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RESEARCH ARTICLE

Congestive Heart Failure and Upper Digestive Endoscopic Lesions

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Objective: To evaluate the impact of congestive heart failure and the most important clinical and pathological factors on severe upper digestive mucosal lesions. **Methods**: The study included 749 patients referred for upper digestive endoscopy, divided into two groups: 140 subjects with congestive heart failure (study group) and 609 subjects without heart failure (control group). **Results**: Severe endoscopic lesions quantified according to Lanza score (OR = 3.84, 95% IC: 2.62-5.62), active/inactive gastritis (OR = 2.07, 95% CI: 1.36-3.14), intestinal metaplasia and/or gastric atrophy (OR = 2.42, 95% CI: 1.67-3.52) were significant more frequent among patients with heart failure. Anemia (OR = 3.65, 95% IC: 2.48-5.37) and all investigated comorbidities, as well as alcohol consumption (OR = 1.60, 95% IC: 1.10-2.34) and smoking (OR = 1.76, 95% IC: 1.17-2.64) were more frequent in the study-group. Dividing the patients with cardiac insufficiency according to the severity of their endoscopic lesions, the male gender (OR = 2.76, 95% IC: 1.35–5.61) and daily low-dose aspirin consumption were found to be more frequent among patients with severe endoscopic lesions (OR = 7.71, 95% IC: 3.62–16.40), while anticoagulant therapy and alcohol consumption were borderline associated with mucosal lesions (p=0.08). **Conclusions**: Male patients and aspirin consumers with heart failure, but not those with *H. pylori* infection seem to be more prone to develop upper digestive endoscopic lesions, while alcohol consumption or anticoagulant therapy could be other modifiable factors associated with severe endoscopic lesions in a congestive gastro-duodenal mucosa.

Keywords: congestive heart failure, endoscopic gastro-duodenal lesions, anemia

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Introduction

Heart failure is a common and potentially fatal condition, being one of the most frequent causes of hospitalization today, with a poor prognosis despite the improvements in diagnosis and medical treatment [1,2]. In 2016 it affected over 60 million people worldwide and despite improvements in modern device-, and pharmacotherapy, it continues to have a high mortality [3].

Congestive heart failure (CHF) can be described as a multi-organ disorder caused by the incapacity of the heart to keep adequate cardiac output to satisfy the body's metabolic needs [4]. It has been established that the cardiovascular system is not the only one affected by heart failure. In CHF, the increased systemic venous congestion is transmitted to the inferior vena cava, which leads to congestion in its draining territories, such as the gastrointestinal tract (GIT) mucosa [5]. Over the last decade, several studies investigated the gastrointestinal changes associated with CHF [5,6]. Structural changes have been previously described in the gastric mucosa, such as mosaic pattern in the stomach, mucosal thickening, antral vascular ectasia, and areas of telangiectasias [6].

Mechanisms of gastrointestinal-related symptoms remain poorly understood despite their common presence and increased morbidity and mortality correlated with their coexistence. The specific involvement of the gastrointestinal system in CHF results in a bidirectional relationship. The systemic volume overload characteristic of CHF is generally associated with concomitant gastrointestinal edema, which can result bacterial translocation into the systemic circulation. Consequent activation of monocytes and excessive release of cytokines lead to systemic inflammation, increased symptoms, and therefore, progression of the disease [4].

Anemia is a very common and well-known comorbidity in patients with CHF and its prevalence increases with the severity of the disease. The true frequency of anemia in CHF patients varies widely, but it has been reported to range between 30% - 50%, depending on the severity of CHF and the population studied [6, 7, 8,9]. Anemia in CHF patients is a multifactorial and multidimensional problem. However, there has been an increasing appreciation for the significance of anemia in the pathophysiology, treatment, and prognosis of CHF [9].

The aim of the present study is to evaluate the influence of CHF and associated clinical and pathological factors on the severity of upper digestive endoscopic lesions.

Methods

The study included 749 patients divided as follows: 140 patients with congestive heart failure (CHF group) and 609

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subjects without congestive heart failure (control group). All patients were hospitalized in Medical Clinic Nr. 3 in Tîrgu Mureș Emergency County Hospital, Romania, and underwent an upper digestive endoscopy. The reasons for endoscopy were specific digestive symptoms, anemia, or screening before initiating an antithrombotic therapy or a major cardiovascular surgery.

Written informed consent was obtained from all subjects before being included in the study. The research was approved by the Ethical Committee of the University of Medicine and Pharmacy of Tîrgu Mureș, Romania. Demographical and clinical data were collected from each patient after structured interviews and clinical examinations.

The diagnosis of CHF was derived from a careful history and based on present and past medical records of the patients. Digestive symptoms questioned were epigastric pain, heartburn, regurgitation, nausea/vomiting. Alcohol consumption was considered at the use of at least 10 units (10 mL) of pure alcohol weekly, while smoking at more than 5 cigarettes/day. To conduct an investigation into drug exposure, medical records of the patients and a structured interview was performed. Patients taking low-dose aspirin (LDA, 75 -100 mg/day), regular daily doses of non-aspirin non-steroidal anti-inflammatory drugs (NSAIDs-ibuprofen, ketoprofen, dexketoprofen, diclofenac) and proton pump inhibitors (omeprazole, pantoprazole, esomeprazole) for more than 2 weeks were considered as exposed to drug. Cut-off values of hemoglobin level for anemia (hemoglobin level of < 12g/dl (7.5mmol/l) in women and <13g/dl (<8.1 mmol/l) in men,) were used according to the WHO definitions [7].

Each endoscopy was carried out by an endoscopist who was not informed about the symptoms and drug exposure. The mucosal lesions were described as erythema, petechiae (hemorrhagic area without mucosal defect), erosions (mucosal defect smaller than 5 mm), or ulcers in both gastric and duodenal mucosa. We used the modified Lanza score (MLS), as followed: Lanza score 0 for no mucosal lesions, Lanza score 1 for one erosion or petechiae, Lanza score 2 for 2–10 erosions or petechiae, Lanza score 3 for more than 10 erosions or petechiae and Lanza score 4 when an ulcer was present [10]. To investigate factors associated with endoscopic lesions we stratified patients in CHF group according to their lesions in severe endoscopic lesions group (Lanza score 2,3,4 - 77 subjects) and controls (Lanza score 0,1- 63 subjects). The Los Angeles Classification System for the endoscopic assessment of reflux esophagitis was used to define esophagitis, but patients in the present study were assigned as having or not any mucosal lesions. During endoscopy, four biopsy specimens were taken, two from the antrum and two from the corpus (from the greater and the lesser curvature). The specimens were routinely processed and examined by a pathologist blinded to symptoms and drug exposure. Mucosal changes in the gastric biopsies were described and classified using the Updated Sydney System. *H. pylori* infection was considered present if the germ was identified on histologic examination in at least one biopsy sample.

All collected data was recorded in a specially designed database.

Statistical Analysis

Qualitative nominal variables were summarized using absolute frequencies (number of cases) and relative frequencies (%). Chi-square and Fisher's exact tests were performed to analyze the associations between possible predictors for congestive heart failure. Value of p lower than 0.05 was considered statistically significant. The odds ratio (OR) and 95% confidence intervals were calculated to quantify the magnitude of the association. GraphPad Prism 6 was used for the statistical analysis.

Results

Bivariate Analysis

Distribution of demographic and clinical characteristics of the patients in two groups are showed in Table I. Male patients were more frequent in the CHF group. Anemia and severe endoscopic lesions were with statistically significant higher frequency in the CHF group (OR = 3.65, 95% IC: 2.48-5.37), (OR = 3.84, 95% IC: 2.62-5.62). LDA and NSAIDs consumption was statistically lower among CHF patients compared with the control group (OR = 0.41, 95% IC: 0.74-0.71).

Gastritis (active/inactive) (OR = 2.07, 95% CI: 1.36-3.14), intestinal metaplasia and/or gastric atrophy in biopsy samples (OR = 2.42, 95% CI: 1.67-3.52) were significantly associated with congestive heart failure, but not with active H. pylori infection (Table I).

The history of ulcer, as well as concomitant diseases (respiratory, liver, renal, or cerebrovascular disease) were significantly more frequent in patients with congestive heart failure (OR = 23.96, 95% CI: 14.75–38.94),. Consumption of gastrotoxic drugs (LDA and NSAIDs) was statistically significant less frequent among patients with CHF, while gastroprotective drugs (PPI) were more frequently taken. Epigastric pain and heartburn were found to be less frequent among patients with heart failure. Alcohol consumption (more than 2 units/day) and smoking (over 5 cigarettes/day) also showed significant association with congestive heart failure.

Dividing patients from CHF group according to the severity of endoscopic lesions (Lanza score) we observed that from all considered predictors, the male gender was positively associated with the severity of endoscopic lesions (OR = 2.76, 95% IC: 1.35–5.61), while alcohol consumption had a tendency toward statistical significance (Table II). LDA consumption was found to be more frequent among patients with CHF and severe endoscopic lesions (OR = 7.71, 95% IC: 3.62–16.40), mean while anticoagulants tended to have a tendency toward significance. Anemia was more frequent in patients with CHF and severe

Table I. The distribution of demographical, clinical, endoscopic and pathological variables in studied groups

Variables	Congestive heart failure group N= 140 (18.70%)		Control Group N=609 (81.30%)		p* value	OR	95% CI
	N	%	N	%			
Male gender	89	63.57	263	43.18	< 0.0001	2.29	1.57-3.35
Anemia	68	48.57	125	20.52	< 0.0001	3.65	2.48-5.37
Drug consumption							
Anticoagulants	65	46.42	30	4.92	< 0.0001	16.73	10.20-27.44
NSAIDs	25	17.85	512	84.07	< 0.0001	0.04	0.02-0.06
PPIs	83	59.28	285	46.79	0.0086	1.65	1.14-2.40
LDAa	17	12.14	151	24.79	0.0010	0.41	0.24-0.71
Endoscopic findings							
Severe endoscopic lesions	77	55	147	24.13	< 0.0001	3.84	2.62- 5.62
Esophagitis	30	21.42	141	23.15	0.73	0.90	0.57- 1.41
Biliary reflux	48	34.28	218	35.79	0.76	0.93	0.63-1.37
Histologic findings							
Reactive gastropathy	34	24.28	154	25.28	0.91	0.94	0.61-1.45
Active/inactive gastritis	106	75.71	366	60.09	0.0005	2.07	1.36-3.14
GA/IMb	78	55.71	208	34.15	< 0.0001	2.42	1.67-3.52
H. pylori infection	47	33.57	220	36.12	0.62	0.89	0.60-1.31
Comorbidities							
Ulcer history	81	57.85	33	5.41	< 0.0001	23.96	14.75-38.94
Cerebrovascular disease	13	8.66	15	2.46	0.001	3.75	1.74-8.08
Renal disease	64	45.71	41	6.73	< 0.0001	11.67	7.36-18.47
Liver disease	80	57.14	213	34.97	< 0.0001	2.47	1.70-3.60
Respiratory disease	69	49.28	77	12.64	< 0.0001	6.71	4.46-10.10
Osteoarticular disease	61	43.57	155	25.45	< 0.0001	2.26	1.54-3.30
Symptoms							
Epigastric pain	61	43.57	367	60.26	0.0004	0.50	0.35-0.73
Heartburn	14	10	193	31.69	< 0.0001	0.23	0.13-0.42
Regurgitation	7	5	42	6.89	0.56	0.71	0.31-1.61
Nausea/vomiting	34	24.28	132	21.67	0.49	1.15	0.75-1.78
Social behaviours							
Alcohol consumptionc	58	41.42	186	30.54	0.0162	1.60	1.10-2.34
Smokingd	45	32.14	129	21.18	0.0076	1.76	1.17-2.64

* Obtained from Chi-square or Fisher's exact tests; [a] Low-dose aspirin; [b] Glandular atrophy/ Intestinal metaplasia; [c] Over 5 cigarettes/day; [d] More than 2 units/day, 1 unit = 10mL pure alcohol.
OR: odds ratio; CI: 95% confidence interval; NSAIDs: nonsteroidal anti-inflammatory drugs; PPI: proton pump inhibitors.

endoscopic lesions, in comparison with no-lesions group, but without statistical significance, while *H. pylori* infection was not associated with the severity of endoscopic lesions.

Discussion

Cardiovascular diseases (CV), including CHF, are the leading cause of morbidity and mortality worldwide. Physiologically, the gastrointestinal tract is one of the most intensely perfused organ, and mucosal gastric congestion is expected in CHF, due to the increase systemic venous pressure, which is transferred to the portal circulation through the hepatic venous bed [6,11]. Our results sustain that CHF by itself seems to be a factor influencing the severe gastro-duodenal endoscopic lesions, but not esophageal ones. Reactive gastropathy changes involve the congestion of superficial mucosal capillaries alongside with prominent mucin depletion, foveolar hyperplasia, and fibro-muscular replacement of the lamina propria. These changes appear after various type of aggressors, like alcohol consumption, biliary reflux and gastrotoxic drug consumption, having an impact on the balance of the gastric epithelium developing a constellation of mucosal changes [12]. In our study, the frequency of reactive gastropathy histologic changes were comparable in patients with and without CHF and were non-significant less frequent in patients with CHF and severe endoscopic lesions. Our results support the possible role of other aggressive factors (*H. pylori* infection, aging mucosa) on endoscopic lesions occurrence, not only the congestion in upper digestive tract.

Infection with *H. pylori* may be directly or indirectly involved in the pathogenesis of cardiovascular diseases. Altered iron metabolism is one of the leading mechanism of H. pylori, which can contribute to cardiovascular diseases [13]. In our study, *H. pylori* was not more frequent in patients diagnosed with congestive heart failure (p=0.62). In a geographical area with a high prevalence of *H. pylori* infection, the histologic changes of gastric mucosa in elderly patients are usually related to early acquisition of infection. In our research, the inflammatory and premalignant histological gastric changes were more common in patients with heart failure (OR = 2.42, 95% IC: 1.67–3.52) as they were older age than patients in the control group (69.75 ± 0.76 years old for cases vs. 54.10 ± 0.55 years old for controls), but these findings seemed to not influence the frequency of endoscopic lesions.

Table II: The distribution of studied variables in patients with CHF divided according to their endoscopic lesions

Variables	Severe endoscopic lesions group N=77 (55%)		No lesions group N=63 (45%)		p* value	OR	95% CI
	N	%	N	%			
Male gender	57	74.02	32	50.79	0.0051	2.76	1.35-5.61
Age >70	43	55.84	36	57.14	1.00	0.94	0.48-1.85
Anemia	40	51.94	28	44.44	0.39	1.35	0.69-2.63
Drug consumption							
Anticoagulants	41	53.24	24	38.09	0.08	1.85	0.93-3.64
NSAIDs	17	22.07	8	12.69	0.18	1.94	0.77-4.87
PPIs	48	62.33	35	55.55	0.48	1.32	0.67-2.60
LDAa	57	74.02	17	26.98	< 0.0001	7.71	3.62-16.40
Histologic findings							
Active/inactive gastritis	62	80.51	44	69.84	0.16	1.78	0.81-3.89
GA/IMb	45	58.44	33	52.38	0.49	1.27	0.65-2.50
Reactive gastropathy	15	19.48	19	30.15	0.16	0.56	0.25-1.22
H. pylori infection	29	37.66	18	28.57	0.28	1.51	0.73-3.08
Comorbidities							
Ulcer history	48	62.33	33	52.38	0.30	1.50	0.76-2.95
Cerebrovascular disease	10	12.98	3	90.47	0.14	2.98	0.78-11.36
Renal disease	35	45.45	29	46.03	1.00	0.97	0.50-1.90
Liver disease	48	62.33	32	50.79	0.17	1.60	0.81-3.15
Respiratory disease	42	54.54	27	42.85	0.17	1.60	0.81-3.13
Osteoarticular disease	34	44.15	27	42.85	1.00	1.05	0.53-2.06
Symptoms							
Epigastric pain	29	37.66	32	50.79	0.12	0.58	0.29-1.15
Heartburn	7	9.09	7	11.11	0.78	0.80	0.26-2.41
Social behaviours							
Alcohol consumptionc	37	48.05	21	33.33	0.08	1.85	0.92-3.68
Smokingd	29	37.66	16	25.39	0.14	1.77	0.85-3.68

* Obtained from Chi-square or Fisher's exact tests; [a] Low-dose aspirin; [b] Glandular atrophy/ Intestinal metaplasia; [c] Over 5 cigarettes/day; [d] More than 2 units/day, 1 unit = 10mL pure alcohol; OR: odds ratio; CI: 95% confidence interval; NSAIDs: nonsteroidal anti-inflammatory drugs; PPI: proton pump inhibitors.

In our present study, anemia appeared to be more frequent in patients with CHF, but not in those with endoscopic lesions. The approach of the underlying mechanism of anemia in patients with CHF is very difficult, in most cases, more than one etiology is involved. Such factors are bone marrow dysfunction, renal dysfunction, abnormal steroid metabolism, hemodilution, resistance to erythropoietin, the use of drugs for the treatment of CHF, chronic inflammation, hematinic deficiencies, decrease of food intake, reduction of intestinal absorption, and blood losses by the GIT [6, 7, 8, 9]. Among anemic CHF patients the most frequent form of hematinic deficiency, besides folate and vitamin B12 deficiency, is represented by iron deficiency [14, 15, 16]. An other important factor which may induce anemia is chronic gastrointestinal blood loss. Many patients with CHF use antithrombotic treatments, antiplatelet and/or anticoagulants. These drugs promote the blood loss by the entire GIT from various mucosal lesions [17, 18, 19, 20]. Furthermore, gastrointestinal conditions that do not usually induce bleeding, frequently associate iron deficiency anemia due to impairment of iron metabolism [21]. Our results support the important role of other combined mechanism except for bleeding from upper digestive endoscopic lesions in anemic patients with CHF that required a more complex approach.

The consumption of gastro-toxic drugs (NSAIDs, LDA), was less frequent in patients with CHF, while anticoagulants were more frequent, as the international therapeutic guideline recommends their use in treatment or secondary prevention of the underlying conditions. Among all questioned variable, the aggressive effect of antiplatelet therapy (LDA), in a vulnerable congestive gastric mucosa was supported by our present and past results, while the role of anticoagulants should be further investigated in larger studies [22]. It has been demonstrated that daily LDA consumption reduces the risk of cardiovascular diseases, however, it also associates adverse effects, mostly in the gastrointestinal tract. These complications can range from mild upper events (dyspepsia, petechiae, or erosions) to severe events (peptic ulcer disease and bleeding) [23,24]. Based on present observations, antiplatelet therapy should be cautioned in patients diagnosed with CHF, and gastroprotective therapy should be offered in high risk patients.

The presence of epigastric pain and heartburn were negatively associated with CHF, probably due to the selection of the cases: controls usually referred for symptoms, while cases for bleeding risk assessment. Different results were obtained in a study of 57 patients with congestive heart failure complaining from GI symptoms [5,11].

Our findings suggest that male gender was more frequently associated with CHF and severe lesions on endoscopy. In our previous research we obtained similar results regarding the severity of endoscopic lesions in patients consuming LDA [17]. Male gender presents cardiovascular diseases more commonly than females, due to hormonal differences [25]. On the other hand, they are more

frequently affected by duodenal ulcer in relationship with *H. pylori* infection [26]. This association should be further questioned in larger studies adjusted for the most important confounding factors (smoking, alcohol consumption) [27,28].

Patients suffering from CHF usually have at least one comorbidity and the severity of the heart failure leads to increasing numbers of comorbidities. The high number of comorbidities in our study was associated with the elderly population suffering from heart failure. Renal disease and anemia were the most common comorbidities found in a study conducted by van Deursen [29]. Similar results were found in our study, but the comorbidities did not appear to influence the severity of endoscopic lesions.

In this study, alcohol use was borderline correlated with endoscopic lesions, probably due to its additive aggressive effect on the gastrointestinal mucosa. Similar findings were described in a research that investigated bleeding in aspirin consumers [30]. Alcohol is considered to contribute to the development of cardiovascular diseases. Regular light alcohol drinking (< three drinks per day) may confer protective effects on heart failure associated with coronary heart disease. The protective effect disappears in heavy drinking (> three drinks per day) with an increases risks to develop cardiomyopathy, supraventricular arrhythmias, and systemic hypertension [31,32].

To the best of our knowledge this is the first study investigating histological and endoscopic upper digestive findings in a Romanian population with CHF. It's limitations are represented by the lack of regressions and adjustments based on confounding factors that will be approached in further studies. The present research questioning the impact of various demographical, clinical and histologic parameters on endoscopic lesions in patients with CHF may offer important clues for preventive strategy development in Romanian population, characterized by a high frequency of *H. pylori* infection and its consequences (ulcer, premalignant lesions, cancer).

Conclusions

Based on our findings, we can conclude that male patients and low-dose aspirin consumers with CHF, but not those with *H. pylori* infection seem to be more prone to develop upper digestive endoscopic lesions, while anticoagulants and alcohol consumption could be associated with severe endoscopic lesions in a congestive gastro-duodenal mucosa.

Authors' contribution

Adriana-Stela Cosma (Conceptualization; Data curation; Formal analysis; Writing –original draft)
Claudia Bănescu (Conceptualization; Data curation; Methodology; Supervision; Validation; Writing – review & editing)
Simona Mocan (Investigation; Validation)
Beáta Balla (Investigation; Writing – review & editing)
Anca Negovan (Conceptualization; Data curation; Investigation; Methodology; Supervision; Writing – review & editing)

Conflict of interest

None to declare.

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