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Clinical Features and Surveillance of Very Late Hepatocellular Carcinoma Recurrence After Liver Transplantation

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Background: This study aimed to assess patterns of hepatocellular carcinoma (HCC) recurrence after liver transplantation (LT) and to establish long-term surveillance protocols for late HCC recurrence.

Material/Methods: The 232 LT recipients experiencing subsequent HCC recurrence were categorized as Group 1, early recurrence (within 1 year of LT; n=117); Group 2, late recurrence (occurring in years 2–5; n=93); and Group 3, very late recurrence (after year 5; n=22).

Results: Recurrence was detected by only elevated tumor marker levels in 11.1%, 30.1%, and 45.5% of patients in Groups 1, 2, and 3, respectively (p<0.001). The proportion of intrahepatic and extrahepatic metastases was similar in all 3 groups. Common sites of extrahepatic metastasis were the lung and bone; these were also similar across the 3 groups. Overall post-recurrence patient survival rates were 60.2% at 1 year, 28.2% at 3 years, 20.5% at 5 years, and 7.0% at 10 years. Median post-recurrence survival periods were 10.2, 23.8, and 37.0 months in Groups 1, 2, and 3, respectively.

Conclusions: While the pattern of HCC recurrence was similar regardless of time of recurrence, post-recurrence survival was significantly longer in patients with later recurrence. Long-term surveillance for HCC recurrence beyond 5 years after LT is recommended.

MeSH Keywords: **Carcinoma, Hepatocellular • Neoplasm Metastasis • Neoplasm Recurrence, Local**

Abbreviations: **AFP** – α-fetoprotein; **CT** – computed tomography; **HCC** – hepatocellular carcinoma; **LT** – liver transplantation; **PIVKA-II** – proteins induced by vitamin K antagonist or absence-II

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Background

Liver transplantation (LT) is an established treatment for patients with liver cirrhosis and small hepatocellular carcinomas (HCCs). While the risk of HCC recurrence is reduced by careful patient selection according to the institutional eligibility criteria, HCC recurrence cannot be prevented and remains a key cause of death in LT recipients [1–5].

Since it is not possible to prevent HCC recurrence completely, post-transplant surveillance for HCC is essential, although the duration and interval of follow-up evaluation is the subject of some debate. HCC recurrence usually occurs during the first a few years after LT, and very late recurrence after 5 years is rare. Because of the relatively low incidence of very late HCC recurrence, it has been reported that long-term post-LT surveillance is not sufficiently cost-effective [6]. However, long-term follow-up data obtained from a high-volume LT center has identified that such patients constitute a small but not insignificant number of recipients [7,8]. However, the clinicopathological features of LT recipients showing very late HCC recurrence and their post-recurrence prognosis have not yet been reported in detail.

This study aimed to assess the pattern of HCC recurrence and post-recurrence prognosis after LT and to establish long-term surveillance protocols for very late HCC recurrence.

Material and Methods

Patient selection

The LT database at our institution was searched to identify patients who underwent LT for HCC over a 14-year period from January 2000 to December 2013. Patients experiencing subsequent HCC recurrence before December 2016 were included in the analysis. HCC recurrence was defined as direct detection of lesion(s) in any metastatic site by imaging study, usually without pathological confirmation by biopsy. *De novo* HCC occurrence was not taken into account in this study as its occurrence is extremely rare.

Follow-up was conducted retrospectively until December 2017 through a medical record review and assistance from the National Health Insurance Service. The patient follow-up period was, therefore, ≥48 months or until patient death. The post-recurrence follow-up period was ≥12 months or until patient death. All patients were followed up to determine survival status. The study protocols were approved by the Institutional Review Board of Asan Medical Center (AMC-IRB 2017-0576).

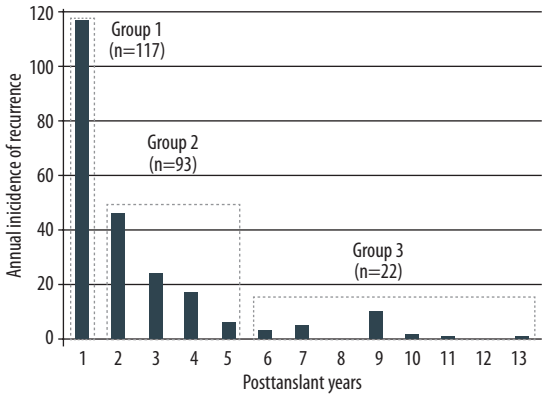

Figure 1. Annual incidence and grouping of hepatocellular carcinoma recurrence after liver transplantation.

Patient grouping according to the timing of HCC recurrence

Patients experiencing HCC recurrence were categorized into 3 groups according to the time of HCC recurrence after LT: Group 1, early recurrence (within year 1); Group 2, late recurrence (occurring in years 2–5); and Group 3, very late recurrence (after 5 years; Figure 1). The present study focused on patients in Group 3 (those with very late HCC recurrence).

Post-transplant surveillance and treatment for HCC recurrence

All LT recipients with a past history of HCC received follow-up examinations every month during the first year and every 3 months thereafter. Detailed follow-up protocols based on the relative risk of HCC recurrence have been published previously [7]. Measurement of α-fetoprotein (AFP) and proteins induced by vitamin K antagonist or absence-II (PIVKA-II) was routinely performed at outpatient clinic visits. The general principles of treatment for recurrent HCC lesions were applied to LT recipients with HCC recurrence [7,9,10]. Initial treatment comprised locoregional therapy, including transarterial chemoembolization, radiofrequency ablation, radiotherapy, and surgical resection; and patients received chemotherapy as the final treatment modality.

Statistical analysis

Continuous variables are reported as the means and standard deviation or median with ranges and were compared using the *t* test or analysis of variance (ANOVA). Categorical variables were compared using the chi-square or Fisher's exact test. Survival curves were generated using the Kaplan–Meier method and compared using the log-rank test. A p-value <0.05 was considered to indicate a statistically significant difference. Statistical analyses were performed using SPSS version 22 (IBM, New York, NY, USA).

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Table 1. Pretransplant characteristics of liver transplantation recipients according to the time of hepatocellular carcinoma recurrence.

	Group 1 (n=117)	Group 2 (n=93)	Group 3 (n=22)	p-Value		
				Group 1 *vs.* 2	Group 1 *vs.* 3	Group 2 *vs.* 3
Age at LT, years	53.1±6.3	53.5±6.2	53.7±5.3	0.73	0.31	0.42
Age at recurrence, years	53.6±6.3	55.8±6.3	61.5±5.5	0.98	0.29	0.29
Sex, Male/Female, n	108/9	82/11	21/1	0.31	0.51	0.46
Background liver disease, n (%)				0.42*	0.072*	0.24*
HBV	106 (90.6)	81 (87.1)	17 (77.3)			
HCV	6 (5.1)	4 (4.3)	5 (22.7)			
ALD	2 (1.7)	5 (5.4)	0			
Others	3 (2.6)	3 (3.2)	0			
MELD score, mean ±SD	13.1±6.7	12.6±6.4	17.4±7.5	0.59	0.29	0.18
Pre-LT AFP, median, ng/mL	49.9	22.5	16.5	0.045	0.027	0.088
Pre-LT PIVKA-II, median, mAU/mL	43	29	18	0.29	0.56	0.47
LT type, n (%)				0.15	0.36	0.53
Living-donor	107 (91.5)	90 (96.8)	22 (100)			
Deceased-donor	10 (8.5)	3 (3.2)	0			
Explant Milan criteria, n (%)				0.058	0.071	0.51
Within	50 (42.7)	52 (55.9)	14 (63.6)			
Beyond	67 (57.3)	41 (44.1)	8 (36.4)			
Explant UCSF criteria, n (%)				0.18	0.53	0.86
Within	66 (56.4)	61 (65.6)	14 (63.6)			
Beyond	51 (43.6)	32 (34.4)	8 (36.4)			
Explant AMC criteria, n (%)				0.24	0.079	0.28
Within	78 (66.7)	69 (74.2)	19 (86.4)			
Beyond	39 (33.3)	24 (25.8)	3 (13.6)			
Salvage LT, n (%)				0.54	0.043	0.071
Yes	20 (17.1)	13 (14.0)	0			
No	97 (82.9)	80 (86.0)	22 (100)			

HBV – hepatitis B virus; HCV – hepatitis C virus; ALD – alcoholic liver disease; MELD – model for end-stage liver disease; AFP – α-fetoprotein; PIVKA-II – proteins induced by vitamin K antagonist or absence-II; LT – liver transplantation; UCSF – University of California, San Francisco; AMC – Asan Medical Center. * Comparison of HBV *vs.* non-HBV.

Results

Study subjects

Among 3850 adult patients undergoing LT during the study period, 1486 recipients had a diagnosis of HCC. By December 2016, 232 of these patients (15.6%) had been diagnosed with HCC recurrence and were included in the analysis.

Comparison of patient profiles according to the timing of HCC recurrence

Figure 1 shows the annual incidence of HCC recurrence; 117 (50.4%) were in Group 1, 93 (40.1%) were in Group 2, and 22 (9.5%) were in Group 3. The pretransplant clinical features of study subjects according to the time of HCC recurrence are summarized in Table 1.

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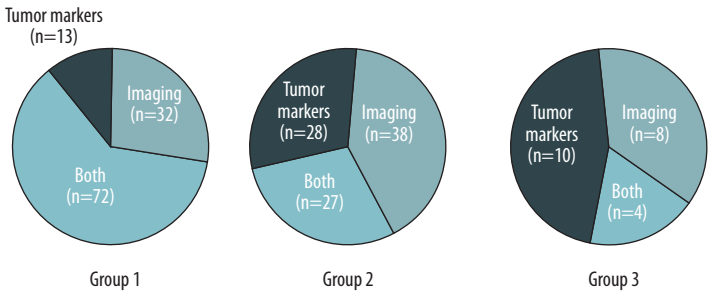

Figure 2. Comparison of the initial methods of diagnosing hepatocellular carcinoma according to the time of tumor recurrence. Both indicate concurrent detection of abnormal findings from tumor marker and imaging studies.

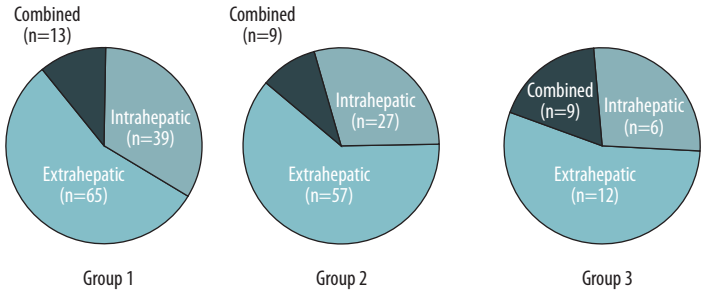

Figure 3. Comparison of the sites of initial hepatocellular carcinoma recurrence according to the time of tumor recurrence. Combined cases indicate combined intrahepatic and extrahepatic recurrences.

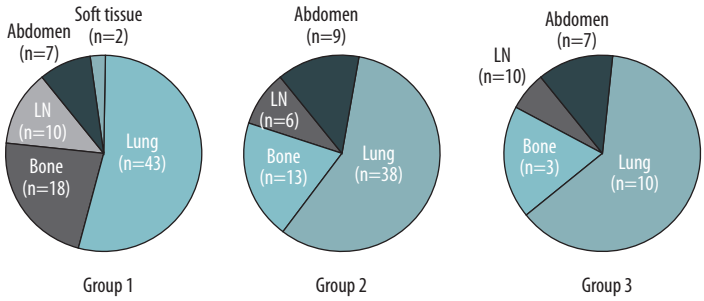

Figure 4. Comparison of the common sites of initial extrahepatic hepatocellular carcinoma recurrence according to the time of tumor recurrence. LN – lymph node.

Patterns of HCC recurrence according to the time of recurrence

The initial method of diagnosing HCC recurrence is shown in Figure 2. The recurrence detection rates by elevation of tumor marker (AFP and/or PIVKA-II) levels only were 11.1% in Group 1, 30.1% in Group 2, and 45.5% in Group 3 (Group 1 *vs.* 2, p<0.001; Group 1 *vs.* 3, p<0.001; Group 2 *vs.* 3, p=0.17).

The sites of initial HCC recurrence are shown in Figure 3. The proportion of intrahepatic, extrahepatic, and combined intrahepatic-extrahepatic metastases were 33.3%, 55.6%, and 11.1% in Group 1; 29.0%, 61.3%, and 9.7% in Group 2; and 27.3%, 54.5%, and 18.2 in Group 3, respectively. No statistically significant differences in isolated intrahepatic recurrence were seen between the groups (Group 1 *vs.* 2, p=0.51; Group 1 *vs.* 3, p=0.58; Group 2 *vs.* 3, p=0.87).

The common sites of initial extrahepatic HCC recurrence are shown in Figure 4. The proportions of lung and bone metastases were 55.1% and 23.1% in Group 1, 57.6% and 19.7% in Group 2, and 62.5% and 18.8% in Group 3, respectively. No statistically significant differences in lung and bone metastases were seen between the groups (Group 1 *vs.* 2, p=0.88; Group 1 *vs.* 3, p>0.99; Group 2 *vs.* 3, p>0.99).

Patient profiles and survival outcomes

The overall patient survival rate was 84.9% at 1 year, 49.6% at 3 years, 33.6% at 5 years, and 19.0% at 10 years (Figure 5A). The post-recurrence survival rate was 60.2% at 1 year, 28.2% at 3 years, 20.5% at 5 years, and 7.0% at 10 years (Figure 5B). Overall patient survival was seen to differ according to the timing of HCC recurrence because they represent a summation of the disease-free survival period and post-recurrence

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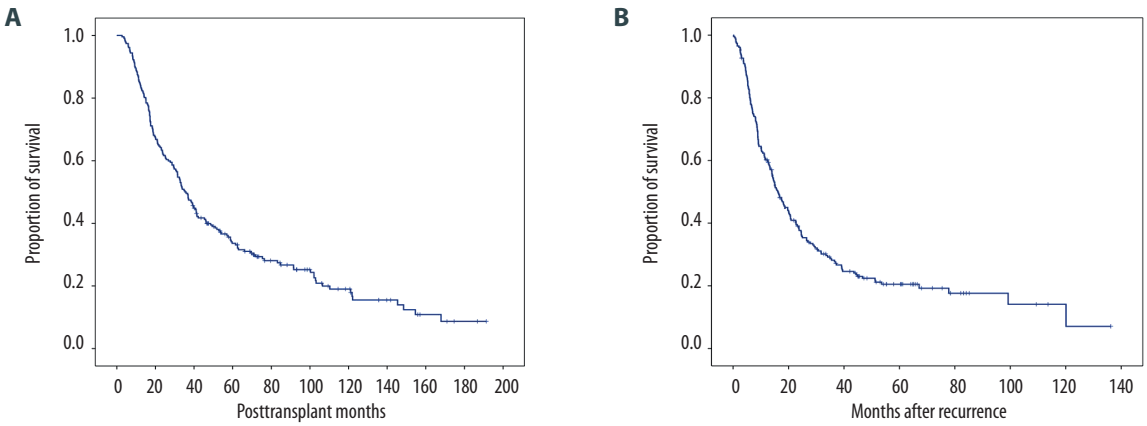

Figure 5. Overall patient survival curve (**A**) and post-recurrence patient survival curve (**B**) in 232 liver transplant recipients diagnosed with hepatocellular carcinoma recurrence.

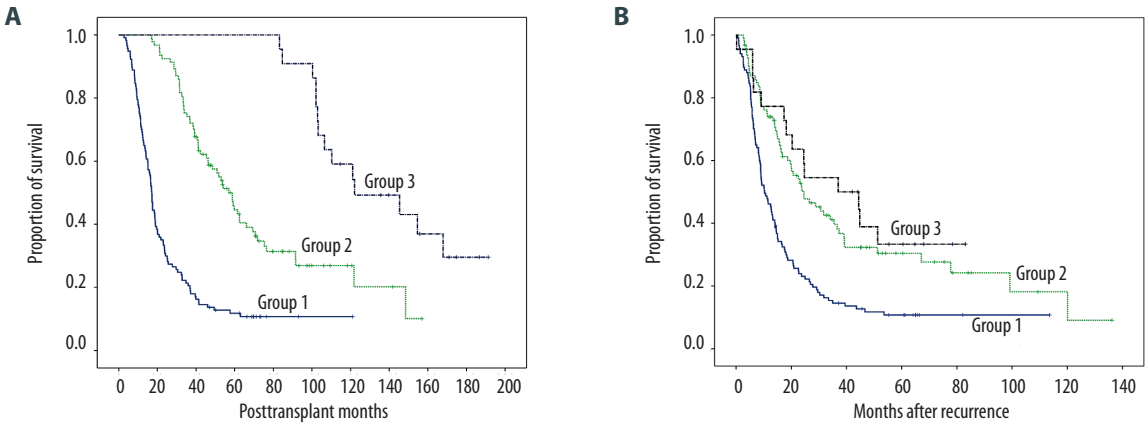

Figure 6. Overall patient survival curve (**A**) and post-recurrence patient survival curve (**B**) according to the time of hepatocellular carcinoma recurrence.

survival period (p<0.001, Figure 6A). The median post-recurrence survival period was 10.2 months in Group 1, 23.8 months in Group 2, and 37.0 months in Group 3. Group 3 therefore demonstrated a significantly longer post-recurrence survival period than Group 1 (p=0.001), but a similar survival period to Group 2 (p=0.71, Figure 6B).

Sensitivity of AFP to detect very late HCC recurrence

Figure 7 shows the correlation between pretransplant and initial post-recurrence AFP levels in the 22 patients who

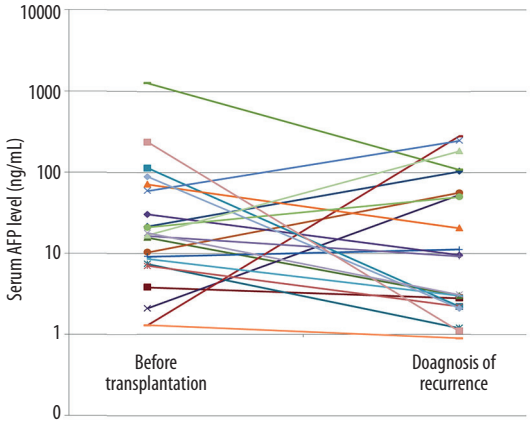

Figure 7. Changes of the serum α-fetoprotein (AFP) levels measured before transplantation and at the time of recurrence diagnosis in 22 patients diagnosed with very late hepatocellular carcinoma recurrence (>5 years after liver transplantation).

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showed very late HCC recurrence. The reference cutoff value for AFP is 7.5 ng/mL at our institution. Six patients showed AFP ≤7.5 ng/mL prior to LT, 2 of which (33.3%) showed AFP >7.5 ng/mL at the time of HCC recurrence. When confined to pretransplant AFP <20 ng/mL, only 5 of 13 patients (38.5%) showed AFP >7.5 ng/mL at the time of HCC recurrence. In 16 patients showing pretransplant AFP >7.5 ng/m, 10 patients (62.5%) showed AFP >7.5 ng/mL at the time of HCC recurrence. In 9 patients showing pretransplant AFP >20 ng/mL, 6 patients (66.7%) showed AFP >7.5 ng/mL at the time of HCC recurrence.

Discussion

The risk of post-transplant HCC recurrence is a major concern in LT recipients as it is the most common cause of patient death. The risk of HCC recurrence increases with broader LT eligibility criteria; therefore, prudent selection of LT candidates is important to reduce the risk of post-transplant HCC recurrence [11]. Cases of advanced HCC, where tumor characteristics are beyond the parameters set out in the Milan criteria, are often associated with early HCC recurrence; 42.3% of our patients exhibiting early HCC recurrence had HCCs within the Milan criteria. In contrast, in our study, 55.9% of patients exhibiting very late HCC recurrence had HCCs within the Milan criteria.

The results of this study revealed that the patterns of post-transplant HCC recurrence did not differ with the time of recurrence. In all post-transplant periods, the site of initial HCC recurrence was most commonly extrahepatic, followed by intrahepatic and combined intrahepatic-extrahepatic metastases. The most common sites of extrahepatic metastasis were the lung and bone. Therefore, all recurrent HCCs were most commonly characterized by distant metastasis. By contrast, the post-recurrence prognosis differed significantly according to the time of recurrence. It is well known that early HCC recurrence often results in very poor prognosis as these HCCs may have aggressive tumor biology [12]. In our study, the patients with early recurrence showed a median post-recurrence survival period of 10.2 months. By contrast, patients with late and very late recurrence showed a significantly longer survival period of 23.8 and 37 months, respectively. These findings suggest that HCCs showing late and very late recurrences may have less aggressive tumor biology, resulting in a delay in tumor recurrence as well as an improved response to locoregional treatments. However, it should be considered that post-transplant tumor recurrence itself is overt evidence of aggressive tumor biology.

The potential for longer post-recurrence survival in patients with late and very late recurrences highlights the importance of long-term surveillance. If the post-recurrence prognosis had been as poor as that of early recurrence, it could be considered reasonable to regard long-term surveillance as being less cost-effective. However, real-world data indicate a survival benefit associated with the timely diagnosis of very late recurrence and we suggest that these findings should be reflected in the surveillance protocols for HCC recurrence.

Considering the sporadic occurrence of very late HCC recurrence, follow-up surveillance protocols should be logistic rather than bottom-trawling and should consider the actual incidence and patterns of recurrence. We have previously proposed a systematized long-term follow-up protocol [7], in which the protocol in the first 5 years is individualized according to the relative risk of HCC recurrence; after 5 years, a uniform follow-up protocol is proposed because most patients have a similar risk of HCC recurrence at that time. Cancer surveillance protocols include 3 components: the nature of the diagnostic testing, the frequency of testing, and the duration of follow-up surveillance. For a surveillance protocol that is applicable after 5 years, the follow-up period is extended to be life-long. The nature and frequency of testing can be personalized to achieve a cost-effective approach and a high degree of patient compliance.

Blood AFP measurement is a simple test that can be performed along with other routine laboratory tests during outpatient clinic visits. In patients who had overexpression of AFP prior to LT, there is a high probability of AFP elevation at the time of HCC recurrence [7]. Therefore, AFP testing should be performed routinely at outpatient clinic visits. PIVKA-II, another serum tumor marker of HCC, has a complementary role in the diagnosis of HCC, although its sensitivity and specificity are lower than those of AFP [13–15]. Since concurrent testing of AFP and PIVKA-II improves the sensitivity for detecting HCC recurrence, we have performed both AFP and PIVKA-II tests on follow-up of all HCC patients, including LT recipients, at our center since 2006. The usual interval for blood tumor marker testing is 3 months in our institution at 5 years after LT. Small but progressive increases in tumor markers within the normal range are often neglected, but we suggest that this can be an important clue leading to diagnosis of occult HCC recurrence [16]. In a Japanese follow-up study using AFP and PIVKA-II levels assessed every 1–2 months, confirmation of HCC recurrence with imaging study took 17–208 days after the increase in the levels of tumor markers [17].

Imaging tests are essential for the detection of HCC recurrence as well as other abnormalities, such as *de novo* malignancy following LT. Considering the high frequency of lung metastasis and risk of *de novo* lung cancer [18–21], we perform concurrent chest computed tomography (CT) scanning at the time of abdomen-pelvis CT. In our center, patients who are >5 years after LT and who had an overexpression of AFP or PIVKA-II prior to transplantation usually undergo CT scanning every 2 years.

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By contrast, if the pretransplant expression of AFP and PIVKA-II is normal, the CT scan interval is often shortened to <2 years.

This study has some limitations. This was a retrospective, single-center study conducted in an area where hepatitis B virus is endemic, and the majority of our patients underwent living-donor LT. A strength of this study is that the survival status of all patients was followed to completion.

Conclusions

The results of the present study show that the patterns of HCC recurrence are similar regardless of the time of recurrence. However, post-recurrence survival was significantly longer in patients with late or very late recurrence. The pretransplant expression status of HCC tumor markers can be valuable indicators and enable personalized surveillance protocols to be established using tumor markers and imaging studies.

Cnflicts of interest

None.

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