ORIGINAL PAPER

DOI: http://dx.doi.org/10.15403/jgld-3795

# Different Prevalence of Alarm, Dyspeptic and Reflux Symptoms in Patients with Cardia and Non-cardia Gastric Cancer

**Caspar Franck[1], Nadja Zimmermann[1], Elisabetta Goni[2], Hans Lippert[3], Karsten Ridwelski[4], Martin Kruschewski[5], Nicole Kreuser[6], Philipp Lingohr[7], Claus Schildberg[8], Nikolaos Vassos[9], Oliver Waidmann[10], Ulrich Peitz[11], Hauke Lang[12], Peter P. Grmminger[12], Christiane Bruns[13], Lothar Veits[14], Michael Vieth[14], Markus Moehler[15], Florian Lordick[16], Ines Gockel[6], Johannes Schumacher[17], Peter Malfertheiner[1,2], Marino Venerito[1]**

See **Authors' affiliations** at the end of the paper.

## ABSTRACT

**Background & Aims**: Symptoms of patients with gastric cancer (GC) are often unspecific and differences in symptoms between patients with cardia and non-cardia GC have been poorly investigated. We aimed to characterize symptoms of patients with cardia and non-cardia GC.

**Methods**: Patients with cardia (Siewert type II and III) and non-cardia GC were recruited in the German multicenter cohort of the Gastric Cancer Research (staR) study between 2013 and 2017. Alarm, dyspeptic and reflux symptoms at the time of presentation were documented using a self-administered questionnaire.

**Results**: A completed self-administered questionnaire was available for 568/759 recruited patients (132 cardia GC, 436 non-cardia GC, male 61%, mean age 64 years). Dyspeptic symptoms were more common in patients with non-cardia GC (69.0 vs. 54.5%, p=0.0024). Cardia GC patients reported more frequently alarm symptoms (69.7 vs. 44.7%, p<0.0001), and were more likely to have Union for International Cancer Control (UICC) stage III-IV (54.1vs. 38.9%, p=0.0034). Especially, dysphagia and weight loss were more common in patients with cardia GC (49.2 vs. 6.4 %, p<0.0001 and 37.1 vs. 25.7%, p=0.02, respectively). No differences between the two groups were observed with respect to reflux symptoms. Patients with alarm symptoms were more likely to have UICC stage III-IV at presentation (69.4 vs. 42.9%, p<0.0001).

**Conclusions**: In clinical practice the symptom pattern at presentation may serve as a hint for tumor localization. Despite the fact that they are common in the general population, dyspeptic symptoms offer a chance for earlier GC detection. Thus, in patients with dyspeptic symptoms who fail empiric approaches, endoscopy should not be delayed.

***Address for correspondence:***
**Marino Venerito**, MD
Department of Gastroenterology, Hepatology and Infectious Diseases
Otto-von-Guericke University Hospital
Leipziger Straße 44
39120 Magdeburg, Germany

**Key words:** gastric cancer – cardia gastric cancer – non-cardia gastric cancer – stomach neoplasms – cardia – cohort study – weight loss – deglutition disorders.

**Abbreviations**: EGD: esophagogastroduodenoscopy; GC: gastric cancer; *H. pylori: Helicobacter pylori*; UICC: Union for International Cancer Control.

## INTRODUCTION

Gastric cancer (GC) is responsible for over 1,000,000 new cases and estimated 783,000 deaths in 2018, making it the fifth most frequently diagnosed cancer and the third leading cause of cancer death worldwide [1]. According to the localization, GC can be classified in non-cardia (arising in the stomach at or beneath the gastric fundus) and cardia GC. Cardia GC can be further classified according to Siewert in type II and type III, with the main tumor mass located at or beneath the Z-line, respectively. For the sake of completeness, Siewert type I cancers are mainly esophageal adenocarcinomas invading the Z-Line, typically arising on Barrett´s metaplasia. According to the most recent global cancer statistics, one fifth of all GC patients have cardia GC.

The incidence and mortality of GC shows a clear downward trend all over the world, including Germany [2, 3]. However, this is not true for the subgroup of cardia GC, for which the incidence has increased over the last decades in the western world [4]. There are marked etiological differences between cardia and non-cardia GC. Definite risk factors for cardia GC include obesity, nicotine consumption, reflux disease and a medium or higher socio-economic status [5-9]. In contrast, non-cardia GC is strongly associated with *Helicobacter pylori* (*H. pylori*) infection [10, 11]. High salt and nitrosamine intake, vitamin deficiency (A, C, E) disorders and high meat consumption are other risk factors for non-cardia GC [12-16].

Received: 30.05.2021
Accepted: 30.09.2021

Cardia and non-cardia GCs also differ in gender distribution, age of disease onset and histopathological characteristics. Indeed, male gender and older age are associated with cardia GC. Finally, patients with cardia GC are more likely to have an advanced tumor stage and a lower 5-year survival rate, with predominant intestinal histological type according to the Laurén classification [17, 18].

There are no specific early symptoms for GC. Patients with GC are often asymptomatic for a long period or report unspecific symptoms [19]. If any, then mostly dyspeptic symptoms are present in earlier stages of GC. Dyspeptic symptoms are highly prevalent in the general population and in general not suggestive of an underlying malignant disease. Indeed, the risk of gastroesophageal malignancy is estimated to be less than 1% in patients with dyspeptic symptoms [17, 18]. Nonetheless dyspeptic symptoms and especially if they are recurrent may lead to referral of the patient to endoscopic examination of the upper gastrointestinal tract with the coincidental detection of early-stage GC. Alarm symptoms usually occur when the disease is in a more advanced and most often, non curable stage [20]. However, alarm symptoms are not specific either to predict malignancy among patients with dyspeptic symptoms [21, 22]. According to recent international guidelines, alarm symptoms, but not "unspecific" dyspeptic complaints, warrant an endoscopic investigation [23, 24]. However, this clinical practice seems not appropriate for GC detection in a curable stage and leads often to both, unnecessary diagnostics and missed or delayed diagnosis of GC [25, 26].

In a retrospective multi center cohort study on 18,365 US American GC patients published in 1993, more than half of the patients presented with weight loss (alarm symptom) or abdominal pain (dyspeptic symptom). However, differences between symptoms or tumor stages at presentation of patients with cardia and non-cardia cancer were not described [27].

The aim of the present study is to characterize the symptoms at the time of diagnosis of patients with cardia and non-cardia GC in a German multicenter cohort study.

## METHODS

The Gastric Cancer Research (staR project) is a scientific initiative that aims to elucidate the genetic causes of GC in the European population. Some results of the program have already been published [28, 29]. Within the staR project, a cohort of 568 patients with diagnosis of GC treated in different German centers was recruited between April 2013 and May 2017. From each study, participant discharge letters and medical reports of esophagogastroduodenoscopy (EGD) and histology were obtained from the treatment centers. The study was approved by the Ethics Committee of the Otto-von-Guericke University Hospital of Magdeburg (number 170/12) and was in accordance with the Helsinki Declaration of 1975, as revised in 1983. All patients provided written informed consent. All study participants received a structured questionnaire, consisting of 142 items, providing information on demographics and medical abnormalities. The self-administered questionnaire was fully answered by 387 patients, whereas for the remaining 181 a complementary telephone interview was necessary. Finally, 568 answered questionnaires were available for analysis.

For the purpose of the present study, only items focusing on patient's medical history, symptoms, examinations leading to diagnosis, tumor localization, staging and histological type/grading of the carcinoma were evaluated. Patients were specifically asked about *H. pylori* infection and eradication therapy as well as gastrointestinal symptoms occurring within 12 months before GC diagnosis. Gastrointestinal symptoms included alarm symptoms (dysphagia, weight loss, bleeding signs, vomiting), dyspeptic symptoms (postprandial distress, epigastric pain) and reflux symptoms [30, 31]. In particular, bleeding signs were defined as hematemesis, melena, syncope or anemia. With respect to the dyspeptic symptoms, they were defined as follows: 1) postprandial distress: meal-related symptoms such as postprandial fullness and early satiation and 2) epigastric pain: meal-unrelated symptoms such as epigastric pain or burning. Reflux symptoms were defined as heartburn, retrosternal pain and/or sourish burping.

Symptoms at presentation, tumor localization, histological Laurén type and TNM classification were retrieved from the discharge letter. In the present study, type II and type III GCs according to the Siewert classification will be regarded as cardia GCs, whereas GCs sparing the Z-line will be regarded as non-cardia GCs [32]. Patients with at least one positive test among histology (from records), *H. pylori* serology (from records), a positive rapid urease test or an eradication therapy documented in the past (records, questionnaire or interview) were considered *H. pylori* positive. We classified patients with negative results in all tests as *H. pylori* negative.

Clinical data of patients with cardia- and non-cardia GC were compared by the Fisher´s exact test and odds ratios (OR). The corresponding 95% confidence intervals (CI) were generated. For all comparisons a statistical p-value $< 0.05$ (two-sided) was considered as significant. In order to further explore the association between alarm symptoms and GC location, a multivariate logistic regression analysis was performed using SPSS (IBM SPSS Statistics version 27 software). In this analysis, the OR for alarm symptoms, was adjusted according to tumor localization, tumor stage $\geq 3$, Union for International Cancer Control (UICC)-stage $\geq$ III and Laurén histological subtype.

## RESULTS

**Patients' Histopathological Features**

Baseline characteristics of the study population are shown in Table I. Overall, 61% of the recruited cohort were men. Mean patient age was 64 years. 34.5% of GC patients were younger than 60 years at diagnosis. Almost half of the detected tumors (51%) showed an intestinal tumor type according to the Laurén-classification. With respect to the histological grading, the vast majority of cases (93%) showed a moderate or poorly differentiation (G2 or G3, respectively). *Helicobacter pylori* status was available in 362/568 (63.7%) GC patients. Overall, 199/362 GC patients (55.0 %) had an active or past *H. pylori* gastritis. In particular, roughly one third had an active *H. pylori* infection (39.8 %), whereas 15.2% received previous eradication therapy. The majority of patients had non-cardia GC (76.8 %).

**Table I.** Baseline characteristics of gastric cancer patients

| Features* | N (%) |
|---|---|
| Gender (n=568 male) | 348 (61.3) |
| Age (years±SD) | 64 ± 11.5 |
| Histological type (Laurén) (n=488) | |
| intestinal | 251 (51.4) |
| diffuse | 192 (39.3) |
| mixed | 45 (9.2) |
| Tumor stage (n=506) | |
| T1-2 | 284 (56.1) |
| T3-4 | 222 (43.9) |
| Lymph node stage (n=474) | |
| N0 | 244 (51.5) |
| N+ | 230 (48.5) |
| Metastasis (n=300) | |
| M0 | 246 (82.0) |
| M1 | 54 (18.0) |
| Histological grading (n=517) | |
| G1 | 29 (5.6) |
| G2 | 168 (32.5) |
| G3 | 312 (60.3) |
| G4 | 8 (1.5) |
| *Helicobacter pylori* infection (n=362) | |
| *Helicobacter pylori* positive# | 199 (55.0) |
| - active infection | 144 (39.8) |
| - past infection | 55 (15.2) |
| *Helicobacter pylori* negative | 163 (45.0) |
| Localization (n =568) | |
| cardia | 132 (23.2) |
| non-cardia | 436 (76.8) |

*n varies among the features because some information could not be retrieved for all recruited patients; introduced SD: standard deviation; # patients with serological or histological evidence of *H. pylori*, positive rapid urease test or previous eradication therapy were regarded as *H. pylori* positive

**Clinical and Histopathological Features of Cardia and Non-cardia Gastric Cancer**

The distribution of clinical and histopathological features between cardia and non-cardia GC is shown in Table II. Cardia GC was more common in men than women (80.3 vs. 19.7%, p<0.0001). In the analysis according to age (< 60 vs. ≥ 60 years) no differences were observed between the two groups. Patients with non-cardia GC had more frequently an active or past *H. pylori* infection compared to patients with cardia GC (60.1 vs. 38.4%, p=0.0005). Patients with cardia GC were more likely to have a GC of intestinal type according to the Laurén-classification (71 vs. 45.9%, p<0.0001) and with a better differentiation grade (G1-2: 48.7 vs. 34.9%, G3-4: 51.3 vs. 65.1%, p=0.0072). Furthermore, cardia GCs were more likely to show advanced tumor stages (T3-4) than non-cardia GC (55.5 vs. 40.3%, p=0.0043) and a UICC stage III-IV at presentation (54.1 vs. 38.9%, p=0.0034).

**Symptom Distributions between Cardia and Non-cardia Gastric Cancer**

The prevalence of presenting symptoms according to the tumor localization is outlined in Table III. In the entire cohort, dyspeptic and alarm symptoms were present in 29.2% and 17.3% of the patients, respectively, whereas 36.4% reported to have both dyspeptic and alarm symptoms. 17.1% indicated neither dyspeptic nor alarm symptoms. In the subgroup younger than 60 years, 45.1 % of the patients presented with alarm symptoms.

Alarm symptoms were significantly more common in patients with cardia GC (69.7 vs. 44.7%, p<0.0001). In particular, patients with cardia GC were more likely to present

**Table II.** Distribution of clinical and histopathological features in patients with cardia and non-cardia gastric cancer*

| Features | Cardia N (%) | Non-Cardia N (%) | p | OR (95%CI) |
|---|---|---|---|---|
| Gender (n=568) (%) | n=132 | n=436 | | |
| Male | 106 (80.3) | 242 (55.5) | < 0.0001 | 3.27 (2.05-5.22) |
| Female | 26 (19.7) | 194 (44.5) | | |
| Age (n=562) (%) | n=128 | n=434 | | |
| < 60 y | 35 (27.3) | 160 (36.9) | 0.06 | 0.64 (0.42-1.0) |
| ≥ 60 y | 93 (72.7) | 274 (63.1) | | |
| *H. pylori* status (n=362) (%) | n=86 | n=276 | | |
| positive # | 33 (38.4) | 166 (60.1) | 0.0005 | 0.41 (0.25-0.68) |
| negative | 53 (61.6) | 110 (39.9) | | |
| *Laurén* - type (n = 488) (%) | n=107 | n=381 | | |
| intestinal | 76 (71.0) | 175 (45.9) | < 0.0001 | 2.89 (1.81- 4.59) |
| diffuse or mixed | 31 (29.0) | 206 (54.1) | | |
| Grading (n=517) (%) | n=119 | n=398 | | |
| G1-G2 | 58 (48.7) | 139 (34.9) | 0.0072 | 1.77 (1.17-2.68) |
| G3-G4 | 61 (51.3) | 259 (65.1) | | |
| Metastasis (n=488) (%) | n=113 | n=375 | | |
| M0 | 86 (76.1) | 306 (81.6) | 0.22 | 0.72 (0.43-1.19) |
| M1 | 27 (23.9) | 69 (18.4) | | |
| Tumor stage (n=508) (%) | n=119 | n=387 | | |
| T1-2 | 53 (44.5) | 231 (59.7) | 0.0043 | 0.54 (0.36-0.82) |
| T3-4 | 66 (55.5) | 156 (40.3) | | |
| UICC stage (n=515) (%) | n=122 | n=393 | | |
| I-II | 56 (45.9) | 240 (61.1) | 0.0034 | 0.54 (0.36-0.81) |
| III-IV | 66 (54.1) | 153 (38.9) | | |

*n varies among the features, because some information could not be retrieved for all recruited patients; # serological or histological evidence of *H. pylori,* positive rapid urease test or medical history of previous eradication therapy were counted as positive *H. pylori* status; OR: odds ratio; CI: confidence interval; UICC: Union for International Cancer Control.

**Table III.** Symptom prevalence in patients with cardia and non-cardia gastric cancer

| | Cardia N (%) | Non-Cardia N (%) | OR (95%CI) | p |
|---|---|---|---|---|
| Alarm symptoms: | 92 (69.7) | 195 (44.7) | **2.84 (1.87-4.31)** | **< 0.0001** |
| - Dysphagia | 65 (49.2) | 28 (6.4) | **14.14 (8.46-23.61)** | **< 0.0001** |
| - Weight loss | 49 (37.1) | 112 (25.7) | **1.71 (1.13-2.58)** | **0.02** |
| - Bleeding signs* | 26 (19.7) | 83 (19.0) | 1.04 (0.64-1.70) | 0.90 |
| - Vomiting | 18 (13.6) | 65 (14.9) | 0.90 (0.51-1.58) | 0.78 |
| Dyspeptic symptoms: | 72 (54.5) | 301 (69.0) | **0.54 (0.36- 0.80)** | **0.0024** |
| - Postprandial distress# | 44 (33.3) | 207 (47.5) | **0.55 (0.37-0.83)** | **0.01** |
| - Epigastric pain[a] | 51 (38.6) | 234 (53.7) | **0.54 (0.37-0.81)** | **0.0028** |
| Reflux-symptoms[b] | 28 (21.2) | 77 (17.7) | 1.26 (0.77-2.04) | 0.37 |

* Hematemesis: melena, syncope, anemia; # nausea: bloating, abdominal fullness, postprandial epigastric pain; [a]: upper abdominal pain, sober pain; [b]: heartburn, retrosternal pain, sourish burping; OR: odds ratio; CI: confidence interval.

with dysphagia and weight loss (49.2 vs. 6.4%, p<0.0001 and 37.1 vs. 25.7%, p=0.02, respectively). Dyspeptic symptoms were more prevalent in non-cardia GC patients (69 vs. 54.5%, p=0.0024). In detail, patients with non-cardia GC were more likely to complain about postprandial distress compared to patients with cardia cancer (47.5 vs. 33.3%, p=0.01). Similarly, epigastric pain was reported more often from patients with non-cardia GC (53.7 vs. 38.6%, p=0.0028).

In total, 18.5% of the participants reported reflux symptoms. Interestingly, the prevalence of reflux symptoms did not differ between the two groups (non-cardia GC 17.7 % vs. cardia GC 21.2 %, p=0.37).

**Clinical Aspects According to Tumor Size and Stage**

The prevalence of symptoms according to primary tumor location and UICC tumor stage is shown in Table IV, whereas the association of primary tumor size and UICC stage with symptoms is presented in Table V. Alarm symptoms were more common in patients with higher tumor stages (T3-4) (68.8 vs. 44.0%, p<0.0001). Similarly, patients with alarm symptoms were more likely to have UICC stage III-IV at presentation compared to UICC stage I-II (69.4 vs. 42.9%, p<0.0001). On the contrary, neither dyspeptic nor reflux symptoms were associated with tumor size or UICC stage.

In the multivariate logistic regression analysis (Table VI), patients with cardia GC (adjusted OR=2.78, 95%CI: 1.64-4.72, p<0.0001) and those with UICC stage ≥ 3 (adjusted OR=2.24, 95%CI: 1.36-3.70, p=0.002) were more likely to present with alarm symptoms, whereas no independent association between alarm symptoms and T stage ≥ 3 or diffuse or mixed histological type was observed.

## DISCUSSION

To the best of our knowledge, this is the first report comparing the presenting symptoms of patients with cardia and non-cardia GC. In our study dyspeptic symptoms were significantly more common in patients with non-cardia GC, while alarm symptoms occurred more frequently in patients with cardia GC. As expected, and pathophysiologically comprehensible, dysphagia was relatively specific for cardia GC, allowing in clinical practice an obvious hint for tumor localization. Due to the strong peristaltic and big extensibility of the distal esophagus, cardia tumors are often asymptomatic and do not cause dysphagia until they reach large diameters with substantial lumen occlusion. This fits our observation that patients with cardia GC were more likely to have an advanced tumor stage at time of diagnosis. Vice versa, the advanced cancer stage at the time of diagnosis may explain the higher frequency of alarm symptoms in patients with cardia GC.

Other investigated complaints (i.e. weight loss, postprandial distress and epigastric pain), though occurring with statistically

**Table IV.** Prevalence of symptoms according to primary tumor location and UICC tumor stage

| | Cardia | | | | Non-Cardia | | | |
|---|---|---|---|---|---|---|---|---|
| UICC stage (n) | I (29) | II (27) | III (50) | IV (16) | I (155) | II (85) | III (117) | IV (36) |
| Alarm symptoms (%) | 48.3 | 74.1 | 84.0 | 75.0 | 37.4 | 41.2 | 64.1 | 63.9 |
| - Dysphagia | 34.5 | 48.1 | 58.0 | 56.3 | 5.8 | 7.1 | 6.0 | 8.3 |
| - Weight loss | 20.7 | 40.7 | 40.0 | 56.3 | 15.5 | 21.2 | 39.3 | 47.2 |
| - Bleeding signs | 17.2 | 22.2 | 26.0 | 6.3 | 12.9 | 18.8 | 28.2 | 19.4 |
| - Vomiting | 17.2 | 7.4 | 12.0 | 31.3 | 11.6 | 15.3 | 17.1 | 22.2 |
| Dyspeptic symptoms (%) | 58.6 | 55.6 | 52.0 | 68.8 | 65.8 | 82.4 | 67.5 | 75.0 |
| - Postprandial distress | 34.5 | 25.9 | 34.0 | 50.0 | 45.2 | 56.5 | 44.4 | 58.3 |
| - Epigastric pain | 44.8 | 33.3 | 44.0 | 31.3 | 54.2 | 62.4 | 50.4 | 55.6 |
| Reflux-symptoms (%) | 27.6 | 22.2 | 18.0 | 18.8 | 21.9 | 18.8 | 13.7 | 16.7 |

UICC: Union for International Cancer Control

**Table V.** Association between primary tumor extent and UICC tumor stage according to symptoms

| Feature, N (%) | **T3-4 n=215** | **T1-2 n=293** | **OR (95%CI)** | **p** |
|---|---|---|---|---|
| Dyspeptic symptoms | 151 (68.0) | 187 (65.8) | 1.10 (0.76- 1.60) | 0.64 |
| Reflux symptoms | 38 (17.1) | 60 (21.1) | 0.77 (0.49-1.21) | 0.31 |
| Alarm symptoms* | 148 (68.8) | 125 (44.0) | **2.54 (1.77-3.66)** | **< 0.0001** |
| | **UICC III-IV n = 219** | **UICC I-II n = 296** | **OR (95%CI)** | **p** |
| Dyspeptic symptoms | 143 (65.3) | 204 (68.9) | 0.85 (0.59-1.23) | 0.39 |
| Reflux symptoms | 34 (15.5) | 64 (21.6) | 0.67 (0.42-1.05) | 0.09 |
| Alarm symptoms* | 152 (69.4) | 127 (42.9) | **3.02 (2.09-4.36)** | **< 0.0001** |

* Dysphagia, weight loss, bleeding signs, vomiting. For the rest of abbreviations see Table II.

different prevalence between the two groups, do not allow a clear distinction between the entities.

Despite the low sensitivity of alarm symptoms in identifying patients with GC, in clinical practice they are still broadly applied for the selection of candidates for endoscopy, because more valid criteria are missing. This strategy is not in keeping with the current recommendations of the American College of Gastroenterology (ACG) and Canadian Association of Gastroenterology (CAG), which suggest for dyspeptic patients aged < 60 years, "test-and-treat" for *H. pylori* infection and empiric PPI treatment as first approach, even in the presence of alarm features, whereas endoscopy is not generally recommended [33]. However, this strategy would have delayed the diagnosis of many of the GC patients recruited in our study. Indeed, in our cohort, 34.5% of GC patients were younger than 60 years at the time of diagnosis and 45.1% of them presented with alarm symptoms. Recently, a registry-based study with data on GC incidence by year of diagnosis, gender, and age from 92 cancer registries in 34 countries, have shown alarming incidence increases in younger age groups (below 50 years of age) in both low-incidence and high-incidence populations [34, 35]. Based on our data and the current epidemiological facts, alarm symptoms should not be underestimated irrespective of the age of the patient, nor should endoscopy be neglected.

Dyspeptic symptoms were highly prevalent in our study cohort irrespective of the tumor location. Indeed, roughly 30% of our entire study cohort presented with dyspeptic but no alarm symptoms. Because of their widespread incidence in the population, dyspeptic symptoms are unspecific for early GC detection. According to our observation, dyspeptic symptoms should not be underestimated, and in cases with no improvement to empiric approaches, endoscopy should not be delayed, even in younger patients.

There are no studies with which our results can be directly compared. In a multicentric Norwegian study 855 GC patients from 1982 to 1984 were examined with regard to unintentional weight loss and its consequences for surgical care [36]. Two groups were compared with each other: 1) altogether esophagus, cardia and antrum cancer with 2) any other site. Similar to our investigation, loss of weight was more common in patients in the first group than in other localizations. Also, in line with our study weight loss was observed more often in patients with advanced tumor stages. However, it should be noted that our distinction between cardia and non-cardia GC is not entirely comparable to the Norwegian investigation. Furthermore, in contrast to our study, symptoms other than weight loss were not explored.

Likewise, in an American registry-based study from 1993 with 18,365 GC patients using a questionnaire data, weight loss, abdominal pain and nausea were the most common complaints at presentation [27]. However, in contrast to our study, no detailed systematic analysis of the symptoms and especially no classification regarding the primary tumor site were performed.

Recently, the VAGAS score for the prediction of overall survival of metastatic gastro-esophageal cancer patients (including also esophageal squamous cell carcinoma) has been proposed [37]. The score is largely based on alarm symptoms: stenosis diagnosed by endoscopy and weight loss were significantly associated with a shorter survival, while dyspepsia, ulcer or active bleeding and Her2 positivity were positive prognostic markers. However, in this analysis, no differentiation between cardia and non-cardia GC was performed, though the poor prognostic factor "stenosis in endoscopy" may be rarely found in GC of the corpus or antrum. This finding is in keeping with our data, confirming our observation that a large proportion of patients with cardia cancer present when the disease is already in an advanced stage.

In line with previous studies, *H. pylori* infection was more prevalent in patients with non-cardia GC compared with patients with cardia GC [38]. *Helicobacter pylori* prevalence in our cohort (55% in the overall cohort and 60% in the non-cardia GC cohort) was lower than expected. However, histological assessment of *H. pylori* after surgical resection and/or in patients with advanced atrophic changes of the gastric mucosa is more likely to be negative, whereas *H. pylori* serology was only available for a small number of our patients.

Another potential limitation of our study is the retrospective, self-reported and therefore subjective assessment of patients´ symptoms. Further, the presence of a hiatal hernia, which might influence dyspeptic symptoms, was not prospectively recorded. Finally, our study lacks a control group of patients without cancer undergoing EGD, which would have supplemented our results.

## CONCLUSIONS

Our study showed the differences between the presenting symptoms of patients with cardia and non-cardia GC,

**Table VI** Prevalence of alarm symptoms according to tumor characteristics

| Feature, N (%) | Alarm symptoms | OR (95 % CI) | p-Value * | adjusted OR (95% CI) | p-Value# |
|---|---|---|---|---|---|
| Cardia cancer | 92 (69.7) | 2.84 (1.87-4.31) | <0.0001 | 2.78 (1.64-4.72) | <0.0001 |
| UICC stage ≥ III | 152 (69.4) | 3.02 (2.09-4.36) | <0.0001 | 2.24 (1.36-3.70) | 0.002 |
| T stage ≥ 3 | 148 (68.8) | 2.54 (1.77-3.66) | <0.0001 | 1.37 (0.83-2.25) | 0.22 |
| Diffuse or mixed type ~ | 127 (53.4) | 0.96 (0.67-1.37) | 0.86 | 1.15 (0.76-1.73) | 0.51 |

*Fisher test; #multivariate logistic regression; ~histological type according to the Laurén classification.

whereby all investigated complaints may be present in both groups and are relevantly overlapping. Solely, dysphagia was relatively specific for cardia GC. Thus, in clinical practice the symptom pattern at presentation may serve as a hint for tumor localization. Though common in the general population, dyspeptic symptoms offer a chance for earlier detection of non-cardia GC. Given the new epidemiologic facts, both alarm and dyspeptic symptoms should not be underestimated, nor should be endoscopy neglected in young patients. The identification of cost-effective methods for early GC diagnosis also in middle- and low-risk regions is an urgent need.

**Conflicts of interest:** O.W. received honoraria from Bayer, BMS, Celgene, Ipsen, Novartis, Roche and Shire; he is a member of the Advisory boards of Amgen, Bayer, BMS, Celgene, Eisai, Falk, Merck, Novartis, Roche, Servier and Shire, and received support for conducting clinical trials from Medac, Novartis and MSD. P.G. is proctor for Intuitive Surgical. M.Vieth received honoraria by FALK, Malesci, Olympus, Shire. F.L. received personal fees from Amgen, Astellas, Astra Zeneca, Biontech, Eli Lilly, Elsevier, Infomedica, Merck, MSD, Roche, Servier, grants, personal fees and non-financial support from BMS. P.M. is involved in speakers' bureau or consulting: Biocodex, Biohit, Danone, Mayoly-Spindler. M.Venerito received honoraria from Nordic Pharma, Merck Serono, Bayer Vital, Lilly and Sirtex, and is a member of the advisory boards of Ipsen, Lilly, Nordic Pharma, BMS, MSD, Eisai and Amgen. C.F., N.Z., E.G., H.L., K.R., M.K., N.K., P.L., C.S., N.V., U.P., H.L., C.B., L.V., M.M., I.G. and J.S. declare that they have no conflict of interest.

**Authors' affiliation:** 1) Dept. of Gastroenterology, Hepatology and Infectious Diseases, Otto-von-Guericke University Hospital, Magdeburg; 2) Dept. of Internal Medicine II, Ludwig Maximilians University Hospital, Munich; 3) Dept of General, Visceral, Vascular and Transplantation Surgery, Otto-von-Guericke University Hospital, Magdeburg; 4) Dept. of Surgery, Municipal Hospital, Magdeburg; 5) Dept. for General, Visceral und Thoracic surgery, Frankfurt (Oder) Municipal Hospital, Frankfurt (Oder); 6) Dept. of Visceral, Transplant, Thoracic and Vascular Surgery, University Hospital of Leipzig, Leipzig: 7) Dept of General, Visceral, Thoracic and Vascular Surgery, University Hospital Bonn, Bonn; 8) Dept. of General Surgery, University Hospital Brandenburg, Brandenburg Medical School Theodor Fontane, Brandenburg; 9) Division of Surgical Oncology and Thoracic Surgery, Department of Surgery, Mannheim University Medical Center, University Heidelberg, Mannheim; 10) Dept. of Gastroenterology and Hepatology, University Hospital of Frankfurt a. Main, Frankfurt; 11) Dept. of Gastroenterology, Raphaelsklinik Muenster, Muenster; 12) Dept. of Surgery, University Medical Center of the Johannes Gutenberg-University, Mainz; 13) Dept. of General, Visceral, Tumor and Transplantation Surgery, University Hospital Cologne, Cologne; 14) Institute of Pathology, University of Erlangen-Nuremberg, Klinikum Bayreuth, Bayreuth; 15) First Medical Clinic and Policlinic, University Medical Center of Johannes Gutenberg-University Mainz, Mainz; 16) Dept. of Oncology, Gastroenterology, Hepatology, Pulmonology, and Infectious Diseases, University Cancer Center Leipzig (UCCL), Leipzig University Medical Center, Leipzig; 17) Center for Human Genetics, Philipps University Marburg, Marburg, Germany

**Authors' contributions:** M.Venerito designed the research study. All authors were involved in the data acquisition. C.F., N.Z. and M.Venerito analyzed the data. C.F. and M.Venerito drafted the manuscript. All authors critically revised the manuscript, approved the final version to be published, and agree to be accountable for all aspects of the work.

**Acknowledgements**: This study was supported by the German Research Foundation (DFG) (SCHU 1596/6-1, KN 378/3-1, LO 1147/1-1 and VE 917/1-1).

## REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394–424. doi:10.3322/caac.21492
2. Barnes B, Kraywinkel K, Nowossadeck E, et al. Robert Koch Institut - Bericht zum Krebsgeschehen in Deutschland 2016. Robert Koch Institute 2016. [Cited 2021 Jan 27]. doi:10.17886/rkipubl-2016-014
3. Ang TL, Fock KM. Clinical epidemiology of gastric cancer. Singapore Med J 2014;55:621-628. doi:10.11622/smedj.2014174
4. Crew KD, Neugut AI. Epidemiology of gastric cancer. World J Gastroenterol 2006;12:354–362. doi:10.3748/wjg.v12.i3.354
5. Du X, Hidayat K, Shi BM. Abdominal obesity and gastroesophageal cancer risk: Systematic review and meta-analysis of prospective studies. Biosci Rep 2017;37:BSR20160474. doi:10.1042/BSR20160474
6. O'Doherty MG, Freedman ND, Hollenbeck AR, Schatzkin A, Abnet CC. A prospective cohort study of obesity and risk of oesophageal and gastric adenocarcinoma in the NIH-AARP diet and health study. Gut 2012;61:1261–1268. doi:10.1136/gutjnl-2011-300551
7. Zaridze D, Borisova E, Maximovitch D, Chkhikvadze V. Alcohol consumption, smoking and risk of gastric cancer: Case-control study from Moscow, Russia. Cancer Causes Control 2000;11:363–371. doi:10.1023/a:1008907924938
8. Gammon MD, Schoenberg JB, Ahsan H, et al. Tobacco, alcohol, and socioeconomic status and adenocarcinomas of the esophagus and gastric cardia. J Natl Cancer Inst 1997;89:1277–1284. doi:10.1093/jnci/89.17.1277
9. Derakhshan MH, Malekzadeh R, Watabe H, et al. Combination of gastric atrophy, reflux symptoms and histological subtype indicates

two distinct aetiologies of gastric cardia cancer. Gut 2008;57:298–305. doi:10.1136/gut.2007.137364
10. An international association between Helicobacter pylori infection and gastric cancer. The EUROGAST Study Group. Lancet 1993;341:1359–1362. doi:10.1016/0140-6736(93)90938-D
11. Talley NJ, Zinsmeister AR, Weaver A, et al. Gastric adenocarcinoma and Helicobacter pylori infection. J Natl Cancer Inst 1991;83:1734–1739. doi:10.1093/jnci/83.23.1734
12. Wang XQ, Terry PD, Yan H. Review of salt consumption and stomach cancer risk: Epidemiological and biological evidence. World J Gastroenterol 2009;15:2204–2213. doi:10.3748/wjg.15.2204
13. D'Elia L, Rossi G, Ippolito R, Cappuccio FP, Strazzullo P. Habitual salt intake and risk of gastric cancer: A meta-analysis of prospective studies. Clin Nutr 2012;31:489–498. doi:10.1016/j.clnu.2012.01.003
14. Joossens JV, Hill MJ, Elliott P, et al. Dietary salt, nitrate and stomach cancer mortality in 24 countries. Int J Epidemiol 1996;25:494–504. doi:10.1093/ije/25.3.494
15. Buiatti E, Palli D, Decarli A, et al. A case-control study of gastric cancer and diet in Italy: II. Association with nutrients. Int J Cancer 1990;45:896–901. doi:10.1002/ijc.2910450520
16. González CA, Jakszyn P, Pera G, et al. Meat intake and risk of stomach and esophageal adenocarcinoma within the European Prospective Investigation Into Cancer and Nutrition (EPIC). J Natl Cancer Inst 2006;98:345–354. doi:10.1093/jnci/djj071
17. Vakil N, Moayyedi P, Fennerty MB, Talley NJ. Limited value of alarm features in the diagnosis of upper gastrointestinal malignancy: systematic review and meta-analysis. Gastroenterology 2006;131:390–401. doi:10.1053/j.gastro.2006.04.029
18. Oustamanolakis P, Tack J. Dyspepsia: Organic versus functional. J Clin Gastroenterol 2012;46:175–190. doi:10.1097/MCG.0b013e318241b335
19. Schmidt N, Peitz U, Lippert H, Malfertheiner P. Missing gastric cancer in dyspepsia. Aliment Pharmacol Ther 2005;21:813–820. doi:10.1111/j.1365-2036.2005.02425.x
20. Bowrey DJ, Griffin SM, Wayman J, Karat D, Hayes N, Raimes SA. Use of alarm symptoms to select dyspeptics for endoscopy causes patients with curable esophagogastric cancer to be overlooked. Surg Endosc 2006;20:1725–1728. doi:10.1007/s00464-005-0679-3
21. Meineche-Schmidt V, Jørgensen T. "Alarm symptoms" in patients with dyspepsia: A three-year prospective study from general practice. Scand J Gastroenterol 2002;37:999–1007. doi:10.1080/003655202320378167
22. Wallace MB, Durkalski VL, Vaughan J, et al. Age and alarm symptoms do not predict endoscopic findings among patients with dyspepsia: A multicentre database study. Gut 2001;49:29–34. doi:10.1136/gut.49.1.29
23. Maconi G, Manes G, Porro GB. Role of symptoms in diagnosis and outcome of gastric cancer. World J Gastroenterol 2008;14:1149–1155. doi:10.3748/wjg.14.1149
24. Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF):S3-Leitlinie Magenkarzinom, Langversion 2.01 (Konsultationsfassung). 2019.
25. Lee SW, Chang CS, Yeh HJ, Lien HC, Lee TY, Peng YC. The Diagnostic Value of Alarm Features for Identifying Types and Stages of Upper Gastrointestinal Malignancies. Gastroenterol Res 2017;10:120–125. doi:10.14740/gr826w
26. Maconi G, Kurihara H, Panizzo V, et al. Gastric cancer in young patients with no alarm symptoms: focus on delay in diagnosis, stage of neoplasm and survival. Scand J Gastroenterol 2003;38:1249–1255. doi:10.1080/00365520310006360
27. Wanebo HJ, Kennedy BJ, Chmiel J, Steele G Jr, Winchester D, Osteen R. Cancer of the stomach: A Patient Care Study by the American College of Surgeons. Ann Surg 1993;218:583–592. doi:10.1097/00000658-199321850-00002
28. Heinrichs SKM, Hess T, Becker J, et al. Evidence for PTGER4, PSCA, and MBOAT7 as risk genes for gastric cancer on the genome and transcriptome level. Cancer Med 2018;7:5057–5065. doi:10.1002/cam4.1719
29. Weise F, Vieth M, Reinhold D, et al. Gastric cancer in autoimmune gastritis: A case-control study from the German centers of the staR project on gastric cancer research. United European Gastroenterol J 2020;8:175–184. doi:10.1177/2050640619891580
30. Madsen LG, Bytzer P. The value of alarm features in identifying organic causes of dyspepsia. Can J Gastroenterol 2000;14:713-720. doi:10.1155/2000/783950
31. Agréus L. Natural history of dyspepsia. Gut. 2002;50 Suppl 4:iv2–iv9. doi:10.1136/gut.50.suppl_4.iv2
32. Siewert JR, Stein HJ. Classification of adenocarcinoma of theoesophagogastric junction. Br J Surg 1998;85:1457–1459. doi:10.1046/j.1365-2168.1998.00940.x
33. Moayyedi PM, Lacy BE, Andrews CN, Enns RA, Howden CW, Vakil N. ACG and CAG Clinical Guideline: Management of Dyspepsia. Am J Gastroenterol 2017;112:988–1013. doi:10.1038/ajg.2017.154
34. Arnold M, Park JY, Camargo MC, Lunet N, Forman D, Soerjomataram I. Is gastric cancer becoming a rare disease? A global assessment of predicted incidence trends to 2035. Gut 2020;69:823–829. doi:10.1136/gutjnl-2019-320234
35. Venerito M, Ford AC, Rokkas T, Malfertheiner P. Review: Prevention and management of gastric cancer. Helicobacter 2020;25 Suppl 1:e12740. doi:10.1111/hel.12740
36. Haugstvedt TK, Viste A, Eide GE, Søreide O. Factors related to and consequences of weight loss in patients with stomach cancer. The norwegian multicenter experience. Norwegian Stomach Cancer Trial. Cancer 1991;67:722–729. doi:10.1002/1097-0142(19910201)67:3<722::aid-cncr2820670332>3.0.co;2-r
37. Puhr HC, Pablik E, Berghoff AS, et al. Viennese risk prediction score for Advanced Gastroesophageal carcinoma based on Alarm Symptoms (VAGAS score): characterisation of alarm symptoms in advanced gastro-oesophageal cancer and its correlation with outcome. ESMO Open 2020;5:e000623. doi:10.1136/esmoopen-2019-000623
38. Cavaleiro-Pinto M, Peleteiro B, Lunet N, Barros H. Helicobacter pylori infection and gastric cardia cancer: Systematic review and meta-analysis. Cancer Causes Control 2011;22:375–387. doi:10.1007/s10552-010-9707-2