Table 2. Result of serum CGA level

Characteristics	pNET	PC	CP	AIP	Normal
Total					
Number	69	50	50	20	112
CGA level (ng/mL)					
Mean ± SD	407.8 ± 984.6*	91.8 ± 101.8†	93.6 ± 57.5†	69.9 ± 52.4	62.5 ± 48.3
PPI use (%)					
Yes					
Number	19 (27.5)	19 (38.0)	28 (56.0)	9 (45.0)	N/A
CGA level (ng/mL)					
Mean ± SD	297.7 ± 389.1	155.9 ± 129.8‡	107.6 ± 66.9‡	98.5 ± 64.2‡	
No (%)					
Number	50 (72.5)	31 (62.0)	22 (44.0)	. 11 (55.0)	112 (100)
CGA level (ng/mL)					
Mean ± SD	449.6 ± 1132.8*	52.5 ± 51.2*	75.7 ± 37.1	46.6 ± 24.1	62.5 ± 48.3

Significant difference between each group was evaluated by Scheffe's multiple comparison. *$P < 0.01$ versus normal. †$P < 0.05$ versus pNET. Significant difference between with or without PPI use in the same group was evaluated by Student *t*-test.; ‡$P < 0.05$ versus no PPI use. AIP, autoimmune pancreatitis; CGA, chromogranin A; CP, chronic pancreatitis; PC, pancreatic cancer; pNET, pancreatic neuroendocrine tumor; PPI, proton pump inhibitor.

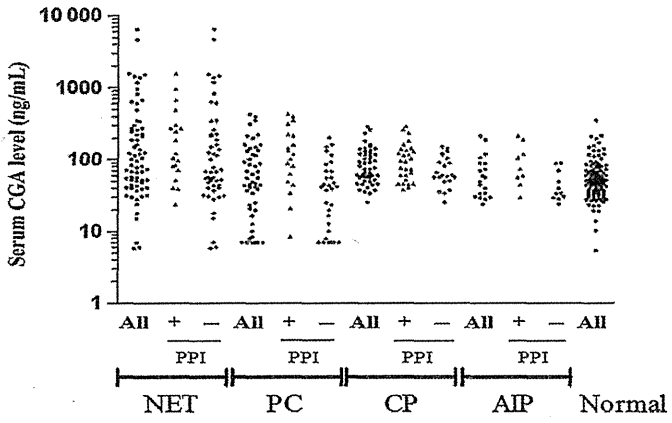

Fig. 1. Distribution of serum chromogranin A level in this study.

(Table 4). With respect to the tumor classification, pNET patients with non-functioning tumors or gastrinomas characteristically had high serum CGA levels exceeding the cut-off value, especially patients with gastrinomas, in which 16/17 (94%) had a high serum CGA level beyond the cut-off value. Only 1 of the 10 patients with insulinomas had a high serum CGA level above the cut-off value. With respect to the tumor size, 73% (11/15) of pNET patients with tumors larger than 2 cm had high serum CGA levels beyond the cut-off value. By contrast, only 27% (9/33) of pNET patients with tumors smaller than 2 cm had high serum CGA levels that were higher than the cut-off value. Eighty-six percent (24/28) of patients with liver metastases had serum CGA levels that exceeded the cut-off value. By contrast, only 32% (13/41) of patients without liver metastases had serum CGA levels that exceeded the cut-off value. Multivariate analysis revealed that PPI use and the presence of liver metastases were the only factors that were significantly associated with the presence of a serum CGA level beyond the cut-off value (Table 5).

Correlation coefficient between pancreatic neuroendocrine tumor and other factors. Lastly, we calculated the correlation coefficient between the serum CGA level and the level of other tumor markers or hormones (Fig. 3a). Both serum neuron specific enolase (NSE) and gastrin correlated with the serum CGA level; the correlation coefficient was 0.489 for NSE and 0.621 for gastrin. The same result was obtained by partial correlation analysis for PPI, indicating that these correlation coefficients did not interfere with PPI use. Scatter plots for the relationship between the CGA and NSE or gastrin are shown in Figure 3(b,c).

Discussion

To the best of our knowledge, this study is the first detailed investigation of the serum CGA level in patients with pancreatic diseases, including pNET, in Japan. Our study demonstrates that the serum CGA levels in Japanese patients with pNET are higher than in patients with other pancreatic diseases and controls, demonstrating that assessing the serum CGA is a useful marker for diagnosing pNET in Japan. Previously, serum CGA was generally accepted as a useful marker for diagnosing or assessing the outcome of treatment in patients with pNET in the West and the USA.[1,14–17,29] There are two reports investigating the usefulness of the serum CGA level in an Asian population with NET,[30,31] but there are none in a Japanese population. An investigation of the potential usefulness of the serum CGA levels in Japan is important for a number of reasons. It cannot be assumed that the results of Western patients can be extrapolated to Japanese patients with possible NET because there are differences between Japan and the West with respect to the epidemiology and the therapeutic effects in patients with pNET.[4,10,11] Furthermore, studies report differences in the serum/plasma levels of other tumor markers, such as PSA levels or alpha-fetoprotein levels, between Japanese/Asian populations and Western populations.[13,25] This raises the possibility that these differences may also extend to differences between populations in the serum CGA level in patients with pNET. Furthermore, the recent development of effective therapies for treating patients with advanced pNET raises the possibility that earlier diagnosis of these tumors may increase the survival rate, which has not been reported. However, presently, in Japan, no serum marker is generally used for diagnosing pNET, which is in part because none has been verified in a Japanese population as a useful marker for pNET. For these reasons, in the present study we attempted to determine

Table 3. Single and multiple regression analysis for CGA in patients with pNET

Factor	Number	Single regression analysis			Multiple regression analysis (r^2 = 0.44)	
		β	*R*	*P*-value	β	*P*-value
Sex	69	441.11	0.23	0.063	551.59	0.061
Age	69	−2.11	0.03	0.807		
PPI use	69	−151.85	0.07	0.571	−147.60	0.056
Tumor classification	69	−84.05	0.08	0.537	−72.29	0.589
Histological grade	69	315.65	0.22	0.073	186.26	0.287
Tumor size	69	−2.754	0.01	0.987		
Liver metastasis	69	667.33	0.34	0.005*	622.04	0.005*
Presence of MEN-1	69	−83.19	0.02	0.845		

*Significant difference. CGA, chromogranin A; MEN-1, multiple endocrine neoplasia type 1; pNET, pancreatic neuroendocrine tumors; PPI, proton pump inhibitor.

(a)

Group	Number	Mean	S.D.	Variance	Cut-off level	Sensitivity	Specificity	Accuracy
pNET	69	407.8	964.6	969336.7	78.7	53.6	78.6	69.1
Normal	112	62.5	48.3	2331.2				

(b)

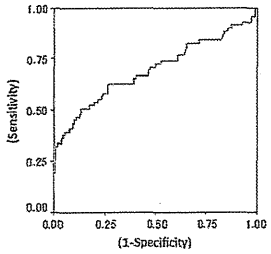

Fig. 2. (a) Result of discriminant function calculated in this study. (b) Receiver operating characteristic curve of chromogranin A for patients with pancreatic neuroendocrine tumors versus normal.

whether the serum CGA is a useful marker in Japan, as found in the West and the USA.

It is sometimes difficult to distinguish between a pNET and other pancreatic diseases, particularly between PC and a non-functioning pNET. Therefore, in the present study, we specifically evaluated whether the assessment of the serum CGA level is a useful marker in differentiating between pNET and other pancreatic diseases. It is reported that CGA levels can be elevated in patients with PC and CP,[24] and there is a case report of a patient with AIP with an elevated serum CGA level.[32] In the present study, the average serum CGA level seems high in patients with PC, CP or AIP, but the difference is not significantly different compared with the controls. The results are conflict with those reported previously for other countries.[24]

Because PPI use is known to be a significant factor for elevating serum CGA levels,[15,33–35] we examined the effect of PPI on the serum CGA levels in our Japanese patients. We found that PPI significantly increased the serum CGA levels in our patients, which was particularly true in patients with PC, CP or AIP. In patients not using PPI, the serum CGA level of patients with these pancreatic diseases was almost equivalent to that of the controls, respectively. These results indicate that the serum CGA level is a useful marker in differentiating between pNET and other pancreatic diseases and controls; however, this is only true if patients are not taking PPI. To more accurately distinguish between pNET and other pancreatic disease, PPI should be discontinued or replaced by histamine2-receptor antagonists for 2 weeks before measurement[34,35]

In Japan, prior to this study, the normal range of CGA had not been investigated or determined. Therefore, we systematically evaluated the upper limit of the standard value of the serum CGA in Japanese people by calculating the best cut-off value of CGA, which distinguishes patients with pNET from

Table 4. Univariate analysis for the factors that elevate serum CGA level in patients with pNET

Factor	Total (n = 69)	<Cut-off (n = 32)	Cut-off < (n = 37)	*P*-value
Age (years)				
Mean ± SD	57.5 ± 13.9	55.7 ± 15.1	57.2 ± 13.1	0.883
Sex (%)				
Male	39	18 (46.2)	21 (53.8)	1
Female	30	14 (46.7)	16 (53.3)	
PPI use (%)				
Yes	19	5 (26.3)	14 (73.7)	0.058
No	50	27 (54.0)	23 (46.0)	
Tumor classification (%)				
Non-functioning	39	22 (56.4)	17 (43.6)	<0.0001*
Functioning (%)				
Gastrinoma	17	1 (5.9)	16 (94.1)	
Insulinoma	10	9 (90.0)	1 (10.0)	
Others	3	0 (0.0)	3 (100)	
Histological grade (%)				
G1	40	21 (52.5)	19 (47.5)	0.290
G2	22	8 (36.4)	14 (63.6)	
Tumor size (pancreas) (%)				
<2 cm	33	24 (72.7)	9 (27.3)	0.004*
>2 cm	15	4 (26.7)	11 (73.3)	
Liver metastasis (%)				
Yes	28	4 (14.2)	24 (85.7)	<0.0001*
No	41	28 (68.3)	13 (31.7)	
Presence of MEN-1 (%)				
Yes	6	2 (33.3)	4 (66.6)	0.679
No	63	30 (47.6)	33 (52.3)	

P-value was calculated using 2 × 2 χ^2-test or Fisher's exact test. *Significant difference. MEN-1, multiple endocrine neoplasia type 1; PPI, proton pump inhibitor.

Table 5. Multivariate analysis (logistic regression analysis) for the factors that elevate serum CGA level in patients with pNET

Factor	Parameter estimate	*R*	*P*-value	Odds ratio (95% confidence interval)
PPI use	1.5144	0.16	0.038*	4.55 (1.09–18.94)
Tumor classification	0.5106	0	0.159	1.67 (0.82–3.39)
Liver metastasis	2.8367	0.39	0.0001*	17.06 (4.28–68.02)

P-value was calculated using 2 × 2 χ^2-test or Fisher's exact test. *Significant difference. MEN-1, multiple endocrine neoplasia type 1; PPI, proton pump inhibitor.

controls. Discriminant analysis revealed that the best cut-off value of the serum CGA for distinguishing patients with pNET from controls was 78.7 ng/mL, which had a sensitivity and specificity of 53.6% and 78.6%, respectively, for identifying patients with pNET. This cut-off value can be used as the upper limit of the standard value of Japanese people if this assay is used. Previous studies in Western patients report a sensitivity of serum CGA in any neuroendocrine tumor of 53–92%,[14,16,36,37] which is 50–74% in patients with pNET;[38–40] we also observed this range, demonstrating that this tumor marker has a similar sensitivity in Japanese and Western patients for identifying pNET.

In some studies[31,37,38,41] but not in others[40,42] in the West, the extent of metastatic disease and, in particular, the presence of metastatic liver diseases is one of the factors that is most frequently associated with elevated serum CGA levels and in some studies in proportion to the magnitude of increase.[37,38,40–42] In our study, both univariate and multivariate analyses revealed that the presence of liver metastases was associated with elevation of the serum CGA level in patients with pNET. In addition, in our study, the pNET group includes patients who developed liver metastases after resection of the primary pancreatic tumor as well as those with liver metastases at presentation. These results suggest that the serum CGA may also be a useful marker for detecting relapse in postoperative Japanese patients with pNET postresection. This conclusion is supported by the results from a number of Western studies.[17,43] In the univariate analysis, tumor classification and tumor size were also significantly associated with a serum CGA level exceeding the cut-off value for distinguishing between pNET and controls. This result is in agreement with some,[1,36–38,41] but not all Western studies[39] examining the effect of the primary tumor size and/or tumor classification on the serum CGA levels. With respect to tumor classification, pNET are heterogeneous tumors with different subtypes, and they may behave differently.[44] In our study, the serum CGA

(a)

Factor	Number	Correlation coefficient		Partial correlation coefficient for PPI	
		R	P value	R	P value
CA19-9	58	0.173	0.194	0.177	0.187
CEA	61	0.073	0.578	0.099	0.448
NSE	62	0.489	<0.0001*	0.489	<0.0001*
Pro-GRP	48	0.079	0.594	0.083	0.581
Insulin	58	-0.002	0.989	-0.003	0.982
Gastrin	51	0.621	<0.0001*	0.633	<0.0001*

PPI; proton pump inhibitor CA19-9; carbohydrate antigen 19-9 CEA; carcinoembryonic antigen NSE; neuron specific enolase Pro-GRP; Pro-gastrin-releasing peptide
*: significant difference

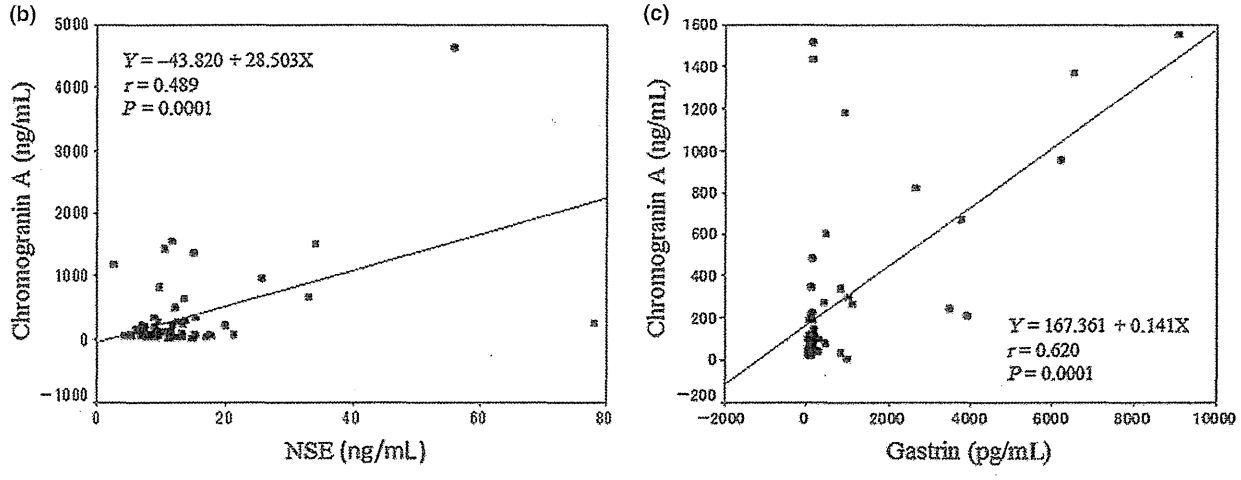

Fig. 3. (a) Correlation coefficient between serum chromogranin A levels and tumor markers in patients with pancreatic neuroendocrine tumors. Scatter plots for relationship (b) between serum chromogranin A and neuron specific enolase (c) between serum chromogranin A and gastrin.

level in patients with non-functioning pNET or with gastrinomas tend to be higher, and those with insulinomas have lower serum CGA levels, which indicates that assessing the serum CGA is likely to be more useful for non-functioning pNET and gastrinomas than for insulinomas. This conclusion is supported by the results of the correlation analysis between the serum CGA levels and serum gastrin levels in patients with pNET. These results are consistent with studies in Western patients that show a similar difference in the serum CGA levels for the subtype of pNET;[36–38,45] however, these findings differ from other studies in Western patients that do not report this correlation.[39] Our results demonstrate that it is important to consider tumor classification of pNET when measuring the serum CGA levels in Japanese patients.

Neuron specific enolase has been used as a marker for neuroendocrine tumors, especially neuroendocrine carcinoma.[36,39,46] In our study, the correlation analysis revealed that the serum CGA levels correlated with the serum NSE levels in patients with NET G1/G2. However, when the serum cut-off value of NSE was set at the level that was defined as the upper limit of normal in our institution, the sensitivity was only 25.8%. This result indicates that the serum CGA level is a more useful marker with higher sensitivity than the serum NSE level for pNET. These results are consistent with other Western studies that generally show that assessing the serum NSE is less accurate than assessing the serum CGA level in patients with either pNET or GI-NET.[36,39,46]

In addition to the points raised above, there are a number of additional conditions that can affect the CGA level. In some cases, pNET may be part of MEN-1.[1,47] Patients with MEN-1 develop endocrine tumors in multiple organs and these can affect the serum CGA levels.[17,41,45] In our study, the serum CGA levels were not significantly different between patients with pNET and co-occurring MEN-1 and those with pNET without MEN-1. The incidence of co-occurring MEN-1 in patients with pNET is different between Japan and other countries,[4] which may be associated with the difference between the results of this study and those reported previously.[17,41,45] In addition, a number of clinical conditions can result in slight elevations of the serum CGA levels, including renal sufficiency and hepatic dysfunction;[2,14,48] such conditions were not evaluated in the current study. In addition, serum CGA levels can vary with different measurement kits or samples; that is, serum or plasma.[15,48–50] In general, blood samples for measuring the serum CGA level should be collected in the resting state because the serum CGA is released with catecholamine in neuroendocrine cells by sympathetic stimulation.[51] We should standardize the conditions when measuring the CGA levels in Japan (e.g. whether the serum or plasma should be used, whether the level should be measured by RIA or IRMA or ELISA, and whether sample collection should be limited to the resting state). In this study, we used serum samples whose collection was not limited to the resting state using an ELISA kit. The CGA levels in the serum were lower than those in plasma, but there was no conclusion regarding which was better.[50] ELISA has been reported as one of the best techniques for determining the CGA level.[49,52] Furthermore, the results of the present study were similar to those of other reports that did not demonstrate whether the sample had to be collected in the resting state.[38–40] For these reasons, we considered the conditions set in this study as applicable.

In conclusion, this study demonstrates that the serum CGA level is a useful marker in patients with pNET in Japan as well as in Western countries, as previously reported,[1,14,16,29] especially in patients with gastrinomas or non-functioning tumors with the presence of liver metastases and larger tumors. pNET are uncommon and variable diseases, as described above; therefore, the availability of a tumor marker should be clinically helpful for diagnosis and treatment. The diagnosis of these patients is of particular importance at present because of the description of newer treatments, which are effective for patients with advanced disease. Our studies suggest that the serum CGA levels may fulfill this need; however, it is important for clinicians to remember that other clinical factors can affect serum CGA levels, such as PPI use, which should be factored into the interpretation of the results.

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Disclosure Statement

The authors have no conflict of interest to declare.

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