly household income, and residential year in Ulleung.
Abbreviations: OR, odds ratio; CI, confidence interval

Table 3 shows the association of risky health behaviors with HBsAg and anti-HCV positivity. Tattooing, one of the various risky health behaviors related to blood-borne infections, and knowledge

of liver diseases showed a statistically significant association with HBsAg positivity. Unexpectedly, individuals with tattoos showed lower odds of HBsAg positivity than those without tattoos. Moreover, HBsAg positivity was statistically and significantly associated with knowledge of hepatitis B and C but not with knowledge of liver cirrhosis. On the other hand, anti-HCV positivity showed a statistically significant association between anti-HCV positivity and cupping therapy at certified clinics, it can be said that the certification status of institutions offering cupping treatment was an important factor.

4. Discussion

The purpose of this study was to estimate the prevalence of hepatitis B and C viruses in Ulleung County, a medically vulnerable area that is reported to have a high incidence of liver cancer and, determine the factors underlying their high incidence.

4.1. HBsAg and Anti-HCV Prevalence

The present study revealed that HBsAg positivity in Ulleung was 7.19%. In South Korea, many serological studies on hepatitis B were conducted in the 1980s [11-14]. In the 1980s, the HBs Ag positivity rate ranged from 8% to 10%, but the disease burden gradually decreased with the introduction of the vaccination program in 1983 [14]. Since 1998, when nationwide immunization began, HBsAg positivity decreased from 4.6% in 1998 to 2.9% in the 2010s [14]. A study on the global burden of hepatitis B viral infection reported that the HBsAg prevalence in the general population in East Asia in 2019 was 3.02% [15], this rate is lower than that found in this study. The HBsAg positivity rate in Ulleung in this study was similar to the rate in the 1980s. According to the results of the 2021 Korea National Health and Nutrition Examination (KNHANES), the HBsAg positivity rates by age group are as follows: 40-49 years: 3.9%, 50-59 years: 5.7%, 60-69 years: 2.4%, 70 years and older: 3.0% [16]. Comparing these with the present study's results, it can be estimated that the prevalence of HBsAg positivity rate is higher in Ulleung than the national average. To confirm the prevalence of HBsAg in the community as a whole, additional research targeting all age groups, including children, adolescent, or young people is necessary.

In this study, the anti-HCV positivity rate was 1.37%, similar to that reported in previous studies [17-19]. In a study conducted in Jeonnam, where a high rate of liver cancer incidence was confirmed, the anti-HCV positivity was as high as 5.5%. High HCV prevalence is said to be associated with a high incidence of liver cancer in the region [19]. On the other hand, the association between high incidence of liver cancer and anti-HCV prevalence in the present study was not evident.

4.2. Educational Level and Hepatitis B and C Viral Infections

In the present study, HBsAg prevalence increased significantly as the educational level decreased. This is consistent with the results of a Taiwanese study, namely that HBsAg and anti-HCV positivity are inversely related to educational level [20]. In this study, low educational level was found to be a risk factor for hepatitis B but not hepatitis C viral infection. Two hypotheses can explain this phenomenon. First, it can be assumed that high education attainment is conducive to vaccination; further, effective vaccines are available against hepatitis B but not hepatitis C viral infection; therefore, an inverse relationship was found between education level and hepatitis B infection but not with hepatitis C infection. Second, there could be some degree of correlation between the level of education and knowledge of hepatitis B, but this may not be true for knowledge of hepatitis C. In other words, it could be inferred that there is a possibility of insufficient understanding of hepatitis C in the general population. This interpretation is also supported by the results of the present study, where there was an association between the understanding of hepatitis B and C and HBsAg positivity, even after adjusting for general characteristics, including educational level. Such an association was not observed with anti-HCV positivity.

4.3. Risky Health Behaviors and Hepatitis B and C Virus Infections

The risky health behaviors of patients with liver cancer were analyzed according to HBsAg and anti-HCV positivity. In all, 41.9% reported lifetime smoking, similar to the rate reported in the 2022 Ulleung Community Health Survey (39.5%) [21]. Previous studies have reported that both chronic hepatitis B and C and cigarette smoking are risk factors for hepatocellular carcinoma [22-24]. According to the results of a meta-analysis published in 2010, the risk of hepatocellular carcinoma was aggravated with HBV and HCV infection and cigarette smoking [24]. The significant association between HBsAg positivity and lifetime smoking identified in this study supports the results of the results of previous studies. In contrast, no significant association was found between anti-HCV positivity and lifetime smoking status. This result completely contradicts that of a previous study showing that smoking was identified as a risk factor in HCV seropositive individuals, but not in HBV seropositive subjects [20]. Considering both results, further research on the relationship between chronic viral hepatitis and smoking is necessary.

Unexpectedly, the odds for HBsAg positivity were significantly lower in patients with tattoos than in those without. No significant association was observed between anti-HCV positivity and tattooing. This result supports previous research findings, namely that the occurrence of chronic viral hepatitis is not associated with tattoos [25]. Considering such results, the caution should be exercised when using tattooing as a surrogate for other risky health behaviors such as piercing and acupuncture or cupping therapy at non-medical institutions.

Cupping therapy at non-medical institutions was found to be significantly associated with anti-HCV positivity meaning it can be considered a risk factor for hepatitis C infection. Viral transmission is known to be the main infection route for hepatitis B, but not for hepatitis C virus infection [26]. Further, the relationship between cupping therapy at non-medical institutions and HBsAg positivity was not confirmed in previous reports. In addition, no association was identified between acupuncture at non-medical institutions and anti-HCV positivity, indicating that the environment in which cupping therapy was performed was less sterile than that in which acupuncture was performed. In-depth research on the procedures and environments of cupping therapy and acupuncture and the prevalence of hepatitis B and C is needed.

This study had the following limitations. First, only community-based screening tests and survey results were reported, and comparison with a control area was not performed. Second, most study participants participated in the examination when they visited the community health center; therefore, selection bias was inevitable. Third, the use of standardized questionnaires was not possible, therefore, self-developed questionnaires were used and the study participants completed the survey in a self-administered manner. Hence, the risk of random responses cannot be completely ruled out. Nevertheless, the strength of this study is that, to our knowledge, it is the first study to examine the relationship between the incidence of liver cancer and chronic viral hepatitis in Ulleung County. Moreover, as this study was conducted as part of a multi-institutional project, it presents a research method that can be used in vulnerable area where access to medical care is limited and unmet medical needs are widespread. Further studies on chronic viral hepatitis and risky health behaviors in vulnerable areas are needed.

5. Conclusions

There were differences in the risk factors associated with hepatitis B and C infections. While a high HBsAg positivity rate alone may not fully explain the high incidence of liver cancer in Ulleung, it may be a contributing factor. On the other hand, it is difficult to explain the high incidence of liver cancer in regions with a low anti-HCV positivity rate.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board of Kyungpook National University Medical Center (protocol code knuh2018-11-005 and approval date: November 21, 2019).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Data access is provided and managed at the discretion of Daegu Gyeongbuk Regional Cancer Center; visit <http://www.dgcancer.kr/> for more information regarding data inquiries. Computing code can be made available by request of the corresponding author.

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Conflicts of Interest: The authors declare no conflicts of interest.

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