

Chromogranin A: Is It a Useful Marker of Neuroendocrine Tumors?

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A B S T R A C T

Purpose

We evaluated the pattern of chromogranin A (CgA) plasma levels in a large number of patients with neuroendocrine tumors (NETs), in a series of patients with chronic atrophic gastritis (CAG) with and without enterochromaffin-like (ECL) cell hyperplasia, and in healthy participants (HPs).

Patients and Methods

Two hundred thirty-eight patients with NETs, 42 patients with CAG with or without ECL cell hyperplasia, and 48 HPs were studied. All patients underwent a baseline visit, biochemical routine check-up, imaging techniques, endoscopy, and histologic determination.

Results

CgA plasma levels were higher in patients with NETs compared with CAG patients or HPs ($P < .001$). In the NET group, we observed higher CgA levels in patients with diffuse disease compared with patients with local or hepatic disease ($P < .001$). CgA plasma levels were significantly higher in patients with Zollinger-Ellison syndrome compared with other types of endocrine tumors ($P < .001$). We found the best cutoff range between HPs and NET patients to be 18 to 19 U/L (sensitivity, 85.3%; specificity, 95.8%). Comparing all participants without neoplasia (HPs, CAG patients, and disease-free patients) and patients with endocrine tumors, the best cutoff range was 31 to 32 U/L (sensitivity, 75.3%; specificity, 84.2%). Setting the specificity at 95%, the cutoff range was 84 to 87 U/L (sensitivity, 55%).

Conclusion

Our study confirms the high specificity and sensitivity of CgA in diagnosing an endocrine tumor. It is necessary to use a cutoff range of 84 to 87 U/L to obtain a high specificity in diagnosing NETs, with the aim of excluding patients in whom the CgA was elevated as a result of other non-neoplastic diseases.

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INTRODUCTION

Chromogranin A (CgA) is an acidic glycoprotein with a molecular mass of 49 kd that is widely expressed by neuroendocrine cells and constitutes one of the most abundant components of secretory granules.¹ CgA is physiologically released by exocytosis and may be detected in the blood. In particular, when a tumor develops in an endocrine tissue, it becomes the main source of circulating CgA.^{2,3} High CgA levels have been demonstrated in the serum or plasma of patients with different types of endocrine tumors such as pheochromocytoma, medullary thyroid carcinoma, and enterochromaffin and pancreatic islet cell tumors.^{1,4-9} In particular, circulating CgA levels have been claimed to be useful markers for neuroendocrine tumors (NETs), with a high specificity and a sensitivity ranging from 27% to

81%.^{7,10} Recent studies indicate that circulating CgA levels correlate positively with an enterochromaffin-like (ECL) cell mass in patients with autoimmune chronic atrophic gastritis,^{11,12} gastrinoma, and multiple endocrine neoplasia syndrome type 1^{7,13} who may develop potentially malignant gastric carcinoids.¹⁴ However, these studies included only a small number of patients, except for two recent prospective studies; one of these two studies was performed in patients with gastrinomas,¹⁵ and the other study was performed in patients with various types of gastroenteropancreatic (GEP) endocrine tumors.¹⁶ Furthermore, no studies have compared CgA plasma levels in patients with endocrine tumors with CgA levels in patients with chronic atrophic gastritis (CAG).

The aim of this study was to evaluate the pattern of CgA plasma levels in a large number of

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patients with endocrine tumors localized in different tissues and at different stages of the disease, in a series of patients with CAG with and without ECL cell hyperplasia, and in healthy participants (HPs).

PATIENTS AND METHODS

We evaluated 280 consecutive patients and 48 HPs at the Center for the Study and Treatment of Gastro-Entero-Pancreatic Tumors in the Department of Internal Medicine and Gastroenterology, University of Bologna, from January 2004 to June 2006. All 280 patients enrolled underwent a baseline visit including clinical history and a biochemical routine check-up. Imaging techniques (ultrasound, computed tomography, somatostatin receptor scintigraphy, and gastrointestinal endoscopy) were performed to evaluate the presence of neoplasia and its localization and stage. Histologic determinations with a Ki-67% index were performed. In all patients with CAG, we carried out an endoscopy with multiple biopsies in the antrum, body, and fundus to confirm the presence of atrophy and to detect ECL cell hyperplasia.

On the basis of these examinations, the participants were divided into three different groups. Group A included 238 patients with NETs (130 men and 108 women; mean age, 59.1 years; range, 26 to 85 years) localized in the stomach in 14 patients (5.9%), in the lung in 20 patients (8.4%), in the GI tract in 85 patients (35.7%), and in the pancreas in 94 patients (39.5%). In 25 (10.5%) of 238 patients, Zollinger-Ellison syndrome (ZES) was present. These patients were considered as a separate subgroup because, in our previous study, we had already stated that they showed extremely higher CgA levels compared with patients with endocrine tumors without ZES.⁷ The patients were considered disease free when the tumor was totally removed by surgery and when there was no evidence of the disease at imaging techniques. Patients with local disease had a primary lesion with or without positive local lymph nodes, whereas hepatic disease was defined as hepatic metastases with or without local disease. Patients with diffuse disease had distant metastases (other than the liver) with or without local disease.

Group B included 42 patients with CAG (15 men and 27 women; median age, 56.1 years; range, 24 to 79 years); 29 patients (69%) had ECL cell hyperplasia, and 13 patients (31%) did not. Group C included 48 participants without apparent pathologic alterations and considered to be in good health (24 men and 24 women; median age, 55.5 years; range, 19 to 86 years).

None of the 280 patients or 48 HPs had renal insufficiency (evaluated based on the creatinine concentrations), and except the patients with ZES, none of the participants were treated with proton pump inhibitors at the time of the study. All three groups were comparable for sex ($P = .076$) and age ($P = .170$).

Ethics

All patients provided verbal informed consent to participate in the study. The study protocol was approved by the Senior Ethical Committee of the Department of Internal Medicine and Gastroenterology at the Uni-

versity of Bologna and was carried out according to the Helsinki Declaration of human studies.

CgA

Blood samples were obtained after overnight fasting and were collected in tubes containing EDTA. Within 60 minutes after collection, the samples were centrifuged at 6,000 rpm with an ALC 4235A Centrifuge (ALC International, Milan, Italy), and the plasma was stored at -20°C until assay.

The CgA plasma level was measured with a technique previously validated in our laboratory⁷ and commercially available (DAKO CgA ELISA kit; Dako A/S, Copenhagen, Denmark). In brief, the CgA determination uses an immunoenzymatic sandwich methodology. Furthermore, three plasma samples obtained from a pool of our samples with low, medium, and high CgA concentrations were used for the calculation of the intra- and interassay coefficients. CgA was measured within a run and on consecutive days on 12 replicates. The mean coefficient of variation ranged from 2.2% (intra-assay) to 9.5% (interassay), and it was independent of the CgA concentration in the range of the selected samples (20 to 300 U/L). The recovery and the dynamic range of linearity are similar to those reported in the assay kit performance.

Statistics

The descriptive statistics used were means, standard deviations, and frequencies. The CgA plasma concentrations were not normally distributed ($P < .001$; Kolmogorov-Smirnov test) and were positively skewed; thus, a logarithmic transformation was applied before analyzing the data. Data were analyzed using linear general models; one-way and two-way analyses of variance (ANOVA) were used to compare the groups of patients, whereas the relationships between variables were tested using regression analysis. The antilog transformations of the effects evaluated by ANOVA were also reported with their 95% CIs. These effects estimate the fractional comparison of CgA plasma levels between groups of participants. The Student-Newman-Keuls (SNK) post hoc analysis of ANOVA was applied to produce multiple comparisons of means between the different sites of the tumor.

The analyses were performed using SPSS version 13.0 for Windows (SPSS Inc, Chicago, IL). Two-tailed $P < .05$ was considered statistically significant.

RESULTS

Differences Between the Three Groups

The CgA data in the three groups of participants are listed in Table 1. CgA plasma levels were significantly different among the three different groups ($P < .001$); furthermore, we observed lower levels in HPs than in the other two groups ($P < .001$), whereas there was no statistically significant difference between the NET group and the CAG group ($P = .114$). Considering the overall population studied, there was no significant relationship between CgA and sex ($P = .409$) or age ($P = .804$).

Table 1. CgA Plasma Levels in the Three Groups of Participants

Group	No. of Participants	CgA Level (U/L)		P	Effect (%)	
		Mean	SD		Estimate	95% CI
NETs	238	428.1	1,584.3			
Compared with CAG patients				.114	153.5	90.1 to 261.6
Compared with healthy participants				< .001	606.7	367.3 to 1,000.0
CAG*	42	50.1	41.2	< .001	395.3	201.8 to 774.5
Healthy participants	48	10.5	4.7	—	—	—

NOTE. Comparisons among the groups were made using one-way analysis of variance. $P < .001$ among the three groups.

Abbreviations: CgA, chromogranin A; SD, standard deviation; NET, neuroendocrine tumor; CAG, chronic atrophic gastritis.

*P values and effect estimates compared with healthy participants.

Differences Between Subgroups

The CgA data in the subgroups of NET and CAG patients are listed in Table 2 and shown in Figure 1. In the NET group, we observed higher CgA levels in patients with diffuse disease compared with patients with local ($P < .001$) or hepatic disease ($P < .001$). Otherwise, we did not observe a statistically significant difference in CgA levels between patients with local or hepatic disease ($P = .563$). In the disease-free patients, CgA levels were lower than the levels found in patients at any other stage of endocrine neoplastic disease ($P < .001$). In the CAG group, patients with hyperplasia had significantly higher CgA levels compared with patients who did not have hyperplasia ($P = .032$).

Other Subgroup Evaluations

In the NET group, we excluded patients who were disease free at the time of sampling with the aim of better differentiating CgA levels in patients with endocrine tumors compared with patients with CAG to evaluate CgA as a diagnostic parameter of neoplasia. In 170 patients with endocrine tumors, the mean CgA level \pm standard deviation was $594.4 \pm 1,850.0$. CgA levels in patients with neoplasia were significantly higher than the levels in patients with CAG ($P < .001$; effect = 308.5; 95% CI, 180.1 to 528.4); this was true even when we compared patients with local disease with patients with CAG ($P < .006$; effect = 186.0; 95% CI, 120.1 to 288.1).

Pharmacologic Treatment

One hundred twelve (47.1%) of the 238 NET patients were undergoing somatostatin (SST) analog treatment at the time of sampling, including 25 (36.8%) of 68 disease-free patients, 27 (36%) of 75 patients with local disease, 34 (59.6%) of 57 patients with hepatic disease, and 26 (68.4%) of 38 patients with diffuse disease. After adjusting for the stage of the disease (two-way ANOVA), no significant differences in CgA were found between patients undergoing SST analog treatment and untreated patients ($P = .223$), and the SST analog treatment did not significantly affect CgA levels in each of the four different stages of the disease ($P > .189$).

Other Factors in the NET Group

In the NET group, we also evaluated other factors that could modify CgA levels such as the primary localization of the tumor. In Table 3, we reported the mean values of CgA related to the primary site of the tumor. CgA was significantly different among the five different localizations ($P < .001$). According to the different site of neoplasia, the post hoc analysis identified three different groups of patients; patients with lung localization had the lowest CgA values, whereas patients with ZES had the highest CgA values. No significant differences ($P = .780$) were detected among patients with stomach, pancreas, and intestinal tract neoplasias (middle CgA values).

Receiver Operating Characteristic

In Table 4, we reported the area under the curve, the best cutoff range, and the sensitivity and specificity of CgA in the diagnosis of endocrine tumors, comparing different groups. Figure 2 shows the receiver operating characteristic curves. We excluded the 68 patients who were disease free at the time of sampling in the NET group to calculate the receiver operating characteristic curve.

The best cutoff range between HPs and NET patients was 18 to 19 U/L, with a sensitivity of 85.3% and a specificity of 95.8%, and the best cutoff range between CAG and NET patients was 53 to 54 U/L, with a sensitivity of 66.5% and a specificity of 71.4%. Considering the various factors that could have an impact on CgA levels, we also compared all of the participants without neoplasias (HPs, CAG patients, and disease-free patients) and patients with endocrine tumors. The best cutoff range was 31 to 32 U/L, with a sensitivity of 75.3% and a specificity of 84.2%. Setting the specificity at a 95% value, the cutoff was 84 to 87 U/L with a sensitivity of 55% (93 of 170 participants).

To distinguish between patients with limited disease (local and/or liver) and patients with diffuse disease, another ROC curve was constructed, and the best cutoff point was calculated. The area under the curve was 0.805 ± 0.047 . Using 281 to 282 U/L as the best cutoff range, the sensitivity and specificity of CgA were 71.1% and 78.8%, respectively. Setting the specificity at a 95% value, the cutoff was 564 to 603 U/L with a sensitivity of 55% (21 of 38 patients).

Table 2. CgA Plasma Levels in the Subgroups of NET and CAG Patients

Group	No. of Patients	CgA Level (U/L)		P	Effect (%)	
		Mean	SD		Estimate	95% CI
NET						
Diffuse disease	38	2,055.5	3,539.4			
Compared with hepatic disease				< .001	687.3	398.5 to 1,185.4
Compared with local disease				< .001	786.2	468.2 to 1,320.2
Compared with disease free				< .001	5,452.6	3,218.5 to 9,237.4
Hepatic disease	57	187.2	237.4			
Compared with local disease				.563	114.4	72.4 to 180.7
Compared with disease free				< .001	793.3	497.1 to 1,266.1
Local disease*	75	163.5	312.5	< .001	693.5	448.5 to 1,072.4
Disease free	68	12.3	10.7	—	—	—
CAG						
Hyperplasia†	29	56.7	41.0	.032	172.7	105.2 to 283.6
No hyperplasia	13	35.3	39.2	—	—	—

NOTE. Comparisons among the subgroups were made using one-way analysis of variance. Abbreviations: CgA, chromogranin A; NET, neuroendocrine tumor; CAG, chronic atrophic gastritis; SD, standard deviation. *P values and effect estimates compared with disease free. †P values and effect estimates compared with no hyperplasia.

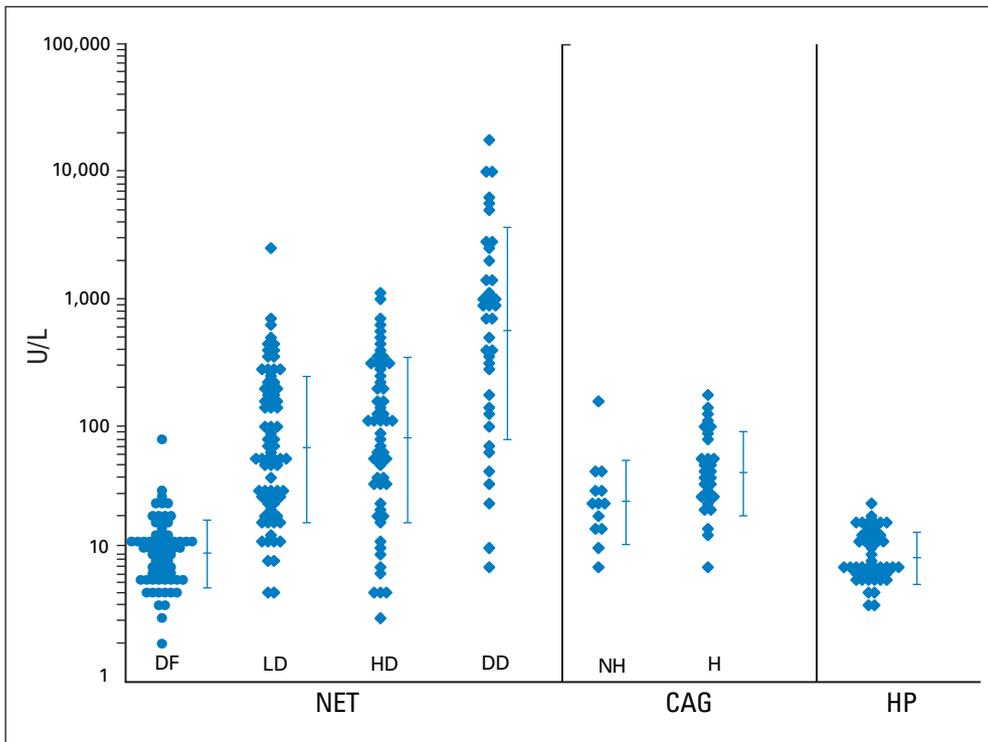


Fig 1. Distribution of chromogranin A levels in 238 patients with neuroendocrine tumors (NETs) divided into four subgroups (disease free [DF], local disease [LD], hepatic disease [HD], and diffuse disease [DD]), in 42 patients with chronic atrophic gastritis (CAG) divided into two subgroups (no hyperplasia [NH] and hyperplasia [H]), and in 48 healthy participants (HP). Mean values \pm standard deviations are reported.

DISCUSSION

Circulating CgA levels have been said to be a useful marker for NETs, with a high specificity and sensitivity, but most studies included only a small number of patients.^{7,10} In the present study, we investigated the diagnostic value of plasma CgA in a large number of patients with endocrine tumors localized in different tissues and at different stages of the disease compared with a series of patients with CAG, with and without ECL cell hyperplasia, and HPs. In agreement with previous studies, our findings demonstrate that abnormally high plasma CgA levels are a characteristic feature of patients with endocrine tumors^{7,13,16} and patients with CAG.¹²

We have found that patients with endocrine tumors showed higher levels of CgA than HPs.^{7,13,16} Using a best cutoff range of 18 to 19 U/L, we obtained a specificity of 95.8% and a sensitivity of 85.3%. These findings are in agreement with others reported in the literature, where a variable cutoff value from 17 to 34 U/L was identified, with a variable specificity (83% to 91%)^{13,17-19} and sensitivity (79% to 92%).^{7,13,17-19} In our series, the higher specificity obtained was a result of the careful selection of HPs in whom the various causes of CgA elevation were not present.

Similarly, we found that patients with tumors showed higher levels of CgA than patients with CAG, even if we only considered patients with localized disease. The best cutoff range between CAG and NET patients was 53 to 54 U/L, with a sensitivity of 66.5% and a specificity of 71.4%. The fact that there were higher levels of CgA in patients with tumors and also in patients with localized tumors compared with patients with CAG has never been mentioned before in the literature. Furthermore, according to Peracchi et al,¹² patients with CAG showed levels of CgA significantly higher than HPs.

In the present study, we have also observed that patients with endocrine tumors showed progressively higher CgA levels as the dis-

ease progressed.^{6,7,16} This increase in levels was not statistically significant between patients with local and hepatic disease, but it became significant between patients with localized and diffuse disease (distant lymph node, lung, bone, and spleen metastasis). The best cutoff range identified to distinguish between localized (local and/or liver) and diffuse disease was 281 to 282 U/L, with a sensitivity of 71.1% and a specificity of 78.8%. Setting the specificity at the 95% value, the cutoff was 564 to 603 U/L with a sensitivity of 55% (21 of 38 patients). This finding is important to speculate as to whether a disease is localized or diffuse based on the CgA levels because diffuse disease is related to a poorer prognosis and needs an aggressive therapeutic approach.^{20,21}

In the CAG group, we observed higher CgA levels in patients with ECL cell hyperplasia, and this finding was in agreement with other data already published by Peracchi et al.¹² In this article,¹² plasma CgA levels in patients with hyperplasia were higher compared with levels in

Table 3. CgA Plasma Levels in NET Patients According to the Site of Tumor

Tumor Site	No. of Patients	CgA Level (U/L)	
		Mean	SD
Lung	20	46.3	94.6
Stomach	14	78.0	69.2*
Pancreas	94	322.2	952.7*
Intestine	85	380.1	1,224.9*
ZES	25	1,490.5	3,819.3

NOTE. Comparisons among the subgroups were made using one-way analysis of variance. Overall $P < .001$ among the five localizations.

Abbreviations: CgA, chromogranin A; NET, neuroendocrine tumor; SD, standard deviation; ZES, Zollinger-Ellison syndrome.

*No significant differences ($P = .780$) were detected at the post hoc analysis among patients with stomach, pancreas, and intestinal tract neoplasia.

Table 4. Results of the Receiver Operating Characteristic Curve Analysis Comparing Different Groups of Patients

Group Comparison	AUC		Best CgA Cutoff Range (U/L)	Sensitivity		Specificity	
	Mean	SE		No./Total No.	%	No./Total No.	%
NET v HPs	0.928	0.017	18-19	145/170	85.3	46/48	95.8
NET v CAG	0.712	0.035	53-54	113/170	66.5	30/42	71.4
Neoplasia v no neoplasia	0.865	0.020	31-32	128/170	75.3	133/158	84.2
NET: diffuse v limited disease	0.805	0.047	281-282	27/38	71.1	104/132	78.8

Abbreviations: AUC, area under the curve; CgA, chromogranin A; SD, standard deviation; NET, neuroendocrine tumor; HPs, healthy participants; CAG, chronic atrophic gastritis.

patients with CAG without hyperplasia, although this was not statistically significant.

In the present study, we also compared patients with endocrine tumors with those without tumors, such as HPs, patients with CAG, and disease-free patients at the time of sampling, with the aim of obtaining the best cutoff value useful for clinical practice. We have determined a best cutoff range of 31 to 32 U/L, with a sensitivity of 75.3% and a specificity of 84.2%. To eliminate the various causes capable of increasing CgA levels, we set the specificity at 95%, obtaining a cutoff value of 84 to 87 U/L with a sensitivity

of 55% (93 of 170 participants). This value is extremely high compared with previous data in the literature,^{7,13,16,18,22} but it allows us to distinguish between patients who need specific and more accurate diagnostic means to detect endocrine tumors and patients in whom it is first necessary to exclude other putative causes of increasing CgA levels.

Regarding the primary localization of endocrine tumors, we would stress that, in patients with lung tumors, the CgA levels were significantly lower compared with the levels in patients who had GEP tumors. On the basis of this finding, we can speculate that lung tumors

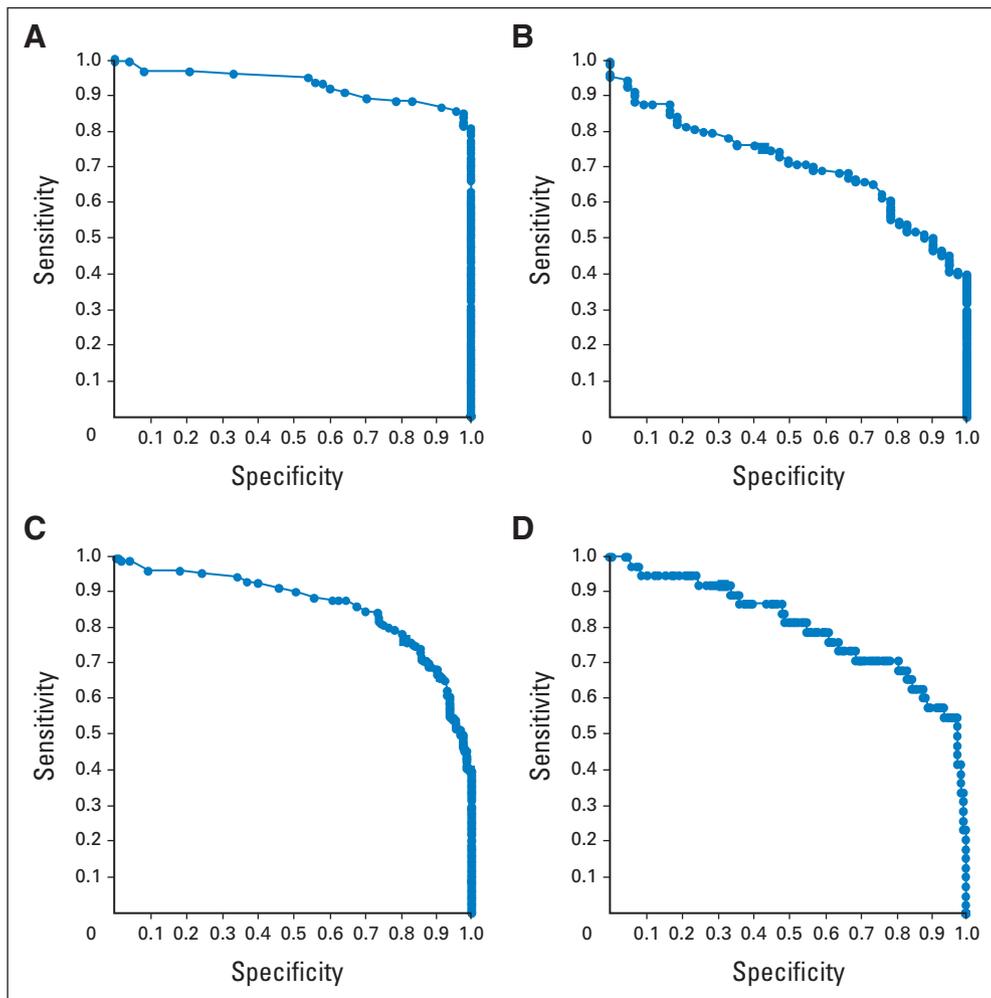


Fig 2. Receiver operating characteristic curves of chromogranin A for various categories of the participants studied. (A) Patients with neuroendocrine tumors (NETs; n = 170) versus healthy participants (HPs; n = 48). (B) NET patients (n = 170) versus patients with chronic atrophic gastritis (CAG; n = 42). (C) All patients with neoplasia (n = 170) versus all patients without neoplasias (n = 158). (D) Patients with diffuse NET (n = 38) versus patients with limited NET (n = 132).

have a lower secretory activity compared with GEP tumors, but further studies based on a higher number of patients are required.

Patients with ZES showed significantly higher levels of CgA compared with patients without gastrin-secreting tumors.^{7,16} This is a result of the trophic action of gastrin on the endocrine cells of the gastric mucosa, which leads to an increase in CgA levels.^{5,23} Therefore, it is important to combine the determination of CgA levels and gastrin when ZES is suspected. In fact, ZES patients do not only have high levels of gastrin, but their CgA levels are also much more elevated compared with patients with other conditions such as CAG.^{7,12,23} In our series, we demonstrated that, in CAG patients, the levels of CgA were higher compared with HPs but lower than the levels found in patients with endocrine tumors and, in particular, in patients with ZES.

In our study, we did not observe statistically significant differences in CgA levels in relation to the primary localization of the endocrine tumor, such as the stomach, gut, or pancreas.^{7,13,17} We found lower CgA levels in patients treated with SST analogs compared with untreated patients, although these differences were not statistically significant.^{22,24} However, we did not consider the change in CgA levels before and after the first dose, but we compared treated versus untreated patients at the same stage of the disease.

In conclusion, our study confirms the high specificity and sensitivity of CgA in the diagnosis of endocrine tumors, but this finding is limited by the choice of carefully selected HPs as a control group. We think that it is necessary to use a cutoff range of 84 to 87 U/L to obtain a high specificity in the diagnosis of endocrine tumors, with the aim of excluding patients in whom the CgA level was elevated as a result of other non-neoplastic conditions. To our knowledge, patients with CgA levels greater than 84 to 87 U/L need to be studied using specific diagnostic means to detect endocrine tumors. On the contrary, in patients with levels less than 84 to 87

U/L but greater than 18 to 19 U/L without evident tumors, it is necessary to exclude all conditions that could result in an increase of CgA, such as chronic renal failure,⁷ proton pump inhibitor treatment,²⁵ and CAG,¹² and only later on do these patients need to undergo specific imaging techniques. This finding is particularly important because it differs from previously reported cutoff values between 17 and 34 U/L. Using our value, we can exclude all patients with high non-neoplastic CgA levels who often undergo unnecessary examinations that are specific for endocrine tumors.

In conclusion, in our study, we evaluated CgA levels using the DAKO ELISA kit. These data should not be compared with data obtained with other types of commercial kits because, as already stated in numerous studies, the sensitivity and specificity differ between the kits.^{17,19,26}

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The authors indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: Davide Campana, Roberto Corinaldesi, Paola Tomassetti

Provision of study materials or patients: Davide Campana, Paola Tomassetti

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