Impact of Direct Acting Antiviral Drugs in Treatment Naïve HCV Cirrhosis on Fibrosis and Severity of Liver Disease: A Real Life Experience from a Tertiary Care Center of North India

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Background/aims: Treatment of chronic hepatitis C infection with direct-acting antiviral (DAA) drugs has been highly effective, but data regarding benefit in advanced liver disease is relatively scarce in Indian patients. The aim of this study was to determine the effects of DAA in patients with HCV related cirrhosis (compensated/decompensated) who achieved sustained virological response post-therapy at 12 weeks (SVR12). **Methods:** Sixty-three patients with HCV related cirrhosis treated with sofosbuvir based regimen were evaluated. Data regarding baseline demographics, the severity of liver disease and treatment regimen were collected. The primary end point was to evaluate the effect of treatment (SVR12) on the severity of liver disease with the secondary end point being to observe for any adverse events related to treatment. **Results:** Treatment naïve patients with HCV cirrhosis either due to genotype 1 or genotype 3 were divided into two groups: group A (compensated cirrhosis), group B (decompensated cirrhosis). SVR12 in group A was 91.66% (33/37) and in group, B was 73.17% (30/41). Baseline mean liver stiffness measurement (LSM) in group A was 16.81 ± 3.57 kPa which decreased to 11.19 ± 1.75 kPa at SVR12 (P -value <0.0001). Baseline mean APRI and FIB-4 score in group A were 1.228 ± 0.499 and 2.61 ± 1.06 and in group B were 2.156 ± 1.10 and 5.71 ± 2.06 respectively which decrease to 0.415 ± 0.115 and 1.25 ± 0.46 in group A, to 0.759 ± 0.275 and 2.60 ± 1.12 in group B following SVR12 (P value <0.0001). Mean MELD-Na improved from baseline 9.93 ± 2.04 , 20.70 ± 4.52 to 7.21 ± 0.92 , 14.23 ± 4.51 respectively in group A and B at SVR12 (P -value <0.0001). Child–Turcotte–Pugh score improved by 1 in 27.27% (9/33) and ≥ 2 in 76.67% (23/30) of patients in group A and group B respectively. **Conclusion:** There was a significant improvement in severity of liver disease as depicted by the decrease in LSM and other noninvasive marker of fibrosis in patients who achieved SVR12 on DAA therapy. (J CLIN EXP HEPATOL 2017;8:241–249)

Globally over 185 million individuals have chronic hepatitis C infection.¹ HCV is notorious for evading host immune system resulting in chronic infection in the majority of patients (50–90%). The virus has six genotypes, genotype 1 is the most prevalent globally, however, in India genotype 3 is the most frequent accounting for nearly two-thirds of cases with chronic HCV infection.² The prognosis of HCV infection varies according to fibrosis progression, with cirrhosis developing in 5–25% of

patients over a period of 25–30 years.³ Decompensation from HCV-related cirrhosis occurs in 30% of patients over 10 years, with a 3% annual risk of hepatocellular carcinoma (HCC).⁴ Chronic hepatitis C is the only chronic viral infection that can be cured by antiviral therapy. Importantly, successful antiviral treatment can prevent short- and long-term complications of HCV infection in many patients.⁵ The SVR is generally associated with resolution of liver disease in patients without cirrhosis. Patients with cirrhosis remain at risk of life-threatening complications; however hepatic fibrosis may regress and the risk of complications such as hepatic failure and portal hypertension is reduced. Recent data suggest that the risk of HCC and all-cause mortality is significantly reduced, but not eliminated in cirrhotic patients who clear HCV compared to untreated patients and non-sustained virological responders.^{5,6}

METHODS AND MATERIALS

We carried out a prospective, open-label study at the Department of Gastroenterology, Institute of Medical

Keywords: APRI, AST to Platelet Ratio Index, FIB-4, fibrosis-4, CTP, Child–Turcotte–Pugh, MELD Na, Model for End-Stage Liver Disease sodium
Received: 14 September 2017; **Accepted:** 21 November 2017; **Available online:** 6 December 2017

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Abbreviations: APRI: AST to Platelet Ratio Index; CTP: Child–Turcotte–Pugh; FIB-4: fibrosis-4; MELD Na: Model for End-Stage Liver Disease sodium; TE: transient elastography
<https://doi.org/10.1016/j.jceh.2017.11.011>

Sciences, Banaras Hindu University, Varanasi and included patients who had been treated for HCV related cirrhosis with sofosbuvir-based therapy and followed up for SVR12 as the end point of the study. The study was carried out over a period of 15 months from May 2016 to July 2017. The study protocol was approved by the Institutional Ethics Committee.

The study cohort consisted of patients with hepatitis C related cirrhosis (compensated; decompensated) age 18 years or more. Patients who were treatment experienced (IFN or direct acting antiviral (DAA) based), co-infected with HBV or HIV, autoimmune hepatitis, associated comorbid conditions like chronic kidney disease (creatinine clearance <50 mL/min), severe symptomatic cardiac or pulmonary disease, had history of organ transplantation, untreated malignancy which had predicted survival less than 10 years, pregnant females, and those who do not gave consent for inclusion in study, had been excluded.

Eligible patients were assessed at baseline for their severity of liver disease by clinical history and examination, complete blood counts, liver function tests, renal function tests, prothrombin time/INR, HCV RNA and genotype, ultrasonography of abdomen (USG abdomen) esophagogastroduodenoscopy (UGIE), vibration-controlled transient elastography (VCTE) for liver stiffness measurement (LSM). Patients were followed with above tests at end of therapy and sustained virological response post-therapy week 12 (SVR12). Patients were also assessed at regular interval during therapy for any adverse events and were divided into two groups:

- Group A: Patients with compensated cirrhosis, defined as: esophageal or gastric varices seen during upper gastrointestinal endoscopy with no history of variceal bleeding and/or liver stiffness measurement (LSM) ≥ 12.5 kPa on TE along with supportive evidence on ultrasound abdomen and were treated with following drug regimen:
 - (a) Sofosbuvir (400 mg) + ledipasvir (90 mg) for 12 weeks in genotype 1.
 - (b) Sofosbuvir (400 mg) + daclatasvir (60 mg) for 24 weeks in genotype 3.
- Group B: Patients with decompensated cirrhosis defined as: clinical signs and/or symptoms of decompensation of liver disease in form of ascites, jaundice, hepatic encephalopathy (HE), esophageal or gastric variceal bleeding (past or present), hepatorenal syndrome (HRS) and were treated with following drug regimen:
 - (a) Sofosbuvir (400 mg) + ledipasvir (90 mg) with ribavirin (starting dose 600 mg) for 12 weeks in genotype 1 (RBV eligible).
 - (b) Sofosbuvir (400 mg) + ledipasvir (90 mg) for 24 weeks in genotype 1 (RBV ineligible).
 - (c) Sofosbuvir (400 mg) + daclatasvir (60 mg) with ribavirin (starting dose 600 mg) for 12 weeks in genotype 3 (RBV eligible).
 - (d) Sofosbuvir (400 mg) + daclatasvir (60 mg) for 24 weeks in genotype 3 (RBV ineligible).

Study End Points

Primary efficacy endpoint of our study was to assess the effect of SVR12 on the severity of liver disease in patients with HCV related cirrhosis who were treated with DAA while any adverse clinical event related to therapy comprises secondary end point.

Statistical Analysis

The data collected from OPD/IPD of gastroenterology department were analyzed by using statistical software SPSS-version 17.0. The data were presented by mean $\pm$ standard deviation for continuous variables. For categorical variables, the frequency with their relative percentages was given, for comparison paired *t*-test was used. A *P*-value <0.05 was considered as statistically significant.

RESULTS

A total of 200 patients with HCV Infection were evaluated, 108 patients fulfilled inclusion criteria, among them 14 had the virological failure, 29 lost to follow up while 2 died during the study period hence were excluded and 63 patients were included in final analysis who completed follow up for SVR12 ([consort flow chart](#)). Most patients were of middle age group (mean age 48.7 years), males were more common than females (55.6% and 44.4% respectively), genotype 3 infection was most common cause of cirrhosis in both groups [87.87% (29/33) in group A and 63.33% (19/30) in group B].

Baseline characteristics of both groups were measured and are shown in [Table 1](#). Evidence of cirrhosis on USG abdomen was present in 63.6% (21/33) of patients in group A and in all patients of group B (30/30). Upper GI endoscopy demonstrated esophageal varices in 51.51% (17/33) of patients in group A [grade I (*n* = 11), grade II (*n* = 6)] and in all 30 patients (100%) of group B. 19 patients (63.33%) in group B who had esophageal varices were present with hematemesis and/or melena as sign of decompensation.

In group B, ascites was present in 86.66% (26/30) of patients, of this 6.67% (2/30) had associated spontaneous bacterial peritonitis (SBP). Hepatic encephalopathy (HE) was present in 60% (18/30) [grade I/II (*n* = 12), grade III/IV (*n* = 6)] and hepatorenal syndrome (HRS) in 13.3% (4/30) of patients.

Baseline means HCV RNA level in group A and group B was 14.92×10^5 IU/mL and 18.96×10^5 IU/mL respectively.

Baseline APRI, FIB-4, MELD Na score was 1.228 ± 0.49 , 2.61 ± 1.06 , 9.93 ± 2.04 , in group A and 2.156 ± 1.10 , 5.71 ± 2.06 , 20.70 ± 4.52 in group B respectively, SVR12 rate was 91.66% (33/37) in group A and 73.17% (30/41) in group B ([Table 2](#)). Changes from

Chart 1 Consort flow chart.

baseline parameters to SVR12 in both groups are shown in [Tables 3 and 4](#).

Treatment Efficacy

Baseline mean LSM in group A was 16.81 ± 3.57 kPa which has decreased to 11.19 ± 1.75 kPa at SVR12 (P -value <0.0001). Follow up fibro scan performed at SVR12 reclassified these group of patients on various degree of their fibrosis score based on LSM as F2 fibrosis ($n = 9$) F3 fibrosis ($n = 13$) F4 fibrosis ($n = 11$). ([Figure 1](#)).

In group A patient's baseline mean APRI score was 1.228 ± 0.499 which decreased to 0.415 ± 0.115 at SVR12 while baseline mean FIB-4 score was 2.61 ± 1.06 which reduced to 1.25 ± 0.46 at SVR12, the difference in both of the scores at SVR12 was statistically significant (P -value <0.0001). In group B baseline APRI score was 2.156 ± 1.10 which decreases to 0.759 ± 0.275 at SVR12

and these patients also experienced decrease in FIB-4 score from baseline mean of 5.71 ± 2.06 to 2.60 ± 1.12 following SVR12 (P -value <0.0001) ([Figure 3](#)).

In group A MELD-Na score improved in 87.87% (29/33) patients from baseline to SVR12 while remaining unchanged in 4 patients. Mean baseline and SVR12 MELD Na in these patients was 9.93 ± 2.04 and 7.21 ± 0.92 respectively and the difference was statistically significant (P -value <0.0001). In group B 76.66% (23/30) patients showed improvement in MELD Na score while it became worse in 7 patients following SVR12. Baseline mean MELD Na in this group was 20.70 ± 4.52 , which decreased to mean 14.23 ± 4.51 at SVR12 (P -value <0.0001) ([Figures 1 and 2](#)).

CTP score improved by 1 in 27.27% (9/33) and ≥ 2 in 76.67% (23/30) of patients in group A and group B respectively following SVR12.

Table 1 Baseline Characteristics of Patients in Group A and Group B.

	Group A (n = 33)	Group B (n = 30)
Age-years, mean $\pm$ SD (range)	42.2 $\pm$ 11.18 (21–70)	47.2 $\pm$ 11.51 (32–75)
Sex Male, No. (%)	18 (54)	17 (57)
HCV genotype-1	4 (12)	11 (37)
HCV genotype-3	29 (88)	19 (63)
HCV RNA log 10 ⁵ (IU/mL)	14.92 $\pm$ 24.47	18.96 $\pm$ 43.55
Evidence of cirrhosis (USG abd.)	20 (67)	30 (100)
Ascites	–	26 (87)
Spontaneous bacterial peritonitis	–	2 (7)
Hepatic encephalopathy (HE)	–	18 (60)
Hepatorenal syndrome (HRS)	–	4 (13)
Esophageal varices	17 (52)	30 (100)
Class CTP A	33 (100)	–
Class CTP B	–	14 (47)
Class CTP C	–	16 (53)
MELD Na 0–9	13 (39)	–
MELD Na 10–19	20 (61)	13 (43)
MELD Na 20–29	–	16 (53)
MELD Na 20–39	–	1 (4)
Treatment arm		
SOF + LDV 12 week	4	–
SOF + LDV 24 week	–	5
SOF + LDV + RBV 12 week	–	6
SOF + DCV 24 week	29	10
SOF + DCV + RBV 12 week	–	9

HCV, hepatitis C virus; CTP, Child-Turcotte-Pugh; MELD, model for end-stage liver disease; SOF, sofosbuvir; DCV, daclatasvir; LDV, ledipasvir.

Treatment Discontinuation and Adverse Events

Adverse events occurred in about one thirds of patient and were mostly minor. Almost all patients with decompensated cirrhosis (group B) experienced fall in hemoglobin in whom ribavirin was given but treatment modification (stop ribavirin and continue therapy with sofosbuvir combined to ledipasvir or daclatasvir depending on genotype with increase total duration of therapy to 24 weeks) was needed in 3 patients of CTP Class B [genotype 1 ($n = 1$) genotype 3 ($n = 2$)] and 3 patients of CTP Class C [genotype 3 ($n = 3$)]. Other adverse events like an increase in bilirubin and INR were due to hepatic decompensation. Some nonspecific adverse events like dizziness, anxiety,

decreased appetite, body ache, weakness, malaise, headache, and fatigue were present in around 24.4–36.84% of patients. None of the patients in either group required termination of treatment due to development of adverse events (Table 5).

Two patients had died during the study period, the most common cause of death was septic shock accompanied by multi-organ failure none deemed related to treatment.

DISCUSSION

Chronic untreated HCV infection and an increased rate of progression of fibrosis leads to increased risk for advanced

Table 2 Sustained Virological Response at 12 Week (SVR12) According to Genotype.

SVR 12	Genotype-1	Genotype-3
Overall	15/17 (88.23%)	48/60 (80%)
Class CTP A	4/4 (100%)	29/32(90.62%)
Class CTP B	6/7 (85.71%)	8/11 (72.72%)
Class CTP C	5/6 (83.33%)	11/17 (64.70%)

Table 3 Change from Baseline to SVR 12 in Group A.

	Group A baseline	SVR12	P value
Hemoglobin (mg/dl)	12.77 ± 1.36	13.59 ± 0.84	<0.0001
Platelet count ($\times 10^3/\mu\text{L}$)	163.9 ± 48.55	258.18 ± 35.92	<0.0001
Total bilirubin (mg/dL)	1.23 ± 0.60	0.93 ± 0.13	<0.0001
AST Aspartate aminotransferase (U/L)	69.87 ± 30.27	38.27 ± 6.83	<0.0001
ALT Alanine aminotransferase (U/L)	60.36 ± 15.58	30.15 ± 6.29	<0.0001
Albumin (g/dL)	4.07 ± 0.64	4.27 ± 0.3	<0.0001
Creatinine (mg/dL)	0.95 ± 0.18	0.87 ± 0.13	<0.0001
INR International normalized ratio (s)	1.21 ± 0.15	1.09 ± 0.07	<0.0001
Serum Na (mmol/L)	138.45 ± 2.27	140.30 ± 1.15	<0.001
Liver stiffness (kPa)	16.81 ± 3.57	11.19 ± 1.75	<0.0001
AST to Platelet Ratio Index (APRI) score	1.228 ± 0.499	0.415 ± 0.11	<0.0001
Fibrosis-4 score	2.61 ± 1.06	1.25 ± 0.46	<0.0001
MELD Na	9.93 ± 2.04	7.21 ± 0.92	<0.0001

Table 4 Change from Baseline to SVR 12 in Group B.

	Group B baseline	SVR12	P value
Hemoglobin (mg/dL)	10.12 ± 1.88	12.09 ± 1.04	<0.0001
Platelet count ($\times 10^3/\mu\text{L}$)	86.5 ± 22.3	140.8 ± 46.66	<0.0001
Total bilirubin (mg/dL)	2.39 ± 1.37	1.44 ± 0.43	<0.0001
Aspartate aminotransferase (U/L)	64.30 ± 30.18	37.26 ± 11.59	<0.0001
Alanine aminotransferase (U/L)	48.26 ± 21.31	32.06 ± 6.25	<0.0001
Albumin (g/dL)	2.69 ± 0.51	3.18 ± 0.37	<0.0001
Creatinine (mg/dL)	1.14 ± 0.49	1.08 ± 0.15	<0.0001
International normalized ratio (s)	1.78 ± 0.64	1.45 ± 0.29	<0.0001
Serum Na (mmol/L)	131.86 ± 0.99	135.6 ± 3.28	<0.001
AST to Platelet Ratio Index (APRI) score	2.156 ± 1.10	0.759 ± 0.275	<0.0001
Fibrosis-4 score	5.71 ± 2.06	2.60 ± 1.12	<0.0001
MELD Na	20.70 ± 4.52	14.23 ± 4.51	<0.0001

liver disease and liver-related complications.⁷ The efficacy of oral antiviral regimens in the management of patients with compensated liver disease due to chronic HCV infection is now established^{8,9} and data on patients with decompensated cirrhosis are emerging.^{10–12} Achievement of SVR decreases the incidence of complications and overall mortality in patients with advanced fibrosis.¹³ Most of the newer DAAs have low pill burden with minimal side effects making these treatment regimens more tolerable.

We report here our experience in real life cohort of patients with HCV cirrhosis on regression of fibrosis and severity of liver disease who achieved SVR12 on DAA regimens. We noted excellent virological response rate in patients with compensated cirrhosis infected with genotype 1 100% (4/4) and genotype 3 90.62% (29/33) which is similar to other studies.^{14,15} In patients with

decompensated cirrhosis due to genotype 1 SVR12 was 85.71% which was also comparable to other studies^{10,16} while in genotype 3 SVR12 was low [73% in CTP Class B, 65% in CTP Class C] as compared to other studies.^{15,17} Low SVR12 rates observed in our study may be because of small sample size or due to presence of resistant associated sequences (RASs) to DAA which is known to decrease the effect of DAA to >5 folds.¹⁸

Level of HCV RNA does not correlate with stage of disease (degree of inflammation or fibrosis). Available data suggest that fibrosis progression occurs most rapidly in patients with HCV genotype 3 infection.¹⁹ For persons with advanced liver disease (metavir stage F3 or F4), the risk of developing complications of the liver disease such as hepatic decompensation (overall annual incidence rate) was 3.9%.²⁰ Assessment of liver fibrosis is very important in patients with the chronic liver disease to estimate their

Figure 1 Change from baseline to SVR12 in liver stiffness and MELD Na score.

prognosis, liver biopsy has been used to stage liver fibrosis. However, due to its invasiveness, the risk of complications and difficulty of repetition for monitoring changes in fibrosis over time it has a limited use to assess prognosis in chronic liver diseases. Transient elastography (TE) is a non-invasive method for the diagnosis of liver fibrosis by measuring liver stiffness and has good accuracy to predict the presence of cirrhosis,²¹ several studies have shown that TE can predict the presence of clinically significant portal hypertension²² and has been proposed as a useful tool to assess the risk of decompensation in patients with chronic liver disease.^{23,24} In our study, we assessed patients with the noninvasive marker of liver fibrosis and severity of liver disease by measuring AST to Platelet Ratio Index (APRI) fibrosis-4 score based on laboratory values, LSM on fibro scan and by calculating MELD Na score. Hyponatremia is a common problem in patients with advanced liver disease and severity of hyponatremia is marker of severity of cirrhosis (there is a linear increase in mortality by 5% for each mmol decrease in as serum sodium between 125 and 140 mmol/L²⁵) and is not accounted in MELD score, hence patients were evaluated with MELD Na score for severity of liver dysfunction.

In patients with compensated cirrhosis there was significant improvement in noninvasive marker of liver fibrosis as shown by LSM and improvement in APRI, FIB-4 score at SVR12 (P -value <0.0001) follow up fibro scan performed at SVR12 reclassified fibrosis score as patients having F2 fibrosis ($n = 9$), F3 fibrosis ($n = 13$), F4 fibrosis ($n = 11$) based on LSM. The decrease in these fibrosis scores was associated with the decrease in grading [Grade-II to Grade-I ($n = 5$)] and disappearance ($n = 9$)

of esophageal varices which could be correlated as a decrease in hepatic venous pressure gradient (HVPG) in these patients. Hence, assessment of liver fibrosis noninvasively by fibro scan at regular interval during and after achieving SVR might be used as a good surrogate marker for changes in HVPG and its related complications. MELD Na score also improved in association with improvement in liver fibrosis scores which suggested that liver functions also improved following SVR12.

Two meta-analyses showed that achieving SVR after treatment has been associated with improvements in disease progression, liver histology, health-related quality of life, and a reduced risk of HCC and liver-related mortality.^{26,27} Both of these meta-analyses included data from the studies in which patients were treated with IFN based therapy and were followed for durability of SVR and staging of fibrosis by histology. Recent studies have shown that virological response to DAA is associated with fibrosis regression (as measured by LSM) and recovery of liver functionality which can be detected as early as the end of therapy (ETR).^{28,29}

In group B (patients with decompensated cirrhosis) 47% (14/30) patients had CTP Class B cirrhosis and 53% (16/30) patients had CTP Class C cirrhosis. Following SVR12 patients of both classes of cirrhosis showed significant improvement in liver fibrosis (APRI, FIB-4 score) and MELD Na score (P -value <0.0001) although 3 patients in CTP Class B and 4 patients in CTP Class C shows worsening in MELD Na yet it was not marked and assumed to be more worse if patients were not treated. Worsening of MELD Na score was mostly in severely decompensated patients who had grade III-IV hepatic encephalopathy,

Figure 2 Change in MELD Na score at SVR12 in individual patient.

SBP having active esophageal variceal bleeding, however, APRI, FIB-4 scores decreased in these patients. Improvement in CTP score by ≥ 2 was seen in 76.6% (23/30) of patients of group B due to the control of ascites, and improvement in hepatic encephalopathy, jaundice, liver synthetic function following SVR12. These data from our study suggest that patients who achieved SVR12 on oral direct-acting antiviral (DAA) agents had significant improvement in severity of liver disease as evident by regression of fibrosis and improvement in liver synthetic functions.

Several studies also showed improvement in severity of liver disease following SVR.^{10,15,16,18,30} A recent study

which included patients infected with genotype 3 HCV shows SVR12 93% and 82% in compensated and decompensated cirrhosis respectively who were treated with SOF + DCV $\pm$ RBV for 24 weeks with improvement in MELD Score, fibro test. Though rate of hematological as well as non-hematological side effects were around 27–33% yet they were mild and easily manageable, some (6/21) needs treatment modification in terms of increased duration of therapy for 24 weeks mainly due to ribavirin-induced anemia.¹⁷

To our best of knowledge, this is the first study from India which evaluated the effect of SVR12 on stage and severity of HCV related cirrhosis (both GT 1 and GT 3)

Figure 3 Change from baseline to SVR12 in APRI and FIB-4 score.

Table 5 Rates of Adverse Events According to CTP Class Related to RBV.

Adverse effects	CTP B (n = 10)	CTP C (n = 11)	CTP A (N = 33)
Hemoglobin (Hb) fall during treatment, No. (%)	9 (90%)	11 (100%)	–
Lowest Hb during treatment, mean $\pm$ SD	10.1 $\pm$ 1.2	10.2 $\pm$ 1.7	–
Treatment modification due to Hb fall, No. (%)	3 (30%)	3 (27.27%)	–
Other adverse event ^a	5 (33.33%)	7 (36.84%)	8 (24.44%)

^aNausea, dizziness, headache, fatigue [CTP B (n=11); CTP C (n=19)].

that were treated with DAA and found improvement in fibrosis and severity of liver disease following SVR12. We admit that although the number of patients in our study is less nonetheless this study showed that attaining SVR12 leads to significant improvement in severity of liver disease and in noninvasive markers of fibrosis. It would be interesting to see its long term effects on fibrosis by doing liver biopsies in long term studies. Thus this study also paves way for further studies to evaluate the sustained benefit of SVR12 and to detect the prevalence of RASs for DAA in those patients who do not achieve SVR12.

CONCLUSION

The present study evaluates the effect of treatment (SVR12) on fibrosis and severity of liver disease in patients with HCV related cirrhosis who were treated with DAA based therapy. Overall results show that noninvasive markers of fibrosis and severity of liver disease improved significantly following SVR12.

CONFLICTS OF INTEREST

The authors have none to declare.

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