Title: Severity of GERD and Disease Progression

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Abstract:

Background: Many factors may play a role in the severity and progression of Gastroesophageal Reflux Disease (GERD), since pathophysiology is multifactorial. Data regarding progression of GERD are controversial: some reports of increasing esophageal acid exposure (EAE) and mucosal damage were considered as evidence for a stable disease course, while others interprete these findings as disease progression.

The aim of this study is to analyze a large patient-population with persisting symptoms indicative of GERD under Protonpumpinhibitor(PPI)-therapy and identify components characterizing disease severity and progression.

Methods: Patients with symptoms indicative of GERD were included in the study in a tertiary referral center (Frankfurt,Germany). All selected patients were under long-term PPI-therapy with persistant symptoms. All patients underwent investigations to collect data on their physical status, EAE, severity of esophagitis, anatomical changes and esophageal functional defects as well their relation to duration of the disease. Incidence over time was plotted as survival curves and tested with Log-rank tests for the four main disease markers. Multivariate modelling with COX-regression model was used to estimate the general impact of the four main disease markers on the time course of the disease. In order to elucidate possible causal relationships over time, a path analysis (structural equation model) was calculated.

Results: From the database with 1480 data sets, 972 patients were evaluated (542males,430females). Mean age was 50,5 years(range18-89). Mean BMI was 27,2(19-48). The mean time between onset of symptoms and the diagnostic investigations was 8,2 years(1-50). A longer disease history for GERD was significantly associated with a higher risk for LES-incompetence.The mean duration from symptom onset to the time of clinical investigation was 9 years for patients with LES-incompetence (n=563), compared to a mean of 6 years for those with

mechanically intact LES (n=95). A longer period from symptom onset to diagnostics was significantly associated with higher acid exposure. The pathway analysis was significant for the following model:„history“ (p<0,001→LES-incompetence&Hiatal Hernia→(p<0,001)→pH-score“ (p<0,001).

Conclusion: LES-incompetence, the functional deterioration of the LES and the anatomical alteration at the EGJ (Hiatal Hernia) as well as an increased esophageal acid exposure were associated a longer history of suffering from GERD. Path modeling suggests a causal sequence over time of the main disease-parameters, tentatively allowing for a prediction of the course of the disease.

Keywords: GERD, pathophysiology of GERD, esophageal acid exposure, lower esophageal sphincter incompetence, structured equation modeling

Introduction:

Gastroesophageal Reflux Disease (GERD) is determined by excessive esophageal acid exposure caused by several pathophysiologic components (1,2,3), includinglower esophageal sphincter (LES) incompetence, frequency of transient LES relaxations (TLESRs), development of hiatal hernia (HH), impaired esophageal motility (IEM), associated gastric motility problems with duodeno-gastro-esophageal reflux (DGER) or delayed gastric emptying (DGE), and obesity (1-9). All these factors likely contribute to increased esophageal acid exposure (EAE) and symptoms as well as mucosal damage in some patients. Mucosal damage may be visible endoscopically as esophagitis or for some time only be microscopically detectable (1,2,3). Damage to the esophageal mucosa may cause further transmural damage, which can progress into mucosal injury leading to carditis and intestinal metaplasia, Barrett`s esophagus, and even dysplasia/cancer. Additionally, it may damage the underlying esophageal muscle and cause further insufficient esophageal motility and deterioration of the LES (1,2,3,10,11). This process may accelerate further

deterioration of the condition and GERD may develop to a more serious illness (1,2,3).

Nontheless, progression of GERD analysing mucosal damage and/or functional LES-deterioration is discussed controversially to date as some data suggest a stable course of the disease indicating that patients seemed to stay in a certain category of severity over time (12,13). On the other hand, there is also scientific evidence that a subgroup of GERD patients are not stable with regard to disease progression and functional deterioration was documented (3,14,15). Thus, the available data are to date inconclusive(12-17). So far, only potential the progression of GERD to Barrett`s epithelium and further towards intraepithelial neoplasm has been commonly accepted (1,2,3,10,11).
As these are already rather serious deteriorations of the patient`s condition, it is clinically desirable to identify markers for the progression of GERD, such as e.g. the functional deterioration of the esophago-gastric junction (EGJ) as early as possible in the disease course. Therefore, the objective of this analysis was the identification of relevant factors indicating severity and potential for progression of GERD.

Ideally, this research question would be best be investigated in a long-term study with repeated measurement points. However, patients with severe GERD are usually evaluated in clinical practice, followed by a therapeutic decision. This is especially true for advanced cases. A longitudinal observational design would require to leave patients in the need for treatment, untreated or not adequately treated for a longer time period. This is a dilemma and such a design would be unethical.

Nontheless, we, the authors believe that there is a need to follow up on this question, whether it is possible to identify disease markers that are able to describe disease progression, even though estimating the time course might be a challenge. Therefore, a prospective maintained database documenting all patients with symptoms indicative of GERD was used to approach this question by analysing the functional parameters in relation to the time course of these patients with the disease.

Thus, the aim of this study was to identify functional components indicative of the severity of the disease and relate these findings to the duration of symptoms in a large patient-population with persisting GERD-symptoms.

Methods:

The study-design is a single-center retrolective cohort-study in an academic setting, a tertiary referral center for esophageal and gastric functional disease in Frankfurt, Germany. A prospective database for all patients with symptoms indicative of GERD was maintained between 2004 and 2017. Each patient underwent history and physical examination, endoscopy, and investigations in a GastrointestinaI-function laboratory. The study was approved by the hospital institutional review board. All patients gave informed consent for study evaluation and diagnostic work-up, and investigations followed a defined study protocol. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions.

All included patients were under long-term Protonpumpinhitor-(PPI)-therapy with persistent or recurrent symptoms and were referred for complete or partial failure of PPI-therapy. The patients had symptoms indicative of GERD such as heartburn, regurgitation, epigastric burning/pain, belching, and retrosternal pain. Each patient underwent a thorough interview establishing the history of the time course of the disease. Patients with previous anti-reflux operations, other interventional therapies, and other esophageal disorders (i.e. achalasia, dysmotility) were excluded from this analysis.
Progression in GERD with increasing severity can be defined as increasing occurrence of complications over time such as esophagitis, both occurrence and worsening, persistent PPI-drug-dependancy, deteriorating functional status and anatomical changes (increasing size of hiatal Hernia (HH)). Therefore, all patients

underwent assessment of Body Mass Index(BMI) and upper-gastrointestinal-endoscopy. Initially, lesions detected in the esophagus were classified according to Savary and Miller, later this was revised to the Los Angeles classification (1). The increasing severity of esophagitis was scored for further calculation and correlations from 1-5 correspondingly (Savary1=1; Savary2=2; Savary3=3; Savary4=4 without Barrett; or later:LAgradeA=1;LAgradeB=2;LAgradeC=3;LAgradeD=4; Barrett esophagus/ intestinal metalasia=5), reflecting the increasing severity of GERD.
Hiatal hernia size was measured by vertical length, from the beginning of the gastric folds representing the cardia to the waist of the crura during inspiration as detected during endoscopy. Care was taken to measure the vertical length of the hiatal hernia in the beginning of the endoscopy, thus preventing excessive air insufflation into the stomach prior to the assessment to avoid incorrect vertical length measurements.

All patients underwent functional evaluation using standard equipment and validated assessment methods (1,3,5,18). Until 2010, esophageal manometry was based on perfusion technique to determine LES-incompetence (short overall length, short intraabdominal length, weak pressure (3,5)) thereafter High-Resolution-Manometry was used.

The presence of pathologic gastroesophageal reflux causing pathologic EAE (DeMeester pH-Score > 14,7 pathologic) was evaluated by 24h-pH-monitoring with all medications affecting motility and acid suppression stopped 7 days prior to the examination. After 2010 Impedance-pH-monitoring was used.

Statistical analysis:

The aim of this analysis was to identify variables characterizing the severity of the disease and to possibly predict disease progression out of a cross-sectional data set. The disease severity markers used in this analysis were LES-incompetence, pH-score, esophagitis, and Hiatal hernia. Even though the patients were only measured at one point in time, all patients were asked about the onset of symptoms prior to the

time of investigation. Thus information about disease duration, even though self reported, was available. This time-variable is called „history“ throughout the analysis.

The information about the time interval between onset of symptoms and clinical investigation allows for the construction of survival distributions for the four disease severety markers LES-incompetence, pH-score, esophagitis, and Hiatal Hernia (19). Survival distributions were calculated and displayed in graphs showing the „history“ in years on the x-axes and cumulative incidences for LES-incompetence (yes versus no), pH-score (DeMeester-score as marker of esophageal acid exposure: <35;35-69;70-104;105-140;>140), Hiatal Hernia (size:<=1 cm; 2-5 cm) on the y-axes respectively. Differences in the resulting survival distributions between the subcategories for the four disease markers were tested non-parametrically with logrank test (19).

In order to evaluate the predictive capacity of the four disease markers in relation to the time of symptom duration (history) a multivariate COX model was calculated (20,21).
Since the aim of this analysis was to develop a statistical model supporting the clinical judgement of the progression of GERD grounded in cross-sectional data, a path-model based on structural equation analysis was used in order to complement the multivariate analysis. While the multivariate COX model provides an estimate of the connection between the variable „history“ and the four anatomical-functional disease indicators, path analysis allows for testing of the direction of cause-effect statements in non-experimental data. Two hypothesized pathways, based on the pathophysiologic background of the disease, were tested (1,2,3).

Path modeling 1: history → Hiatal Hernia → LES-incompetence → esophageal acid exposure → esophagitis.
This model predicts that a longer time period from symtom onset to appearing in the tertiary clincal center for diagnostic work-up will lead to a higher risk of hiatal hernia, which in turn will lead to LES-incompetence, which will lead to increased esophageal acid exposure, which will in the end lead to more severe esophagitis.

Path modeling 2: history → LES-incompetence& Hiatal Hernia → esophageal acid exposure → esophagitis.
This model predicts that a longer time period from symptom onset to appearing in the tertiary clinical center will lead to a higher risk of LES-incompetence and hiatal hernia, which in turn will lead to increase esophageal acid exposure, which will lead in the end to esophagitis.

Results:

Patient`s characteristics

A total of 1480 patients with foregut symptoms were identified in the prospectively maintained database. After applying the inclusion criteria, 508 patients were excluded due to other identified function esophageal or gastric disorders, prior therapy, or incomplete data. In total, data from 972 patients were evaluated (542males, 430females)(Table1). Mean age was 50,5 years(range18-89). Mean BMI was 27,19(19-48). The mean time between onset of symptoms and the diagnostic investigations was mean 8,2 years(1-50).

The presence of LES-incompetence was 84.7%, while the presence of HH was 78.7%. Regarding IEM 6.1% of patients had ineffective motility in >50% of swallows. Objective finding of GERD by 24h-pH monitoring was documented in 728 patients (82 %). The mean pH-score in this population was 48,8 (normal<14,7). Endoscopic visible esophagitis was present in 64,4%. Barrett`s esophagus was determined endoscopically and histologically in 8,4% of the patients.

Analysis of functional parameters

A longer disease history for GERD was significantly associated with a higher risk for LES-incompetence (log-rank test: p = 0,0002) (Figure 1). The mean duration from

symptom onset to the time of clinical investigation was 9 years for patients with LES-incompetence (n=563), compared to a mean of 6 years for those with mechanically intact LES (n=95).

With regard to the esophageal acid exposure (expressed as pH-score), the picture was similar (Figure 2). Later presentation at the clinic and thus a longer period from symptom onset to diagnostics was significantly associated with higher acid exposure (Figure 2) (<= 35:n=375,7 years, 35-70:n=176,8 years; 70-105:n=64,8 years; 105-140:n=33,13 years; >140:n=30,12 years; log-rank test: p = 0,0003). The effect was most pronounced for the two segments with the highest acid exposure (Figure 2).

While there was no significant association between the grade of esophagitis and the „history“ of the disease (Figure3), patients who waited longer before they seeked help in a tertiary center did appear with larger hiatal hernias (hiatal hernia sizes 0-1cm:n=129,7 years versus sizes 2-5cm;n=483,8 years; log-rank-test: p = 0,0159) (Figure 4).

Multivariate modeling with COX-regression confirmed, that the functional parameters LES-incompetence (p = 0,0005) and esophageal acid exposure (p = 0,0415) were significantly associated with a longer history of symptoms, while there was no effect for hiatal hernia size (Table 2).

The correlation matrix of the raw data, derived from the path analysis, showed that esophagitis correlated strongest with hiatal hernia size, as well as with the pH-score (Table3). However, overall the correlations in this analysis were generally weak, not reaching a level of 0,5. This fact supports the assumption that the clinical parameters, included in this analysis, were basically independent from each other.

While path model 1 did not converge, path model 2 did. The goodness of fit for model 2 was 0,267. The pathways were significant for „history“ (p<0,001,loading 0,323), „LES-incompetence & Hiatal Hernia“(p<0,001,loading 0,398) and „pH-score“ (p<0,001,loading 0,201).

This model with the sequence with the sequence „History → LES-incompetence & hiatal hernia → acid exposure“ suggests that a longer time period from symptom onset to appearing in the tertiary center for diagnostics will lead to a higher risk of LES-incompetence and hiatal hernia, which in turn will lead to a increased esophageal acid exposure, finally causing esophagitis.

Discussion:

Even though this analysis is based on crosssectional data, some limited information about the disease duration was available from the carefully conducted and standardized diagnostic interviews of the patients. On the basis of these data, the analysis revealed that the longer the time from symptom onset to clinical investigations was, the higher was the risk for LES-incompetence, higher pH-score and larger hiatal hernias. A path model supported a causal relationship between longer waiting periods after symptom onset, a higher risk of LES-incompetence and hiatal hernia leading to increased esophageal acid exposure and finally esophagitis.

Patients usually describe the severity of a disease based on their symptoms, which they suffer from and adversely affect their quality of life (1,13,16). Therefore, in practice patients are encouraged to describe the severity of a disease with the frequency and intensity of symptoms. There is evidence, however, that GERD-symptoms do not always reflect an objective representation of accurate diagnosis, nor the severity and progression of GERD (22,23). In the proGERD study there was no correlation between the presence or the intensity of symptoms and the progression of GERD (13). Furthermore, the presentation of symptoms may overlap with other disorders and symptom intensity may depend on the individual patient`s sensitivity and judgement (22,23). Therefore, symptoms alone are not likely a reliable marker of GERD severity and progression.

Without treatment, GERD may develop into more advanced stages of severity with resultant associated complications such as massive hernia, short esophagus, and mucosal metaplasia/dysplasia/malignancy (1,2,3,7,9,10,11,24-26). The ability to identify markers of disease progression and provide early treatment are therefore of great importance.

Evidence in literature provides some information regarding factors for progression of GERD. Boeckxstaens et al. have shown an overview on the pathophysiologic components of GERD including the antireflux barrier, (LES and diaphragmatic components), esophageal clearance function, delayed gastric emptying by motility disorders, and/or gastro-duodenal dysfunctions such as DGER (2). The role of LES-incompetence has been mainly studied by surgical groups, as their diagnostic and therapeutic focus is the functional sphincter defect (3,5,7). Some clinical evidence has been gathered for decades regarding the presence of hiatal hernias and associated GERD (3,24,27). Allison`s observation has stimulated these thoughts and further investigations with precise functional evaluations lend support to the relationship between the presence of HH and severity of GERD (27,28). A close relationship between the extent acid of exposure and the presence of complications of GERD has also been shown (15,24).

Other studies have more or less directly focused on the progression of GERD (10,12-16,26,29-32). A reinterpretation of the proGERD study has shown that in the 5 year-follow-up investigations the progression towards more severe mucosal damage was dependent on the initial stage of esophagitis (33-35). Ten percent of all patients progressed towards Barrett`s esophagus despite PPI therapy (13,33-35). In another study, NERD patients were followed for 10 years, in which these patients with initial positive pathologic acid exposure developed a progression to esophagitis in 94% despite PPI-therapy (16,28). Our results confirm this finding by showing EAE increases with time that symptoms worsen until patients seek medical help.

The mechanical competence of the LES and the progression of the disease has also been studied. Kuster et al. showed that GERD-patients with an incompetent LES have a high probability of suffering from GERD 6-10 years later (26). Falkenback et

al. showed a progression in GERD patients towards Barretts esophagus after 21 years of follow-up, which correlated with LES-length and esophageal acid exposure (17). Lord et al. demonstrated that those patients with severe esophagitis and Barrett`s esophagus despite PPI-therapy were more often associated with LES-incompetence, anatomical changes and/or esophageal acid and bile exposure (26).
Recent evidence shows that histologic findings such as carditis at the Esophago-gastric-Junction (EGJ) are markers of a progression in GERD (35). Reviewing the natural history of GERD by Savarino et al. has shown that there are substantial data on the endoscopic and histologic course of the disease describing progression in a certain percentage of patients, however they emphasize that “up to now, data from different studies did not help to definitively understand the natural history of GERD” (36). Furthermore, it is stated that there “is no information on the results of pathophysiologic tests that might have been performed at least once during the clinical history of patients, although they are the only tool which is able to address an adequate therapy on GERD patients.”
We have focused on exactly these parameters and the statistical analysis supports the assumption that there is a relevant relationship between LES-incompetence and the duration of the disease up to the point of diagnostic investigations. The same accounts for the relationship between increasing esophageal acid exposure and the time development of the disease in a given patient. The longer a given patient with GERD is suffering from this disease the more frequent LES-incompetence can be detected and the more increasing esophageal acid exposure is present. Since we had only data from one investigation available, we had to apply a statistical analysis based on a structured equation modeling and path analysis to approach our question, which has been used elsewhere for similar situations (37-39).
All these investigated patients were under PPI-therapy and still, a portion of these patients, identifyable by functional testing, proving severe functional and anatomical alterations, showed worse functional results, the longer their history of symptom endured. This may reflect progression of the disease, however it is no prove.

A weakness of this study is the lack of a longitudinal investigation with more than one sample of testing. However, we and others mentioned the dilemma of getting an

opportunity to evaluate patients usually more than once, before therapeutic decision making is interrupting the natural course of the disease.
Another weakness of this analysis is the lack of histologic evaluation at the EGJ. Recent evidence shows that an additional sign of early progression of GERD is the presence and the extent of microscopically visible histologic damage at the EGJ such as length of carditis and remaining oxyntic mucosa within the LES (3,10,35). These findings would expand on the information on progression of GERD, but our initial intention was focused on the functional status and defects.

We investigated a large population of patients with symptoms indicative of GERD and analysed potential connections and predictions between pathophysiologic components and disease-severity. The study provides evidence that functional and anatomical factors at the EGJ preventing reflux correlate significantly with the severity of GERD. The role of the LES and the development of hiatal hernias are independent from each other. Since the correlations are weak, a prediction regarding progression based on functional data alone in a single patient, does not allow for this interpretation.

Conclusion

We can conclude from our study that LES-incompetence, the functional deterioration of the LES, the anatomical alteration at the EGJ (Hiatal Hernia) as well as an increased esophageal acid exposure are associated with a longer history, a patient is suffering from GERD. Path modeling supports a causal sequence of developing this disease-parameters over time.

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Table 1: Overview on the patient`s characteristics:

parameter	data
n (male/female)	972 (542 / 430)
age (years) mean	50,5 (18-89)
BMI mean	27,19 (19-48)
Gastrointestinal Quality of Life Index (GIQLI) (normal 121; maximum 144)	91 (33-142)
Duration of symptoms: (time: onset of symptoms-diagnostic work-up in years) (mean)	8,2 years (1-50)
Lower esophageal sphincter incompetence LES (% presence)	84,7%
Hiatal hernia (% presence)	78,7%
Insufficient esophageal motility (% insufficient peristalsis)	> 50%: 6,1% > 30%: 17,7%
Esophageal acid exposure Mean (normal:<14,7) % presence	 48,8 82%
Esophagitis Savary 1-4 / Grade LA:A-D Barrett`s esophagus	 64,4% 8,4%

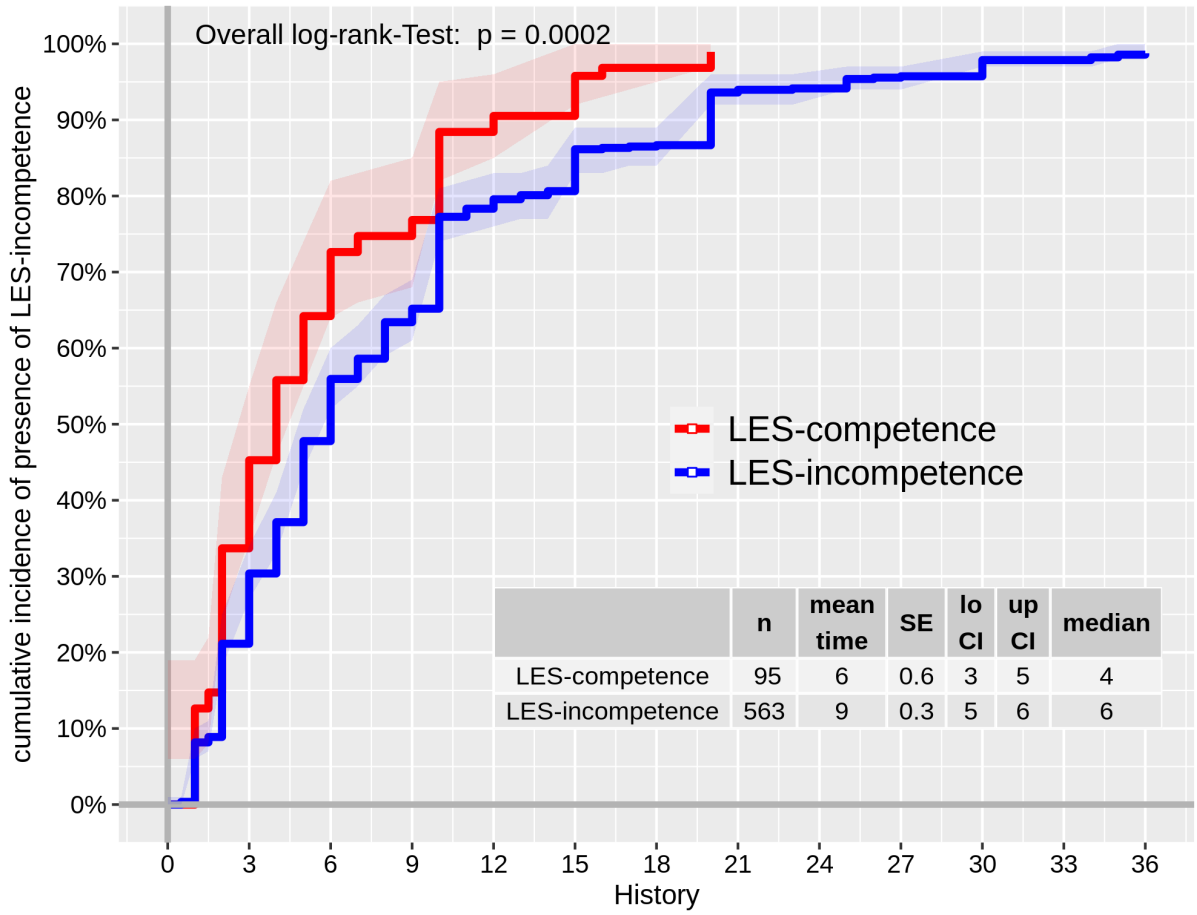
Table 2: Results of Cox-regression regarding the parameters of esophagitis, Hiatal Hernia, LES- incompetence and esophageal acid exposure expressed as pH-score. Methods from (20,21) (Model: p<0,001, R2=0,0335)

Predictors: Cox-regression	p	Hazard-Ratio	Lower 95%-CI	Upper 95%-CI	esteem	SE	Z-value	n
esophagitis	0,5559	0,9828	0,9278	1,0411	-0,0173	0,0294	-0,5889	595
Hiatal Hernia	0,8200	0,9932	0,9365	1,0533	-0,0068	0,0300	-0,2276	595
LES-incompetence	0,0005	0,6567	0,5187	0,8314	-0,4206	0,1204	-3,495	595
pH_score	0,0415	0,9980	0,9962	0,9999	-0,0020	0,0010	-2,0383	595

Table 3: Inter-correlations of the chosen parameters in GERD-patients by Pearson Correlations

correlations	Coefficient r	p-value p	Number of calculated cases	Correlation statistical significant
History with esophagitis	0,067	0,0897	643	no
History with Hiatal Hernia	0,035	0,3782	648	no
History with LES-incompetence	0,124	0,0014	658	yes
History with pH-score	0,142	0,0004	630	yes
Esophagitis with Hiatal Hernia	0,433	<0,0001	903	yes
Esoph. with LES-incompetence	0,163	<0,0001	870	yes
Esophagitis with pH-score	0,240	<0,0001	831	yes
Hiatal Hernia with LES-incomp.	0,151	<0,0001	874	yes
Hiatal Hernia with pH-score	0,192	<0,0001	836	yes
LES-incomp. With pH-score	0,175	<0,0001	852	yes

Legends of Figures:

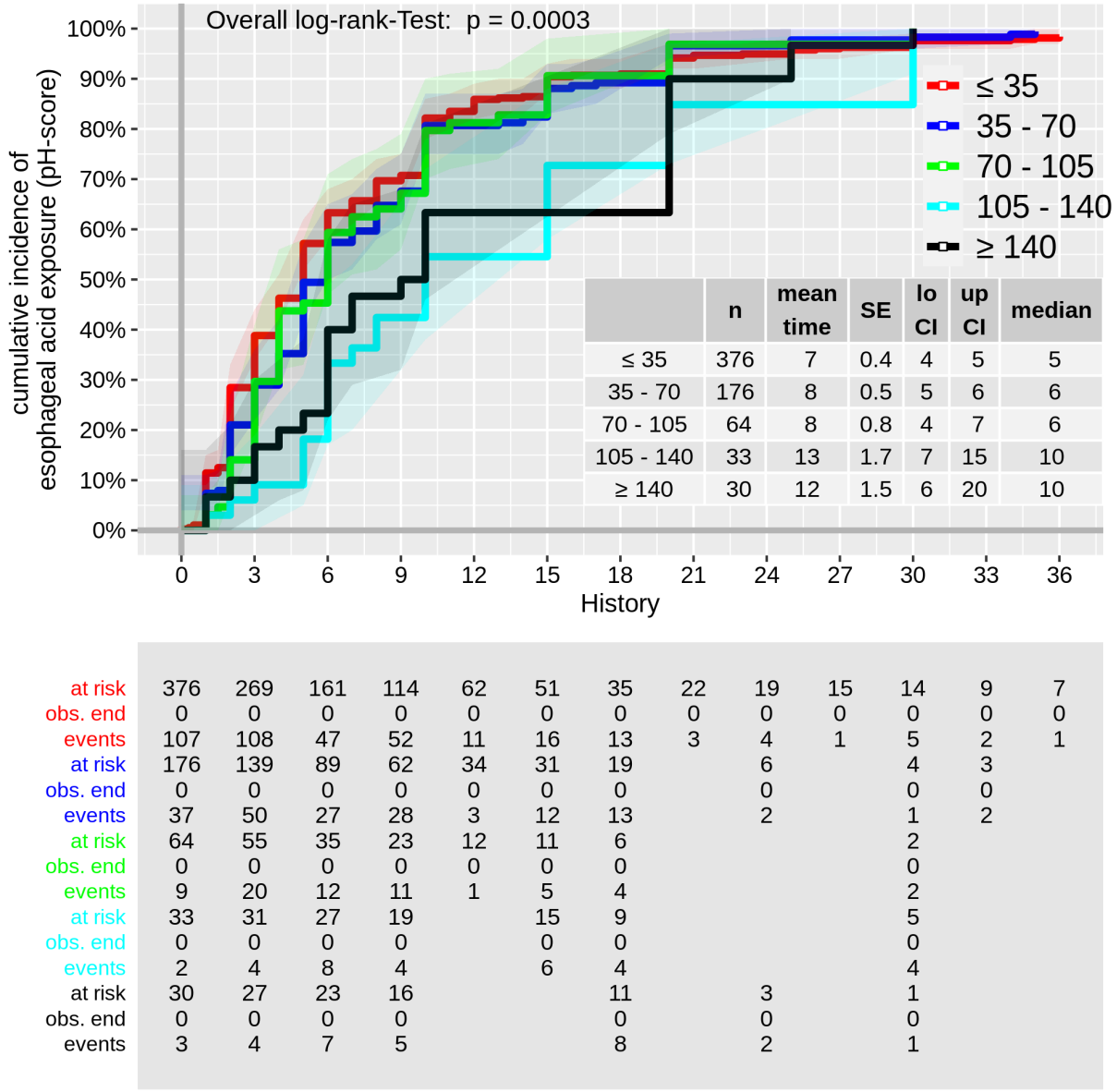


	n	mean time	SE	lo CI	up CI	median
LES-competence	95	6	0.6	3	5	4
LES-incompetence	563	9	0.3	5	6	6

at risk	95	63	34	24	11	9	3						
obs. end	0	0	0	0	0	0	0						
events	32	29	10	13	2	6	2						
at risk	563	444	294	206	122	109	76	36	33	25	24	12	8
obs. end	0	0	0	0	0	0	0	0	0	0	0	0	0
events	119	150	88	84	13	33	40	3	8	1	12	4	1

Figure 1:

Relationship of the presence of LES-incompetence in GERD-patients with “history”, the duration between symptom onset and the clinical visit in a tertiary center for diagnostic investigations in years.



	n	mean time	SE	lo CI	up CI	median
≤ 35	376	7	0.4	4	5	5
35 - 70	176	8	0.5	5	6	6
70 - 105	64	8	0.8	4	7	6
105 - 140	33	13	1.7	7	15	10
≥ 140	30	12	1.5	6	20	10

at risk	376	269	161	114	62	51	35	22	19	15	14	9	7
obs. end	0	0	0	0	0	0	0	0	0	0	0	0	0
events	107	108	47	52	11	16	13	3	4	1	5	2	1
at risk	176	139	89	62	34	31	19		6		4	3	
obs. end	0	0	0	0	0	0	0		0		0	0	
events	37	50	27	28	3	12	13		2		1	2	
at risk	64	55	35	23	12	11	6				2		
obs. end	0	0	0	0	0	0	0				0		
events	9	20	12	11	1	5	4				2		
at risk	33	31	27	19		15	9				5		
obs. end	0	0	0	0		0	0				0		
events	2	4	8	4		6	4				4		
at risk	30	27	23	16			11		3		1		
obs. end	0	0	0	0			0		0		0		
events	3	4	7	5			8		2		1		

Figure 2:

Relationship of a level of esophageal acid exposure (as measured in pH-score) in GERD-patients with “history”, the duration between symptom onset and the clinical visit in a tertiary center for diagnostic investigations in years.

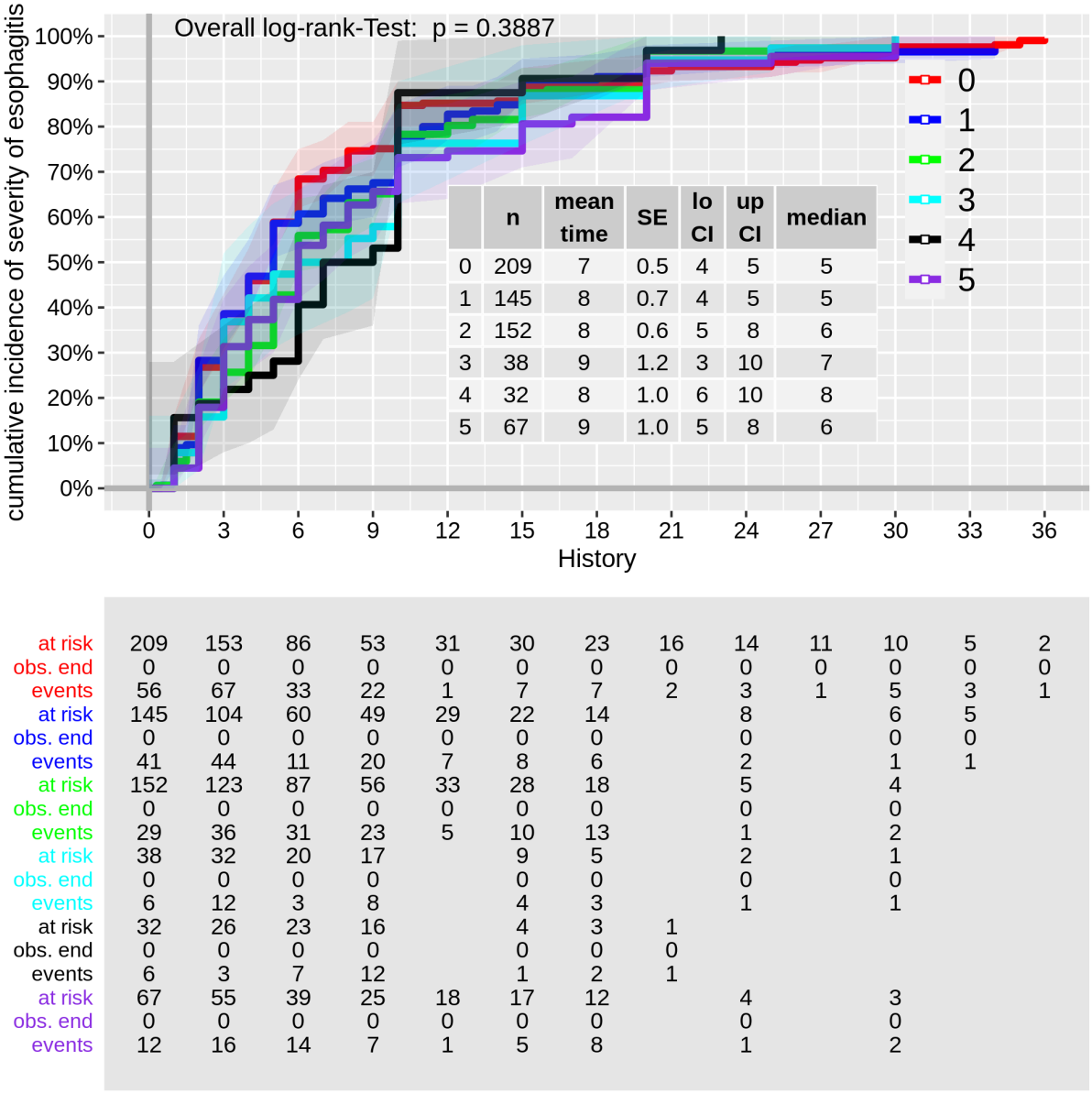


Figure 3:

Relationship of the presence of esophagitis in GERD-patients with “history”, the duration between symptom onset and the clinical visit in a tertiary center for diagnostic investigations in years.

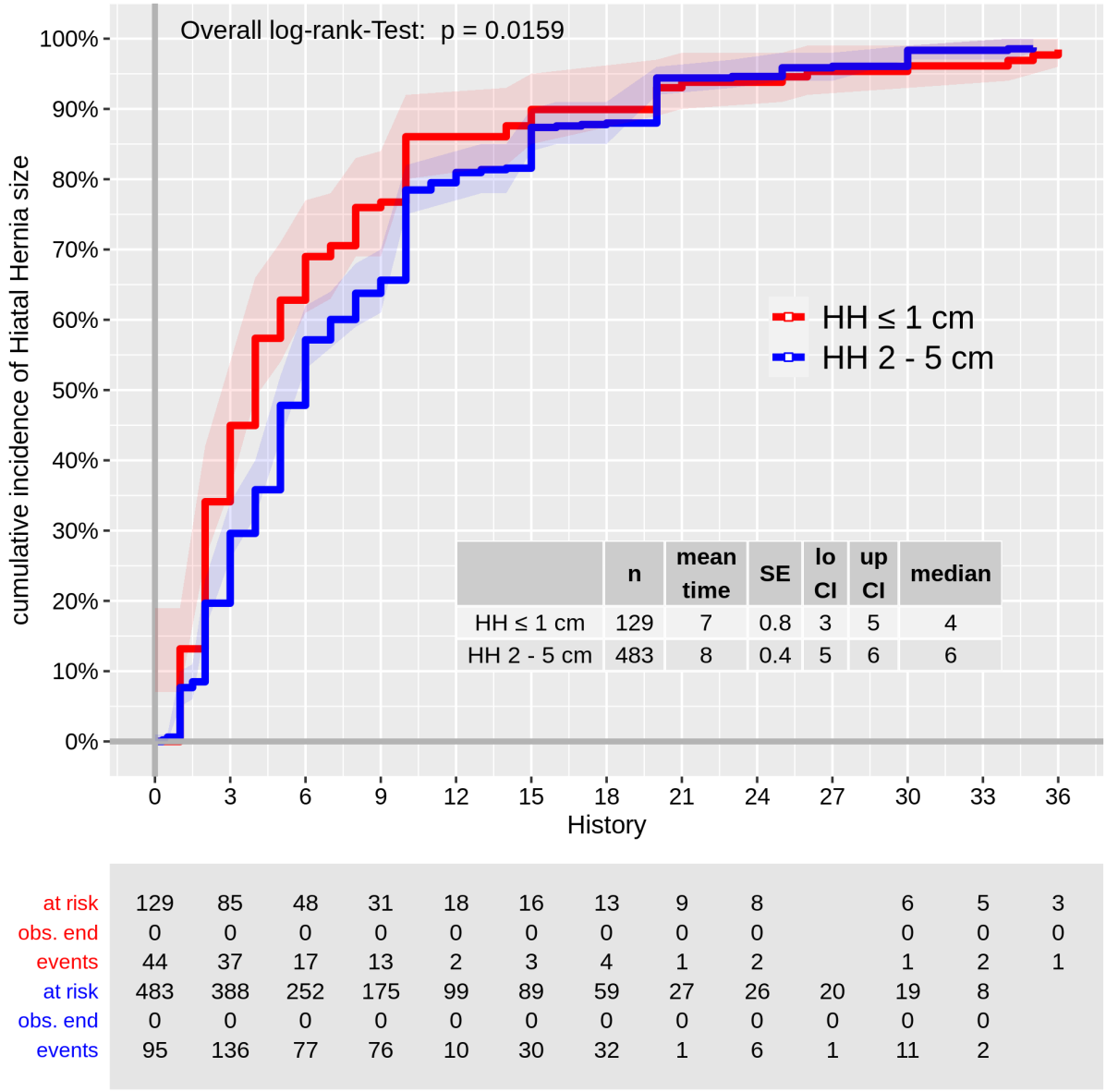


Figure 4:

Relationship of the size of a hiatal hernia (measured in cm) in GERD-patients with “history”, the duration between symptom onset and the clinical visit in a tertiary center for diagnostic investigations in years.