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Letter to Editor

What is the Clinical Relevance between *tnpA* and *tnpB* and *H. pylori*-related severe Gastrointestinal Diseases? A Statistical Analysis on Available Reports

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Helicobacter pylori (*H. pylori*) is a mysterious spiral bacterium that is colonized as gastric-flora in 50% of the world's population [1]. Introduction of this bacterium in 1982 by Barry Marshall and Robin Warren was one of the most revolutionary discoveries in the field of gastroenterology; Todays, *H. pylori* is considered as the causative agent for chronic gastritis, peptic ulcer disease, and gastric adenocarcinoma as well as extra-gastrointestinal diseases [2-3]. There is an enigma!!; surprisingly, the major portion *of H. pylori*-infected individuals remain asymptomatic, and severe clinical outcomes particularly peptic ulcer, and gastric cancer has occurred only in 15-20% of those subjects [4-5].

H. pylori are heterogeneous and each strain have specific virulence factors; therefore, it has been suggested that the risk of susceptibility to severe clinical outcomes is greatly dependent on *H. pylori* specific virulence factors [6]. The putative IS605 transposases (*tnpA* and *tnpB*) are genetic elements that can be integrated in the *cag*-PAI in *H. pylori* genome [7]. The *tnpA* and *tnpB* cause a split in the *cag*-PAI region and might affect the virulence of *H. pylori* as well as final clinical outcomes [8]. However, the putative *IS605* transposases and their effects on the pathogenicity of *H. pylori* are not well understood and need to be more investigated. The aim of this study was to investigate the association between the presence of *tnpA* and *tnpB* and severe clinical outcomes.

We performed a systematic search in several databases including PubMed, Scopus, Embase, and Google scholar using search terms as fellow "*Helicobacter pylori*", "*H. pylori*", "*IS605* transposases", "*tnpA*", and "*tnpB*" to obtain relevant studies on the association between the presence of *tnpA* and *tnpB* and clinical outcomes up to February 2021.We included fully-published articles in the English language to studied the role of *tnpA* and *tnpB* and severe clinical outcomes using statistical analysis by Comprehensive meta-analysis software (Biostat, Englewood, NJ, USA). The frequency of *tnpA* and *tnpB* is expressing by event rate corresponding to 95% confidence intervals (CIs), the odds ratio (OR) with 95% CIs was measured the association between IS605 transposases and severe clinical outcomes i.e. peptic ulcer disease (PUD) and gastric cancer (GC). Heterogeneity was assessed by I^2 index and Cochrane *Q*-test. Finally, the presence of publication bias was determined using Egger's *p* value and Begg's *p* value test [9].

There are 4 studies that investigated the role of *tnpB* and *tnpA* in clinical manifestation which were performed between 207-2017 in two countries including Brazil (*n*= 2) and Iran (*n*= 2). We evaluated data of 1,005 cases (mean age: 44.72 years; males: 365; females: 640). There were 907 *H. pylori* strains were isolated from these patients and the presence of *tnpB* and *tnpA* was studied using polymerase chain reaction (PCR) assay in all included studies.

The frequency of *tnpA* in non-ulcer dyspepsia, peptic ulcer disease and gastric cancer 45.2% (95%CI: 40-50.6%), 53% (95%CI: 48.3-57.7%), and 65.7% (95%CI: 56.4-73.9%were respectively. Otherwise, the frequency of *tnpB* were estimated as 22.4% (95%CI: 17.7-27.8%), 13.6% (95%I: 10.4-17.5%), and 22.7% (95%CI: 14.7-33.4%); respectively in NUD, PUD and GC. Furthermore, there are a positive significant association between *tnpA* and risk of gastric cancer (OR: 3.11; 95%CI: 1.16-8.33; *p* value: 0.02; I^2: 69.28; *Q*-value:

6.51; Begg's *p* value: 0.50; Egger's *p* value: 0.26)but *tnpA* has not significant association with PUD (OR: 1.24; 95%CI: 0.68-2.27; *p* value: 0.47; I^2: 73.82; *Q*-value: 7.64; Begg's *p* value: 0.29; Egger's *p* value: 0.01). In the other hand, there is not significant association between *tnpB* and GC (OR: 2.91; 95%CI: 0.41-21.6; *p* value: 0.28; I^2:83.72; *Q*-value: 12.29; Beeg's *p* value: 0.50; Egger's *p* value: 0.75) or PUD (OR: 0.55; 95%CI: 0.35-0.86; *p* value: 0.008; I^2:92.21; *Q*-value: 25.65; Beeg's *p* value: 0.29; Egger's *p* value: 0.15).

H pylori strains have various virulence factor that contributed in pathogenesis and determination of final clinical outcomes; there are several strain-specific virulence factors that located on *cag*-PAI (cytotoxin-associated genepathogenicity island), a 40 kb foreign DNA region, in this bacterium [14]. The *cag*-PAI contains 31putative genes, type IV secretion system, as well as *cagA* that play keys role in *H. pylori* virulence [14-15]. According to the literature, the *cag*-PAI is divided in two sub-classes by insertion sequence (*IS605*) that mediate *cag*-PAI disruption as well as influenced levels of virulence in *H. pylori* strains [14, 16]. Although the role of the putative *IS605* transposases (*tnpA* and *tnpB*) is not well understood. The result of the current analysis suggested the potential role of *tnpA* in the risk of gastric cancer.

There is ample evidence to support this hypothesis such as 1) the global frequency of *tnpA* among GC cases is significantly higher than *tnpB*; 2) there is signification association between *tnpA* and *cagA* in GC patients, 3) there is a significant association between co-existence of *tnpA* and the blood group antigen binding adhesion, and 4) contribution of *tnpA* in DNA shapes and gene expression [7, 11-12, 17]. However, there is limited information and further investigations are required to confirm the effectiveness of the relation between *tnpA* and gastric cancer.

Conflict of interest

Nil.

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Volume 1 Issue 3 April 2022