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ORIGINAL ARTICLE

Overexpression of TRIM37 is Associated with Unfavorable Outcomes in Gastric Cancer Patients

Jalil Afshar[1], Jamshid Mehrzad[*1], Hassan Mehrad-Majd[*2], Jafar Saeidi[3]

[1]*Department of Biochemistry, Neyshabur Branch, Islamic Azad University, Neyshabur, Iran*

[2]*Cancer Molecular Pathology Research Center, Mashhad University of Medical Sciences, Mashhad, Iran*

[3]*Department of Physiology, School of Basic Science, Neyshabur Branch, Islamic Azad University, Neyshabur, Iran*

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KEYWORDS

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β-catenin

ABSTRACT: TRIM37 expression has been shown to be dysregulated in various types of cancers. This study was aimed to assess the clinical significance and potential utility of TRIM37 expression level as an indicator of prognosis in gastric cancer (GC) patients. The potential correlation between TRIM37 and the levels of β-catenin, Cyclin D and BCL2 was also investigated. qRT-PCR was used to determine the expression levels of TRIM37 in 40 fresh GC and their adjacent noncancerous tissues. Statistical analyses were conducted to evaluate the relationship between TRIM37 expression levels, overall survival (OS), various clinicopathological features, and the expression levels of β-catenin, Cyclin D, and Bcl-2. TRIM37 expression was significantly higher in the cancerous tissue samples compared to noncancerous tissues (Fold change=1.92, P=0.007). Moreover, Kaplan-Meier analysis indicated that high TRIM37 group exhibited shorter OS (P=0.003). TRIM37 overexpression was strongly associated with poor prognosis and predicts unfavorable outcomes in GC patients (HR=1.85, 95%CI: 1.28-2.66, P=0.001). A direct correlation was also observed between TRIM37 and elevated levels of β-catenin, a gene known for its role in cell proliferation among GC patients. TRIM37 overexpression is strongly linked with a poor prognosis in GC patients, highlighting its potential as an independent prognostic factor in GC and providing insight into its possible involvement in cancer development through Wnt/β-catenin signaling pathway. However, additional research is required to validate the potential prognostic value of TRIM37 in gastric cancer.

INTRODUCTION

Gastric cancer (GC) is globally recognized as a prevalent cancer with the 5th rank and the 4th most frequent cause of cancer-related deaths [1]. Despite ongoing advances in surgical procedures, perioperative chemotherapy, and overall patient care, the five-year survival rate for GC remains at a suboptimal level [2]. This persistent occurrence of GC poses a significant global health concern. Extensive research has indicated that various factors contribute to tumor progression and the development of GC, including environmental factors such as diets low in vegetables and fruits but high in salts and nitrates, as well as Smoking. Additionally, infections caused by H.pylori and Epstein-Barr virus, along with genetic alterations (including mutations of CDH1 and CTNNA1 in hereditary diffuse GC, TP53 in Li-Fraumeni syndrome, STK11 in Peutz-Jeghers syndrome, and APC in familial adenomatous polyposis), have also been recognized as key players in GC

*Corresponding author: mehrzadjam@iau.neyshabur.ac.ir; mehradmajdh@mums.ac.ir (J. Mehrzad; H. Mehrad-Majd)
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development [3].

Alongside well-established carcinoembryonic antigen (CEA), CA19-9, CA72-4, and HER2, several biomarkers have emerged as prominent targets in studies, holding potential for therapeutic interventions. These include MET and ERBB2 genes amplification, P16 hypermethylation, K-ras mutations, β-catenin oncogenic activation, APC, E-cadherin, and TP53 mutations, and hMLH1 inactivation, which is linked to microsatellite instability [4, 5]. Nevertheless, the clinical application of these discoveries as targets for diagnosis and/or treatment of GC is currently limited due to the lack of symptoms (such as blood in the stool, vomiting, unexplained and unintentional weight loss, abdominal discomfort, and ets.) until advanced stages. In recent years, molecular biomarkers have gained popularity as early cancer detectors. Therefore, identifying clinical biomarkers and molecular targets that could potentially be used for diagnostic, prognostic and therapeutic objectives in GC remains the significant area of research.

The quest to improve the GG diagnosis and treatment has resulted in the discovery of new biomarkers. These biomarkers include MET, circulating miRNAs, circular RNAs, long non-coding RNAs, and the ITIHI3 protein, alongside associated genes like the TRIM family [4, 6-9]. The TRIM family contains genes that encode proteins with a Tripartite Motif. This motif consists of a B-box domain, RING-finger domain, and a Coiled-coil domain [9, 10]. A growing body of evidence demonstrates that several TRIM family proteins are present in different types of cancers and play a role in regulating cancer growth and development [11].

TRIM37, also known as RNF83 or RFP1, belongs to the TRIM family and is encoded by a gene situated in chromosomal region of 17q23 [12]. Functioning as an E3 ubiquitin ligase, TRIM37 plays a regulatory role in the activity of multiple genes in different types of cancer [13]. Existing evidence suggests that TRIM37 may plays a role in tumor growth, invasion, and metastasis by promoting cell proliferation, inhibiting apoptosis, and enhancing epithelial-mesenchymal transition (EMT), a pivotal process in cancer metastasis [14]. Extensive research has been conducted on TRIM37 expression in various cancers, revealing its dysregulation in the development and progression of numerous malignancies such as hepatocellular carcinoma (HCC) [15], non-small cell lung cancer (NSCLC) [16], pancreatic cancer (PC) [17], and renal cell carcinoma (RCC) [18]. Furthermore, overexpression of TRIM37 has been associated with highly metastatic behavior in primary tumors and poor overall survival in several cancer types.

To date, limited research has explored the clinicopathological and prognostic value of TRIM37 expression in GC. To address this gap, Chen et al. conducted a study examining TRIM37 expression in GC specimens, revealing a correlation between TRIM37 overexpression and poor clinical outcomes [19]. Similarly, Nishibeppu et al, demonstrated that increased TRIM37 expression played a pivotal role in malignant outcome, resulting in a lower survival rate among GC patients [20]. To validate these findings and account for the effect of genetics and ethnicity on GC incidence and mortality, our study was designed to analyze the expression pattern of TRIM37 in a cohort of Iranian patients with GC. Furthermore, we sought to investigate the potential relationship between TRIM37 expression and overall survival. Moreover, to gain insight into the underlying mechanism through which TRIM37 confers its oncogenic role, we examined its correlation with β-catenin, Cyclin D, and BCL2, representative genes for biological pathways involved in Wnt signaling, cell cycle, and apoptosis, respectively.

MATERIALS AND METHODS

Patients and tissues

This cross-sectional study was carried out at our primary teaching hospital from November 2015 to February 2018. Based on the results of a previous investigation, a minimum sample size of 28 patients was determined [21]. Ultimately, a total of 40 patients who underwent endoscopic biopsy procedure in the gastroenterology department and were subsequently confirmed to have GC using pathology tests at the Molecular Pathology Research Center were enrolled in this study. Eligible patients were selected based on the following inclusion criteria: a) Displayed relevant clinical symptoms commonly linked to GC such as dyspepsia, dysphagia, anemia, bleeding, weight loss, anorexia, appetite loss, nausea, reflux, and vomiting, b) Had no previous history

of radiotherapy, chemotherapy, or specific surgery, c) GC diagnosis was validated through pathology. Patients with a history of prior chemotherapy or radiotherapy, and surgery, lack of symptoms, simultaneous presence of any other malignancies, and absence of confirmed GC were excluded from the study. Prior to the study, all patients provided their informed consent by signing consent forms.

RNA isolation and RT-qPCR

The fresh tissue samples, consisting of 40 cancerous and 40 noncancerous samples located more than 5 cm away from tumor sites, were directly submerged in RNAlater (Thermo Fisher Scientific, USA) and stored overnight at 4°C to ensure optimal tissue penetration. Subsequently, they were frozen and stored at -80°C. Total RNA extraction was carried out using Trizol Reagent (Sangon Biotech Co., Ltd., Shanghai, China). The quality and quantity of isolated RNA were determined through agarose gel electrophoresis and measuring the optical density (OD) at 260nm and 280 nm by a Nanodrop ND-1000 (Thermo-Fisher Scientific, USA) respectively. High-quality RNA samples with an OD 260/280 greater than 1.80, were considered suitable and converted into cDNA product using a commercially available kit (Wizbiosolutions, Seongnam, and Gyeonggi, Korea). The expression levels of the target genes were quantified through quantitative real-time PCR (qRT-PCR), employing previously described methodologies [22, 23]. Briefly, each qRT-PCR reaction was performed in a 20 µl reaction volume containing cDNA template, forward and reverse primers specific to each gene (listed in Table 1), SYBR Green RT-PCR master mix, and nuclease-free water.

Table 1. Sequences of forward and reverse primers specific to each gene.

Gene	Forward primer	Reverse primer	Length
β-actin	5'-CACGAAACTACCTTCAACTCC-3'	5'-CATACTCCTGCTTGCTGATC-3'	265bp
TRIM37	5'-TCAGCTGTATTAGGCGCTGG-3'	5'-ACTTCTTCTGCCCAACGACA-3'	106bp
CyclinD	5'-TGGAGGTCTGCGAGGAACA-3'	5'-TCATCTTAGAGGCCACGAACAT-3'	147bp
BCL2	5'-ACGGTGGTGGAGGAGCTCTT-3'	5'-CGGTTGACGCTCTCCACAC-3'	98bp
β-catenin	5'-TCTGAGGACAAGCCACAAGATTACA-3'	5'-TGGGCACCAATATCAAGTCCAA-3'	122bp

A Roche LightCycler® 96 System instrument was used for thermal cycling, in a condition in which the initial activation step was set at 95 °C for 10 minute, then followed by 40 cycles of amplification, with each cycle consisting of 15 seconds at 95°C, 30 seconds at 59°C, and 30 seconds at 72°C. Finally, the termination step was set at 95°C for 10 seconds, 65°C for 60 seconds, and 97°C for 1 second. In order to normalize the expression levels, β-actin was employed as a reference gene. The $2^{-\Delta\Delta Ct}$ method was utilized to ascertain the relative mRNA expression levels. The accuracy and reliability of the results were ensured by measuring triplicate.

Statistical analysis

Statistical analyses were performed using IBM SPSS software version 22 (NY, USA), and the significance level was set as P-value less than 0.05. Expression levels of target genes were compared between cancerous and noncancerous tissues using the paired-samples t-test. Based on the median expression level of TRIM37, patients were divided into two groups (low=20) and (high=20). Student sample t-test, Chi-square, and/or Fisher's exact tests were used to examine the relationship between TRIM37 levels and clinicopathological features. Additionally, the overall survival analysis was performed using Kaplan–Meier analysis and Log Rank (Mantel-Cox) tests, taking into account different levels of TRIM37 expression. Finally, Cox regression uni- and multivariate analyses was applied to assess the impact of TRIM37 and other variables and on patients' survival.

RESULTS

Patients' characteristics

A cohort of 40 GC patients with an average age of 65.73 ± 10.19 were enrolled in this study. Among them, 31 patients (77.5%) were males, while and 9 patients (22.5%) were females. The. Twenty-one people (52.5%) were under 65 years old while 19 people (47.5%) were over 65 years old. Smokers accounted for 45% (18

patients) of the all included patients. Regarding clinical symptoms, 80% (32 patients) experienced weight loss, and 37.5% (15 patients) had anorexia. Abdominal pain, nausea and vomiting, gastroesophageal reflux, and gastrointestinal bleeding were reported by 72.5% (29 patients), 70% (28 patients), 52.5% (21 patients), 37.5% (15 patients), respectively. Anemia was observed in 67.5% (27 patients) during laboratory investigations. In the stratified analysis based on low and high TRIM37 expression levels, no significant differences were observed for all above-mentioned variables except for bleeding (p=0.022), which was more frequent in the high-expression group (Table 2).

Table 2. Baseline characteristics of GC patients based on the TRIM37 expression levels.

Variables		TRIM37 levels		P-value
		Low (n=20)	High (n=20)	
Age (mean ± sd)*		65.30 ± 11.17	66.15 ± 9.39	0.796
Age Composition**	≤65	11 (55.0)	10 (50.0)	0.752
	>65	9 (45.0)	10 (50.0)	
Gender**	Male (%)	15 (75.0)	16 (80.0)	0.705
	Female (%)	5 (25.0)	4 (20.0)	
Anemia**	+	12 (60.0)	15 (75.0)	0.311
	-	8 (40.0)	5 (25.0)	
Weight loss**	+	14 (70.0)	18 (90.0)	0.118
	-	6 (30.0)	2 (10.0)	
Bleeding	Yes	4 (20.0)	11 (55.0)	0.022
	No	16 (80.0)	9 (45.0)	
Dysphagia***	No	1 (5.0)	2 (10.0)	0.554
	Rarely	5 (25.0)	4 (20.0)	
	Yes	14 (70.0)	14 (70.0)	
Tumor location***	Proximal	11 (55.0)	7 (35.0)	0.365
	Body	6 (30.0)	10 (50.0)	
	Distal	3 (15.0)	3 (15.0)	
Smoking**	Yes	7 (35.0)	11 (65.0)	0.204
	No	13 (65.0)	9 (45.0)	
Abdominal Pain**	Yes	14 (70.0)	15 (75.0)	0.723
	No	6 (30.0)	5 (25.0)	
Nausea**	Yes	13 (65.0)	15 (75.0)	0.490
	No	7 (35.0)	5 (25.0)	
Reflux**	Yes	11 (55.0)	10 (50.0)	0.752
	No	9 (45.0)	10 (50.0)	
Anorexia**	Yes	6 (30.0)	9 (45.0)	0.327
	No	14 (70.0)	11 (55.0)	

Independent sample t-test (*), Chi-square (**) and Fisher's exact test (***)

TRIM37 expression was upregulated in cancerous tissues

Gene expression analysis using qRT-PCR revealed a significant increase in the relative expression level of TRIM37 mRNA in cancerous tissue samples compared to adjacent noncancerous tissues (fold change (FC)=1.92, P=0.007) (Figure 1). Our finding suggests that the level of TRIM37 in cancerous tissue was nearly twice as high as that in normal tissue.

Similar results were observed in mRNA expression analysis for β-catenin (FC=2.53, P<0.001), cyclin D (FC=2.36, P=0.028) and Bcl-2 (FC=2.44, P=0.001). Significantly elevated levels of these genes were also observed in cancerous tissues compared to normal tissues

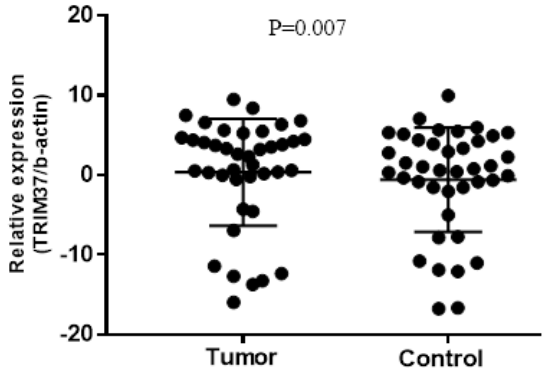

Figure 1. TRIM37 expression level in 40 pairs of cancerous and noncancerous tissues

Correlation between TRIM37, β-catenin, Bcl-2, and

Cyclin D expression levels

A significant direct correlation (r=0.474, P=0.002) was observed between the TRIM37 and β-catenin genes expression levels, indicating a potential interaction between these two genes (Figure 2). However, there was no significant correlation between TRIM37 and the cyclin D and Bcl-2 genes (P>0.05). This indicate that TRIM37 function independently of cyclin D and Bcl-2 and there is no interaction between them.

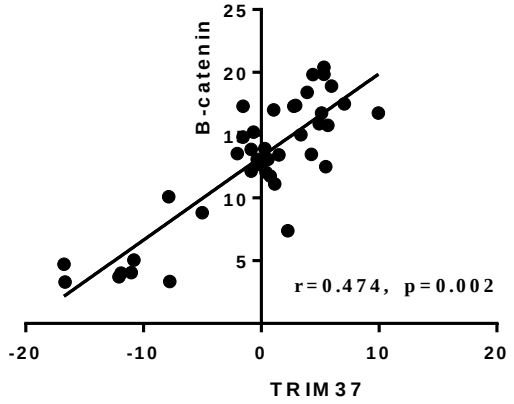

Figure 2. Pearson's correlation analysis measuring the strength of a correlation between the TRIM37 and β-catenin levels in GC patients (r=0.474; P=0.002)

TRIM37 expression and the patients' overall survival

In order to assess the association between the TRIM37 expression level and patients' overall survival, Kaplan-Meier analysis was conducted (Figure 3). Our results showed that patients with high TRIM levels had significantly poorer OS compared to the low group (Log rank test, P=0.027). More specifically, patients with low TRIM37 levels exhibited a median survival time of 39 months, whereas those with high TRIM37 levels sowed a median survival time of 18 months. This indicated that TRIM37 overexpression could potentially be indicative of a negative prognosis for GC patients.

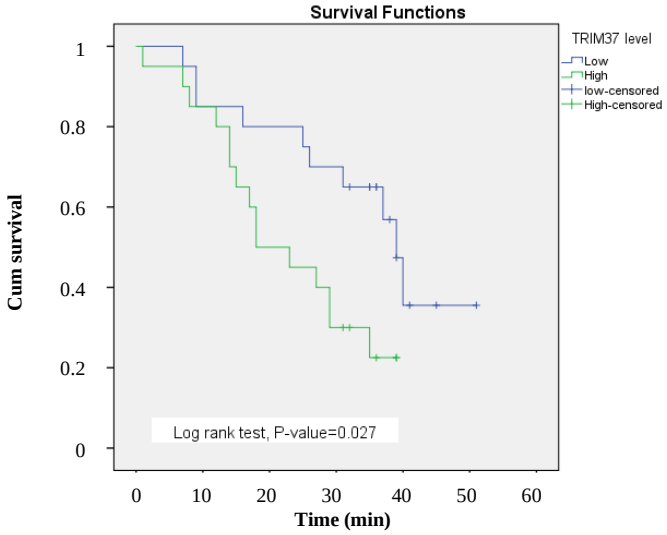

Figure 3. Kaplan-Meier analysis curve showing the correlation between TRIM37 level and the patients' overall survival.

Additionally, Cox regression analyses in uni- and multivariate models were performed to explore variables affecting the OS rate of patients. In the univariate model along with TRIM37 expression (HR=2.49, 95%CI: 1.07-5.76, P=0.034), other variables including gender (P=0.044), smoking (P=0.013), weight loss (P=0.038), anemia (P=0.009), stomachache (P=0.014), and bleeding(P=0.005) were in significant association with OS in patients. However, after conducting multivariate analysis, it was found that only the TRIM37 level remained significantly correlated with an increased risk of mortality for GC patients (HR=2.82, 95%CI: 1.07-7.91, P=0.48). This suggest that TRIM37 may serve as an independent prognostic factor for GC patients (Table 3).

Table 3. COX-regression analyses in univariate and multivariate models for OS of gastric cancer patients

Variables	Univariate analysis		Multivariate analysis	
	HR (95%CI)	P value	HR (95%CI)	P value
TRIM37	2.49 (1.07 -5.76)	0.034	2.82 (1.07-7.91)	0.048
Age	1.05 (0.99-1.09)	0.067	-	-
Sex	0.30 (0.09-0.98)	0.045	1.54 (0.23-10.09)	0.656
Tumor place	1.55 (0.86-2.80)	0.153	-	-
Anemia	0.013 (0.01-0.32)	<0.001	0.001 (0.00-9.69	0.903
Weight loss	0.02 (0.001-0.82)	0.037	0.001 (0.00-2.89)	0.940
Bleeding	0.32 (0.15-0.72)	0.006	1.07 (0.41-2.83)	0.886
Dysphagia	0.87 (0.67-1.17)	0.354	-	-
Abdominal Pain	0.21 (0.07-0.75)	0.015	0.473 (0.11-1.95)	0.301
Smoking	0.33 (0.14-0.798)	0.014	1.34 (0.48-3.71)	0.578
Nausea and Vomiting	0.43 (0.15-1.13)	0.090	-	-
Reflux	1.16 (0.51-2.55)	0.730	-	-
Anorexia	0.56 (0.26-1.23)	0.141	-	-

DISCUSSION

In this study, we compared the expression levels of TRIM37, β-catenin, Cyclin D, and BCL-2 in 40 cancerous tissues and their corresponding adjacent noncancerous tissues. The association of TRIM37 expression levels, with patients' OS, as well as various clinicopathological features were also analyzed. TRIM37 expression was significantly found to be higher in cancerous tissues compared to noncancerous tissues (FC=1.92, p=0.007). This overexpression is strongly associated with shorter OS (P=0.003) and is indicative of

a poor prognosis. In fact, TRIM37 overexpression was an independent predictor for unfavorable outcomes in patients with GC (HR=1.85; 95% CI, 1.28-2.66; P=0.001). Additionally, we observed a direct correlation between TRIM37 expression and increased levels of β-catenin, a gene known to contribute to cell proliferation in GC patients. These results emphasize the significant role of TRIM37 in promoting tumor development through its overexpression with the help of Wnt-β-catenin pathway and its potential capacity as a promising prognostic factor with therapeutic target for GC patients.

Our finding were consistent with previous studies conducted in in this field. A study conducted by Chen et al aimed to explore the impact of TRIM37 on GC cells through both in-vitro and in-vivo experiment models, as well as transwell and metastasis assays. The results of this study revealed that TRIM37 expression was significantly increased in GC tissues and was strongly associated with metastasis and a poor prognosis in GC patients. Furthermore, the study demonestrated that TRIM37 enhances the invasion and metastasis of tumor cells through the activation of SIP1-related EMT pathway. This suggests that that TRIM37 could serve as a promising therapeutic target in GC treatment [19]. Nishibeppu et al. conducted a study to explore the impact of the activation and overexpression of TRIM37 in GC. The researchers observed that TRIM37 gene was commonly upregulated in primary GC tissues, and this elevation was associated with an unfavorable prognosis. Furthermore, they showed that TRIM37 downregulation is associated with inhibited cell proliferation, migration, and invasion in GC cells [20]. In another study by Zhu et al, it was concluded that TRIM37 is likely operating as an oncogene in GC. Knockdown of TRIM37 significantly inhibited GC cell proliferation, halted the cell cycle at the G1-phase, and promoted apoptotic processes. These effects were most likely mediated by the activation of the ERK1/2 signaling pathway, which was achieved through the regulation of cleaved caspase 3 and c-myc. Consequently, the targeting TRIM37 shows promise as a novel therapy for GC treatment [24].

Our findings revealed higher levels of β-catenin expression in gastric cancer tissues, a well-known component of the Wnt signaling pathway. Moreover, we identified a strong correlation between β-catenin and TRIM37 expression. These findings support previous studies by Zhou et al. and Farhadi et al, suggesting that TRIM37 and β-catenin genes interaction may contribute to the progression of gastric cancer [21, 25]. One possible mechanism could involve the modulation of cyclin-dependent kinases (CDKs), downstream targets of β-catenin. Furthermore, our study observed a significant increase in both Cyclin D and Bcl-2 expression levels, concurring with the upregulation of TRIM37 in gastric cancer tissues. While further research is needed, our findings suggest that TRIM37 overexpression in GC tissue may activate the Wnt signaling pathway, potentially reducing the survival and proliferative capabilities of cancerous cells, partly through its involvement with the β-catenin-Cyclin D-Bcl-2 pathway.

Although the study has commendable strengths as a well-defined sampling strategy and a population with ethnic homogeneity, the relatively small sample size and absence of a group of healthy individuals could potentially impact the robustness of the findings. It is also worth noting that subsequent studies should gather sufficient data on patients' clinicopathological features. Furthermore, it is essential to evaluate TRIM37 expression not only at the mRNA level but also through IHC and western blot analysis to assess protein levels.

CONCLUSIONS

In conclusion, our study indicated a significant correlation between TRIM37 overexpression and poor clinical outcomes, as well as decreased overall survival rates in patients with GC. This oncogenic impact of TRIM37 is likely mediated through the Wnt/β-catenin signaling pathway. TRIM37 overexpression may serve as an independent predictor of mortality in GC patients. These findings highlighted the potential value of TRIM37 as a promising target for prognosis and therapy in GC patients.

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ETHICAL CONSIDERATION

The study protocol received ethical approval from the Ethics Committee of Mashhad University of Medical Sciences (IR.MUMS.MEDICAL.REC.1398.606).

CONFLICT OF INTERESTS

The authors declare that they have no competing interests.

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