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Original Article

Relationship Mitral valve prolapse syndrome and duodenal ulcer disease with concomitant autonomic dysfunction

Jannis Kountouras (MD, PhD) [1]
Stergios A. Polyzos (MD, MSc, PhD) [2]
Christos Zavos (MD, PhD) [1]
Evangelos Kazakos (MD, PhD) [1, 3]
Maria Tzitiridou-Chatzopoulou (MD, PhD) [1, 3]
Dimitrios Chatzopoulos (MD, PhD) [1]
Aggeliki Stogianni (MD, PhD) [4]
Maria Touloumtzi (MD) [1]
Stergios Arapoglou (MD, PhD) [1, 5]
Elisabeth Vardaka (PhD) [6]

1. Department of Internal Medicine, Second Medical Clinic, Ippokration Hospital, Aristotle University of Thessaloniki, 54642 Thessaloniki, Macedonia, Greece
2. First Laboratory of Pharmacology, School of Medicine, Aristotle University of Thessaloniki, 54124 Thessaloniki, Macedonia, Greece
3. School of Healthcare Sciences, Midwifery Department, University of West Macedonia, Koila, 50100 Kozani, Macedonia, Greece
4. Department of Radiology, Ippokration Hospital, 54642 Thessaloniki, Macedonia, Greece
5. Fifth Surgical Department, Medical School, Ippokration Hospital, Aristotle University of Thessaloniki, Macedonia, Greece
6. Department of Nutritional Sciences and Dietetics, School of Health Sciences, International Hellenic University, Alexander Campus, Sindos 57400, Macedonia, Greece

*** Correspondence:**
Jannis Kountouras, MD, PhD,
Professor of Medicine, Gastroenterologist, 8 Fanariou St, Byzantio, 551 33, Thessaloniki, Macedonia, Greece

E-mail: jannis@auth.gr
Tel: +30 2310438714

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Abstract

Background: There is no evidence regarding the crucial topic of possible correlation between duodenal ulcer disease and mitral valve prolapse syndrome. We herein investigated the potential relationship between these two disorders.

Methods: Eighty-three hospitalized patients with active duodenal ulcer disease were compared with 31 healthy controls for the presence of mitral valve prolapse syndrome. All participants underwent cardiac examination and echocardiography. Heart rate, systolic and diastolic pressures were estimated in supine baseline and standing positions.

Results: Echocardiographic mitral valve prolapse was present in 36 (43.37%) of the patients and only in 1 (3%) of controls (P=0.001). Auscultatory findings of systolic murmurs (50% vs. 4%, respectively; P=0.001) and symptoms related to the cardiovascular system (i.e., chest pain: 75% vs. 30%, respectively; P=0.001) were more common in patients with mitral valve prolapse than those without it. Heart rate was lesser in patients with mitral valve prolapse in supine location (71.00±1.73 vs. 76.10±1.66, respectively; P=0.04), and was higher in the upright location in patients than those without mitral valve prolapse (91.54±2.73 vs. 83.42±2.71, respectively; P=0.04) and in normal controls (91.54±2.73 vs. 84.06±2.02, respectively; P=0.03). Moreover, blood group O and male gender were more common among the patients with mitral valve prolapse, compared to normal controls (67% vs. 39%, respectively; P=0.03, and 61% vs. 35%; P=0.05, respectively).

Conclusion: Our findings suggest a clinical and genetic relationship between active duodenal ulcer and mitral valve prolapse syndrome connected with autonomic dysfunction. Further studies are warranted to confirm this crucial topic.

Keywords: Duodenal ulcer disease, Peptic ulcer, Mitral valve prolapse syndrome, Autonomic dysfunction, Genetics.

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The prevalence of peptic ulcer disease is significant, affecting approximately 5–10% of the population over a lifetime, with a yearly prevalence ranging from 0.1% to 0.3% (1). It represents a worldwide burden, with the lifetime risk of development varying from 5% to 10% (2). Duodenal ulcers occur four times more frequently than gastric ulcers (3). In a large-scale study with hospitalized patients, the incidence of endoscopic duodenal ulcer was 7.5% (4). Moreover, duodenal ulcer disease (DUD) appears to be a frequent acid-related upper gastrointestinal track pathology, with an increased prevalence predominantly observed in medical practice in Asia (5, 6). The familial aggregation of DUD is well recognized, thereby indicating the occurrence of an underlined genetic basis of this disorder connected with genetic factors and polygenic inheritance has been proposed for DUD. Some additional data also suggest that autonomic dysfunction appears to be implicated in the pathophysiology of DUD (7) via altered gastric acid secretion potentially resulting in the development of duodenal ulcer (8). Furthermore, a possible association between peptic ulcer disease and coronary artery disorder has also been suggested by familial aggregation of both entities (9).

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As in the case of DUD, mitral valve prolapse syndrome (MVP-S) appears to be a frequent valvular heart disorder occurring in 2-3% of the overall population. It represents the most complex form of valve disorder, connected with genetic defects, and can progress to heart failure in 10-15% of cases per year in advanced forms. It is an autosomal inherited abnormality with frequent familial clustering (10). Patients with MVP-S also exhibit autonomic dysfunction, which contributes to a variety of the clinical presentations associated MVP-S (11). After conducting a thorough search in the international literature database PubMed, we were astonished to discover the lack of a correlation study addressing these 2 disorders. This prospective study was conducted to examine the potential correlation among active DUD and MVP-S in patients hospitalized in our clinic. In addition, we used non-invasive hemodynamic procedure to assess the regulation of cardiovascular automatic function in these participants.

Methods

Participants: A total of 83 patients with active DUD and 31 controls participated in this study. Duodenal ulcer had been documented by duodenoscopy or upper gastrointestinal series or both. The sex distribution was 34 women and 49 men. The mean age was 43.76 years (range 19-76 years). Control subjects consisted of 31 normal individuals from our clinic staff who had not complained with gastrointestinal symptoms. The absence of duodenal ulcer was based on endoscopically or radiographic normal features. The sex distribution was 20 women and 11 men. The mean age was 47.0 years (range 21-60 years). Participants included in the present study met the following criteria: (a) age above 18 years; (b) endoscopic and/or radiographic evidence of duodenal ulcer; and (c) willingness to undergo upper gastrointestinal endoscopic and/or x-ray diagnostic procedures.

Patients excluded from the present study met the following criteria: (a) stress, complex, cancer or cancer-like risk ulcers; (b) esophageal pathologies such as varices, gastroesophageal reflux disease and its complications including Barrett's esophagus and esophageal adenocarcinoma; (c) evidence of other pathologies, such as Zollinger-Ellison syndrome, pyloric obstruction, active gastric ulcer and/or bleeding, perforation, upper gastrointestinal tract involvement of inflammatory bowel disorders, and cardio-cerebrovascular diseases; (d) previous upper gastrointestinal tract surgery interventions; (e) inadequate complete endoscopic procedure; (f) pregnancy and breastfeeding; (g) use of antisecretory medications 2 weeks before enrollment, with the exception of permitted antacids; and (h) medication administration provoking ulcer bleeding such as aspirin, anticoagulants, steroids, or antiplatelet treatments for more than 3 days within 28 days before enrollment.

A thorough history and physical examination were conducted prior to diagnostic procedures. All participants provided their informed consent prior to enrollment. The study protocol adhered to the principles of the Declaration of Helsinki and complied with the standards of the Research Ethics Committee of the School of Medicine, Aristotle University of Thessaloniki. Patients were symptomatic at the time of the study. They displayed mainly epigastric pain occurred at post-meal 2-3 h which is characteristic of DUD. Regarding the upper gastrointestinal endoscopic diagnostic procedure, participants underwent the procedure at 9 AM following a 12-h fast and continued fasting for about 8 h post procedure.

Blood pressure, heart rate and oxygen saturation were checked with automated devices. Endoscopic duodenal ulcer was defined only as a lesion with a diameter of at least 0.5 cm. The clinical diagnosis of MVP was indicated by the existence of a mid-to-late systolic click and/or a holo- or late- systolic murmur in the participants. In addition, the symptomatic characteristics of MVP-S were evaluated, including chest pain (characteristic or uncharacteristic), palpitations, fatigue, and shortness of breath. The diagnosis of MVP was established by a characteristic pattern on M-mode echocardiography.

Echocardiographic procedure: Echocardiographic procedure was performed with participants in the partial left lateral decubitus location and with the head of the bed raised 30 degrees. Typical techniques were used with the transducer placed specifically in the parasternal fourth intercostal space, with the ultrasound beam directed perpendicular or cephalad to reduce false positive results. Echocardiographic MVP was identified by posterior motion of the mitral leaflets away from the transducer, exhibiting buckling of the mitral valve leaflets in mid-systole (late systolic prolapse), or displacement on the mitral leaflets posterior to the line connecting the valve's closure and opening points (C-D line), with optimum transducer angulation (holosystolic prolapse). Echocardiographic MVP was considered present if either of these patterns led to the displacement of the valve more than 2 mm posterior to the C-D line. Echocardiograms were considered equivocal if these patterns occurred only while the subject was sitting. All echocardiograms were submitted with an additional 70 random echocardiograms for blind evaluation by two experienced echocardiographers.

Hemodynamic measurements: Heart rate and systolic and diastolic blood pressures were assessed in all participants initially in the supine place after a resting period of 20 minutes. Measurements were taken again 10 minutes after the participants stood up. Readings were recorded each minute, and the values achieved for each state were calculated as the mean of all stabilized readings.

Statistical analysis: Data are presented as mean ± standard error of the mean (SEM) for continuous variables or number and/or frequencies for categorical variables. The Shapiro-Wilk test was introduced to assess the normality of distribution of continuous variables. For group comparisons of normally distributed continuous variables, the independent samples t-test was introduced, while the Mann-Whitney U test was employed for non-normally distributed continuous variables. Fisher's exact test was introduced for the comparisons of categorical variables among groups. Statistical significance was set at a p-value ≤ 0.05. All statistical analyses were made with SPSS Version 29 (IBM Corp., Armonk, NY, USA).

Results

Prevalence of echocardiographic MVP: Echocardiographic MVP was shown in 36 (43.37%) of patients with DUD and only in 1 (3%) of controls (*P*=0.001). All of these patients had either late systolic prolapse (n=26) or holosystolic prolapse (n= 10) pattern on the echocardiogram.

Relationship of blood group and sex to prevalence of MVP: Blood group O (67% vs. 39%, respectively; *P*=0.03) and male gender (61% vs. 35%, respectively; *P*=0.05) were more common in patients with MVP compared to controls (table 1).

Clinical features: The symptomatic features of patients with or without MVP and controls are outlined in table 2. Symptoms related to the cardiovascular system (i.e., chest pain) were more common in the patients with MVP than in those without MVP (75% vs. 30%, respectively*; P*=0.001). Likewise, auscultatory findings of systolic murmurs and systolic clicks were more common in the patients with than in those without MVP (50% vs. 4%, respectively*; P*=0.001). Specifically, the patients with MVP had either holosystolic (n=10) or late systolic (n=8) murmurs whereas systolic click was detected in the remaining 18 patients. Only 6 of patients with MVP had both systolic murmurs and clicks.

Hemodynamic features: The hemodynamic data of patients with or without MVP and controls are given in table 3. Heart rate was lower in patients with MVP than in those without it in supine position (71.00±1.73 vs. 76.10±1.66, respectively; *P*=0.04), and was higher in the upright (standing) position in patients than in those without MVP (91.54±2.73 vs. 83.42±2.71, respectively; *P*=0.04) and in normal controls (91.54±2.73 vs. 84.06±2.02, respectively; *P*=0.03).

Table 1. Prevalence of sex and blood groups in duodenal ulcer patients with or without mitral valve prolapse (MVP) and normal controls

	Sex		Blood Group			
Groups	***M***	***M/F ratio***	***0***	***A***	***B***	***AB***
Patients with MVP n= 36	22 (61) *	1.6:1	24 (67) **	8 (22)	4 (11)	-
Patients without MVP n=47	27 (57.4)	1.5:1	23 (49)	14 (29.8)	8 (17)	2 (4.2)
Normal controls n= 31	11 (35)	1:3	12 (39)	12 (39)	6 (19)	1 (3)

M= male, F= female. Percentages in parenthesis. * *P*=0.05 for comparison with normal controls. ** *P*=0.03 for comparison with normal controls.

Table 2. Characteristics of duodenal ulcer patients with or without mitral valve prolapse (MVP)

	Number of patients	
Symptoms	***With MVP***	***Without MVP***
Chest pain	27 (75) *	14 (30)
Atypical	-	-
Typical Palpitations	20 (56)	22 (47)
Easy fatigability	11 (31)	11 (23)
Shortness of breath	5 (14)	2 (4)
Combination of 2 symptoms	25 (69)	24 (51)

Symptoms	Number of patients	
	With MVP	*Without MVP*
Physical findings		
Mitral systolic murmurs	18 (50) *	2 (4)
Systolic clicks	18 (50) *	2 (4)
Clicks and murmurs	6 (17)	-

Number in parentheses = percent. * *P*=0.001 for comparison with patients without MVP.

Table 3. Hemodynamic data of duodenal ulcer patients with or without mitral valve prolapse (MVP) and normal controls

Groups		Blood Pressure				Heart Rate (beats/min)	
		Systolic		Diastolic			
		S	*ST*	*S*	*ST*	*S*	*ST*
Patients with MVP n=36	**Mean SEM**	118.11±2.92	14.00±3.22	76.96±1.76	77.68±2.18	71.00*±1.73	91.54**±2.73
Patients without MVP n=47	**Mean SEM**	124.13±4.13	118.1±2.37	78.8±1.97	78.1±1.74	76.1±1.66	83.42±2.71
Normal controls n=31	**Mean SEM**	116.03±2.89	109.25±2.62	74.50±1.98	74.25±1.86	75.32±1.40	84.06***±2.02

S = supine, ST = standing. * *P*=0.04 for comparison with patients without MVP and *P*=0.06 with normal controls. ** *P*=0.04 for comparison with patients without MVP and ***P=0.03 with normal controls.

Discussion

To our knowledge, this study indicates, for the first time, that MVP-S occurs more frequently in patients with active DUD than in controls (*P*=0.001), thereby lending support to the suggestion that a novel defined MVP-S linked to DUD may exist. Although the actual pathogenetic mechanism(s) involved in this apparent association is unknown, it is possible that genetic factors influence the development of MVP-S related to DUD. This view is supported by the finding that our patients with DUD and MVP exhibited a significant high blood group O and sex (male) depended expressions. Whether a potential vicinity of specific genes governing these two disorders could elucidate their connection – as this postulation has also been suggested for the association between, for instance, autoimmune thyroid disorders (Graves' disease, chronic lymphocytic thyroiditis) and MVP (12, 13) is at present unsettled. The elevated occurrence of MVP observed in our male participants (61%) is in line, for instance, with a previous published report (14) showed that 57% of patients with sickle cell disease and MVP were similarly males. However, in other previous studies, MVP was found to be substantially more prevalent in females (particularly young and slender subjects) than among males (15). Male gender, blood group O and family history of ulcer are connected with DUD (16); and the occurrence of familial clustering of advanced MVP [mitral regurgitation (MR)], supports a common genetic susceptibility to primary MVP-S (17). Therefore, more large-scale detailed assessments of the relation of blood groups, gender, as well as age, body mass index or other rerated parameters and the prevalence of MVP in patients with DUD are clearly warranted to elucidate this topic.

Specifically, accepting that DUD is not a single disorder, but a heterogenous complex group having a genetic basis, the possible role of genetic factors is indicated by familial aggregation of this disorder, association with sex, blood groups, secretor status and HLA antigens, by studies of pepsinogens and by association with defined genetic syndromes inherited on an autosomal dominant basis. Such related data indicate, for instance, the following: Duodenal ulcers are more frequent in males than in females (3). In addition, familial occurrence of peptic ulcer disease has been recognized, with clear genetic associations such as blood group O and non-secretory status. Peptic ulcer disease is more predominant among patients with blood group O compared to other blood types (18). People with blood group O exhibit the highest risk of DUD (19). Moreover, polygenic inheritance is suggested for peptic ulcer. Based on multivariate logistic regression data, beyond gender (male, OR, 2.27), *HLA-DQA1*01* (OR, 2.21), *HLA-DQB1*06* (OR, 2.67), and CagL/CagA/(< 2) EPIYA C repeats (odds ratio, OR, 5.72, 95% CI; *P*=0.007) appear to independently increase the risk of DUD (20). High serum pepsinogen concentrations signify an increased risk for

DUD (21), and high levels of pepsinogen plus smoking are related with augmented risk for DUD in *Helicobacter pylori* (*H. pylori*) infected patients (22). Moreover, for instance, inherited cytosolic phospholipase-A2 alpha deficiency is connected with duodenal ulcer bleeding diathesis (22); congenital variations of glutathione S-transferase theta 1 (*GSTT1*) and prostate stem cell antigen (*PSCS*) are linked with DUD and, in particular, the C allele of *rs2294008* at *PSCA* was connected with an augmented risk of DUD ($P<0.001$) (23); genetic polymorphisms of interleukins 1 (interleukin-1β *-581C/T* and interleukin-1β -1061C/T genotypes) contribute to the development of DUD owing to aspirin usage (24); and additional polymorphisms also seem to be involved in the pathophysiology of DUD (25).

Like DUD, MVP-S, a significant disorder burden, is also a broadly varied complex group having a genetic basis (10, 26). The possible role of genetic factors is also indicated by familial aggregation of this syndrome, association mainly with female gender (10), and by association with defined genetic syndromes. Specifically, MVP seems to be familial, or a form of syndromes inherited on an autosomal dominant basis such as, Marfan, Loeys-Dietz, or Ehlers-Danlos syndromes, among others (27). Additional genetics also appeared to be implicated in the pathogenesis of MVP-S (10, 27). Therefore, future related studies are needed to investigate the potential involvement of such aforementioned genetic parameters in the pathophysiology of DUD-related MVP-S.

Considering the additional interesting finding of autonomic dysfunction reported in this series, the sinus bradycardia observed in the supine position of our patients with DUD and MVP may suggest the presence of an increased vagal tone while lying down, thereby supporting the theory that an autonomic dysregulation might contribute to certain clinical presentations of MVP-S linked to DUD; increased vagal tone could contribute to bradycardia and sinus arrest, signifying heightened cardiac vagal activity. In contrast, the sinus tachycardia observed in the upright posture of our patients with DUD and MVP may indicate an increased sympathetic tone in the standing position. An augmented sympathetic activity has also been suggested in patients with DUD who had elevated catecholamine concentrations reflecting sympathetic and adrenal medullary activity. A comparable dual autonomic dysfunction was also observed in patients with MVP-S that may be responsible for some “dangerous” arrhythmias complicating this syndrome. Indeed, the presence of a hyperadrenergic condition, linked to a vagotonic state may be implicated in MVP-S-related pathophysiology of supraventricular arrhythmias (including sinus tachycardia, paroxysmal atrial tachycardia and atrial flutter) alternating with events of sinus bradycardia.

Additionally, the occurrence of life-threatening ventricular tachycardia and ventricular fibrillation could be triggered by simultaneously increased adrenergic and vagal tone. Increased vagal tone may also be responsible for sudden death observed in patients with MVP-S (26). It is important to note that the heterogenous natural history of MVP-S is usually connected with its related MR (26). While the majority of patients exhibit almost a normal life expectation without symptoms, about 5-10% develop a severe form of MR. MVP-S can contribute to the pathophysiology of severe MR-related complications, including supraventricular and ventricular arrhythmias, heart failure, and sudden death. In this respect, there may be a connection among ventricular arrhythmias and sudden cardiac death, independently of MR severity (28). Therefore, future research is needed to clarify the potential autonomic dysfunction-related adverse cardiovascular events in patients with DUD and MVP, particularly complicated by MR.

Another clinical feature of our study was the high prevalence of symptoms like chest pain observed in approximately 2/3 of our patients with DUD and MVP, thereby suggesting a potential coronary heart disease; this high prevalence is comparable to that reported in several clinical series in patients with MVP-S (29, 30). In this regard, a possible association of peptic ulcer and coronary disease has been suggested by familial aggregation of both entities and by enhanced catecholamine secretion both in patients with angina pectoris and myocardial infarction and in patients with DUD (9). Nevertheless, symptoms of MVP such as chest pain and/or palpitations are not solely elucidated by the mitral valve pathology. The pathophysiology of such symptoms could be involved metabolic neuroendocrine dysfunction. An additional interesting feature of our study was the significant high prevalence of auscultatory findings of systolic clicks and murmurs in association with the autonomic dysfunction observed in our patients with DUD and MVP. The typical auscultatory finding in MVP syndrome is, as in our cases of the present study, a mid-to-late systolic click which is frequently followed by a high-pitched systolic murmur (31).These characteristic auscultatory findings occur in 10% to 70% of patients with MVP-S (32). In line with the above-mentioned rates, comparable pictures were also obtained in our series: the assessed prevalence of systolic click and murmur was 50% and with both 17%.

As the disorder progresses and the MR becomes overt, the click could diminish, while the murmur could transform

into holosystolic (33). In this respect, our ten patients presented with holosystolic murmurs, thus reflecting the possible presence of MR owning to the progression of MVP in these patients. Symptomatic patients with MVP and auscultatory findings of systolic murmurs may exhibit other serious complications including severe MR and bacterial endocarditis (34–36). Bacterial endocarditis occurs more frequently in patients with MVP-S. In some guide-lines antibiotic prophylaxis is not recommended (37) whereas others consider that such prophylaxis may be introduced in patients with MVP and MR because a wound infection can lead to bacteremia and subsequent endocarditis (38).

The auscultatory findings of systolic and particularly holosystolic murmurs which in association with the autonomic dysfunction observed in our patients with DUD and MVP, may give rise some practical questions such as: Should these patients be followed carefully as a high-risk group? Should these patients receive antibiotic prophylaxis before procedures (e.g., endoscopy) that may produce a bacteremia? And conversely, which is the prevalence of DUD in patients with MVP-S? Such and other related questions need further investigation. Patients with DUD have been associated with a variety of psychiatric disorders (e.g., anxiety neurosis, depression, frustration, hostility) that seem to be important in the genesis of their DUD (39, 40); stressful life events, mainly reacting with excessive anxiety and depression, are important psychologic factors involved in the pathogenesis of DUD (39).

A nervous disposition had been recognized as a predisposing peptic ulcer factor because it was postulated that emotional upset stimulated secretion of gastric juices (41); reactive anxiety, neurosis and type of personality with autonomic dysfunction are correlated with DUD. In this regard, autonomic neuropathy- dysfunction and *H. pylori* infection might be necessary condition for development of DUD (42). Likewise, MVP-S is frequently associated with diverse psychiatric conditions, including, for instance, nervousness, neurosis, depression, panic attacks, agoraphobia, primary disorders of sleep and/or anorexia nervosa and bulimia (43). Patients with MVP-S display autonomic dysfunction symptoms and variability of heart rate variability (11, 44); patients with MVP-S exhibit augmented scores of both autonomic dysfunction and anxiety; and dysfunctions of sympathetic and parasympathetic nervous system are responsible for certain clinical manifestations of this syndrome (11). Whether the latter MVP group of patients with autonomic dysfunction-related psychiatric disorders may be accompanied with high prevalence of DUD and vice versa, remains to be elucidated. The present study has several limitations such as the following: (a) Small number of participants particularly of the mentioned controls the recruitment of whom was not optimal. Thus, a larger statistical population and the limitation of other interventional factors are needed to clarify more precisely the relationship between these two disorders. (b) Lack of evaluation of active *H. pylori* infection, mainly by using histology, the practical diagnostic gold standard for active *H. pylori* load (45), despite this bacterium being a well-established principal cause of DUD in 90-100% of the cases (46). In our series, the exclusion of other causes of DUD such as NSAIDs including aspirin and even Zollinger-Ellison syndrome, signifies that almost all our patients with active DUD and MVP-S could be *H. pylori* positive. (c) Lack of diagnostic and follow-up evaluation of MVP-S by new techniques including echocardiography and doppler echocardiography, cardiac MRI and electrophysiologic analyses. (d) Given the limited data in our study suggesting a generic relationship between these two diseases, a future genetic analysis is warranted to elucidate this issue in depth.

In conclusion, the results of the present study suggest, for the first time, the existence of a possible clinical and genetic relationship among active DUD and MVP-S. Future research related to the pathophysiology of peptic ulcers linked to MVP-S is needed to provide potential strategies for managing this important combined topic.

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Authors' contribution: JK conceived the idea, wrote and revised the manuscript; SAP, CZ, EK, MTC, DC, AS, MT, SA and EV, interpreted data and revised the manuscript. All authors approved the final version to be submitted.

References

1. Tarasconi A, Coccolini F, Biffl WL, et al. Perforated and bleeding peptic ulcer: WSES guidelines. World J Emerg Surg 2020; 15: 3.
2. Lanas A, Chan FKL. Peptic ulcer disease. Lancet 2017; 390: 613-24.
3. Malik TF, Gnanapandithan K, Singh K. Peptic Ulcer Disease. In: StatPearls. Treasure Island (FL): StatPearls Publishing 2023. Accessed 12 Feb, 2023.

4. Han Y, Jung H-K, Chang JY, et al. Identification of distinctive clinical significance in hospitalized patients with endoscopic duodenal mucosal lesions. Korean J Intern Med 2017; 32: 827-35.
5. Shu X, Zhu Z, Fu Y, et al. Mucosal healing effectiveness and safety of anaprazole, a novel PPI, vs. rabeprazole in patients with duodenal ulcers: a randomized double-blinded multicenter phase II clinical trial. Front Med (Lausanne) 2021; 8: 690995.
6. Abe M. Endoscopic finding of hematin represents strong gastric acidity. Ann Gastroenterol 2022; 35: 362-67.
7. Katoh K, Nomura M, Nakaya Y, et al. Autonomic nervous activity before and after eradication of Helicobacter pylori in patients with chronic duodenal ulcer. Aliment Pharmacol Ther 2002; 16: 180-6.
8. Haj Kheder S, Heller J, Bär J, et al. Autonomic dysfunction of gastric motility in major depression. J Affect Disord 2018; 226: 196-202.
9. Ghobadi P, Gholami M, Hasanvand S, et al. Effects of a multidisciplinary management program on symptom burden and medication adherence in heart failure patients with comorbidities: a randomized controlled trial. BMC Nurs 2022; 21: 346.
10. Guicciardi NA, De Bonis M, Di Resta C, et al. Genetic background of mitral valve prolapse. Rev Cardiovasc Med 2022; 23: 96.
11. Bona Olexova L, Visnovcova Z, Ferencova N, Jurko A Jr, Tonhajzerova I. Complex sympathetic regulation in adolescent mitral valve prolapse. Physiol Res 2021; 70: S317-25.
12. Fekri K, Michel CM, Tamilia M. Reversible, severe mitral regurgitation in thyrotoxic Graves' disease. BMJ Case Rep 2021; 14: e239626.
13. Liu YP, Tsai WY, Wang JK, Wu MH. Reversible mitral valve prolapse and mitral regurgitation in children with Graves' disease. J Pediatr Endocrinol Metab 2004; 17: 1211-3.
14. Lippman SM, Ginzton LE, Thigpen T, Tanaka KR, Laks MM. Mitral valve prolapse in sickle cell disease. Presumptive evidence for a linked connective tissue disorder. Arch Intern Med 1985; 145: 435-8.
15. Karashima S, Tsuda T, Kometani M, et al. Severe mitral regurgitation as a result of rupture of mitral valve chordae tendineae in a patient with Graves disease. J Endocr Soc 2018; 2: 1246-50.
16. Abu Farsakh NA. Risk factors for duodenal ulcer disease. Saudi Med J 2002; 23: 168-72.
17. Delling FN, Li X, Li S, et al. Heritability of mitral regurgitation. Circ Cardiovasc Genet 2017; 10: e001736.
18. Teshome Y, Mekonen W, Birhanu Y, Sisay T. The association between ABO blood group distribution and peptic ulcer disease: a cross-sectional study from Ethiopia. J Blood Med 2019; 10: 193-7.
19. Edgren G, Hjalgrim H, Rostgaard K, et al. Risk of gastric cancer and peptic ulcers in relation to ABO blood type: a cohort study. Am J Epidemiol 2010; 172: 1280-5.
20. Kocak BT, Saribas S, Demiryas S, et al. Association between polymorphisms in HLA-A, HLA-B, HLA-DR, and DQ genes from gastric cancer and duodenal ulcer patients and cagL among cagA-positive Helicobacter pylori strains: The first study in a Turkish population. Infect Genet Evol 2020; 82: 104288.
21. Lee SP, Lee SY, Kim JH, et al. Link between serum pepsinogen concentrations and upper gastrointestinal endoscopic findings. J Korean Med Sci 2017; 32: 796-802.
22. Chen TS, Lee YC, Li FY, Chang FY. Smoking and hyperpepsinogenemia are associated with increased risk for duodenal ulcer in Helicobacter pylori-infected patients. J Clin Gastroenterol 2005; 39: 699-703.
23. Tanikawa C, Urabe Y, Matsuo K, et al. A genome-wide association study identifies two susceptibility loci for duodenal ulcer in the Japanese population. Nat Genet 2012; 44: 430-4.
24. Phuc BH, Tuan VP, Binh TT, et al. Comparative genomics of two Vietnamese Helicobacter pylori strains, CHC155 from a non-cardia gastric cancer patient and VN1291 from a duodenal ulcer patient. Sci Rep 2023; 13: 8869.
25. Park S, Liu M, Huang S. Association of polygenic variants involved in immunity and inflammation with duodenal ulcer risk and their interaction with irregular eating habits. Nutrients 2023; 15: 296.
26. Battaglia V, Santangelo G, Bursi F, Simeoli P, Guazzi M. Arrhythmogenic mitral valve prolapse and sudden cardiac death: an update and current perspectives. Curr Probl Cardiol 2023; 48: 101724.
27. Delwarde C, Capoulade R, Mérot J, et al. Genetics and pathophysiology of mitral valve prolapse. Front Cardiovasc Med 2023; 10: 1077788.
28. Vermes E, Altes A, Iacuzio L, et al. The evolving role of cardiovascular magnetic resonance in the assessment of mitral valve prolapse. Front Cardiovasc Med 2023; 10: 1093060.
29. Jiang X, Li J, Zhang X, Chen H. Acute coronary syndrome in a young woman with a giant coronary aneurysm and mitral valve prolapse: a case report and

literature review. J Int Med Res 2021; 49: 300060521999525.
30. Maiello M, Zito A, Cecere A, Ciccone MM, Palmiero P. Chest pain and palpitations in postmenopausal women with mitral valve prolapse: is there a gastro-oesophageal origin? Intern Med J 2022; 52: 848-52.
31. Rajeshwari BS, Sinha A, Sengupta A, et al. Synchrosqueezed Transform based Click Event Segmentation in Phonocardiogram of Mitral Valve Prolapse. Annu Int Conf IEEE Eng Med Biol Soc 2022; 2022: 1997-2000.
32. Liu PY, Tsai KZ, Lin YP, et al. Prevalence and characteristics of mitral valve prolapse in military young adults in Taiwan of the CHIEF Heart Study. Sci Rep 2021; 11: 2719.
33. Boudoulas KD, Pitsis AA, Boudoulas H. Floppy mitral valve (FMV) – mitral valve prolapse (MVP) – mitral valvular regurgitation and FMV/MVP syndrome. Hellenic J Cardiol 2016; 57: 73-85.
34. Alqarawi W, Burwash IG, Krahn AD, Healey JS. Arrhythmic Mitral Valve Prolapse: Risk Assessment and Management. Can J Cardiol 2023; 39: 1397-409.
35. Shah SN, Gangwani MK, Oliver TI. Mitral Valve Prolapse. In: StatPearls. Treasure Island (FL): StatPearls Publishing 2024. Available from: https://www.ncbi.nlm.nih.gov/books/NBK470288/. Accessed 16 Jan, 2023.
36. Wynne J. Mitral-valve prolapse. N Engl J Med 1986; 314: 577-8.
37. Danchin N, Voiriot P, Briancon S, et al. Mitral valve prolapse as a risk factor for infective endocarditis. Lancet 1989; 1: 743-5.
38. Affleck AG, Birnie AJ, Gee TM, Gee BC. Antibiotic prophylaxis in patients with valvular heart defects undergoing dermatological surgery remains a confusing issue despite apparently clear guidelines. Clin Exp Dermatol 2005; 30: 487-9.
39. Ruan X, Chen J, Sun Y, et al. Depression and 24 gastrointestinal diseases: a Mendelian randomization study. Transl Psychiatry 2023; 13: 146.
40. Peters MN, Richardson CT. Stressful life events, acid hypersecretion, and ulcer disease. Gastroenterology 1983; 84: 114-9.
41. Grob GN. The rise of peptic ulcer, 1900-1950. Perspect Biol Med 2003; 46: 550-66.
42. Nomura M, Yukinaka M, Miyajima H, et al. Is autonomic dysfunction a necessary condition for chronic peptic ulcer formation? Aliment Pharmacol Ther 2000; 14: 82-6.
43. Tural U, Iosifescu D V. The prevalence of mitral valve prolapse in panic disorder: a meta-analysis. Psychosomatics 2019; 60: 393-401.
44. Ahmadi M, Ghahremani B, Habibi D, Sadrnia S, Ghandi Y. Effects of mitral valve prolapse on heart rate variability and the autonomic nervous system in children. J Tehran Heart Cent 2022; 17: 140-6.
45. Kountouras J, Doulberis M, Papaefthymiou A, et al. Controlling the impact of Helicobacter pylori-related hyperhomocysteinemia on neurodegeneration. Medicina (Kaunas) 2023; 59: 504.
46. Le LTT, Nguyen TA, Nguyen NA, et al. Antibiotic resistance of Helicobacter pylori in children with gastritis and peptic ulcers in Mekong Delta, Vietnam. Healthcare (Basel) 2022; 10: 1121.