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DGGR-Lipase:
(1,2-o-dilauryl-rac-glycero-3-glutaric acid-(6'-methylresorufin) ester lipase assay)

A retrospective study of 171 feline cases with increased DGGR-Lipase

Diploma thesis

University of Veterinary Medicine Vienna

submitted by

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List of Abbreviations	
CT	Computer tomography
fPLI	Serum feline pancreatic lipase immunoreactivity
DGGR-Lipase	1,2-o-dilauryl-rac-glycero-3-glutaric acid-(6'-methylresorufin) ester lipase assay
AP	Acute pancreatitis
CP	Chronic pancreatitis

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1 Introduction

Pancreatitis is defined as an inflammation of the pancreas. The pancreas is located in the cranial abdomen and belongs to the digestive and endocrine organs. Building digestive enzymes as well as hormones like insulin and glucagon, it can also be classified by the exocrine and endocrine functions. The inflammation of the pancreas can cause mild to severe symptoms, even life-threatening conditions are possible.

Pancreatitis in cats has been underestimated in the past. Different than expected, pancreatitis is as commonly diagnosed in cats as in dogs and humans. Unfortunately, diagnostics and therapy remain very challenging (1).

Clinical signs like anorexia, lethargy, dehydration and vomiting seem to occur frequently but are too unspecific to form a diagnosis (2,3).

When it comes to diagnostic imaging, ultrasonography is the method of choice. The sensitivity of abdominal ultrasound has a wide range. The success highly depends on the experience and expertise of the ultra-sonographer as well es the quality of the ultrasonic device (4).

Histopathology still presents the gold standard for diagnosing pancreatitis in cats (2,5). However, sampling can also lead to severe complications. It is described that intraoperative manipulation as well as the biopsy itself can trigger pancreatitis. Also, ischemia induced pancreatitis can develop due to anaesthesia associated hypotension (1). Considering the possible risks, these methods are rarely used.

Over the last decades additional laboratory tests for diagnosing pancreatitis were invented. In the past an increased amylase was associated with pancreatitis. Due to low sensitivity and specificity the amylase is not considered a valuable test for diagnosing pancreatitis anymore (1,6).

The fPLI (feline pancreas specific lipase) (7) and DGGR-Lipase (1,2-o-dilauryl-rac-glycero-3-glutaric acid-(6'-methylresorufin) ester lipase assay) seem to have particular importance for the diagnosis of pancreatitis (8). These minimal invasive diagnostic methods have led to a more frequent and earlier diagnosis of pancreatitis in cats. This could enable an earlier start of treatment and a better outcome. But still prospective studies for the comparison of the two diagnostic methods are lacking (9,10).

The aim of this study was to examine if the DGGR-Lipase is a useful and reliable diagnostic tool in cats suffering from pancreatitis with and without additional diseases.

The hypothesis was that the DGGR-Lipase may not be used as a single diagnosing tool for pancreatitis in cats (1).

2 Background

2.1 Structure of the Pancreas

The pancreas belongs to the organs of the digestive and the endocrine system, and can be classified into its exocrine and endocrine function (11).

Anatomically, the pancreas is divided into a body (Corpus pancreatis) and two limbs. The right limb (Lobus pancreatis dexter) lies on the inner curvature of the duodenum. The left limb (Lobus pancreatis sinister) is located beside the cranial part of the transverse colon. The pancreatic duct and the bile duct enter the duodenum on the major duodenal papilla. Cats and dogs can have an accessory duct that joins the duodenum on the minor duodenal papilla (11,12).

Only one pancreatic duct that joins the common bile duct before entering the duodenum is something humans and cats have in common (13).

The main blood supply of the pancreas originates out of the cranial mesenteric and the coeliac artery. The pancreatic veins accompany the arteries and drain into the portal vein (14).

The pancreas is innervated by parasympatomithetic and sympatomimethetic nerves. The vagal trunk (Truncus vagalis dorsalis) enables the parasympathetic innervation. The solar plexus (plexus solaris) releases the sympatomimethetic fibres (14).

The lymph fluid is drained by the pancreaticoduodenal lymph nodes (14).

2.2 Physiology

The exocrine pancreas is responsible for the production of various digestive enzymes. These enzymes support the digestion of carbohydrates, proteins and fats. The acini merge into smaller ducts which drain into the main pancreatic duct and finally join the duodenum. The following proenzymes are being secreted by acini cells. They are partially active forms of enzymes and partially inactive, in order to protect the pancreatic tissue from self-digestion.

Trypsinogen, chymotrypsinogen, pancreatic elastase, pancreatic procarboxypeptidases A and B belong to the inactive proteases. The lipases consist out of the active lipase and

cholesterinesterase, as well as the inactive pro-colipase and pro-Phospholipase A2. Also, the nucleases and the alpha amylase are being secreted in an active form.

The enzymes are being released in the zymogen granules and activated by trypsin. Depending on the composition of the diet, the amount of the individual enzymes can differ. To prevent the activation within the pancreas itself a trypsin inhibitor is excreted as well.

The endocrine pancreas consists out of the pancreatic islets. When the level of glucose decreases, alpha cells produce glucagon. This leads to a higher level of blood glucose. High blood glucose levels stimulate beta cells to produce insulin. Delta cells produce somatostatin which can decrease glucagon and insulin concentrations (15).

2.3 Pathophysiology

A Pancreatitis is the inflammation of the pancreatic tissue. It is the most frequent issue of the exocrine pancreas in cats. It can be divided into the acute and chronic form. Both, the acute and the chronic form of the pancreatitis can cause similar clinical signs. Especially chronic Pancreatitis can appear as a primary disease but tend to appear in connection with many other pathologies. The acute and the chronic pancreatitis can only be differentiated through histopathology.

The pancreatic inflammation is triggered by the activation of trypsin within the acinar cells. Several causes, such as oxidative stress, hypotension or blockage of the acinar cell apex in the pancreatic duct are possible. The so-called trypsin inhibitor can only manage to neutralize up to 10% of the intracellular activated trypsin. Then, active digestive enzymes are set free into the pancreatic tissue. These lead to local irritations and the activation of the inflammatory cascade. Additionally, reactive oxygen species and nitric oxide are produced. Neutrophils as well as endothelin 1 and phospholipase A3 are suspected to induct cell necrosis. Pancreatic edema is caused by the increased vascular permeability due to inflammation (3).

2.4 Etiology

Currently there are no signs of an age, sex or breed predisposition for pancreatitis (1,5).

Different genetic associations were found in humans. The correlation between genetics and a pancreatitis in cats has not been studied yet. Also, gender associations could not be proven (3).

Hypertriglyceridemia and obesity, as well as dietary impacts have an important meaning for the development of pancreatitis in dogs (3). Whereas pancreatitis in cats is not associated with body condition score, dietary indiscretion, or drug history (1).

Infections and pancreatitis occurring simultaneously can affect dogs and cats. Although it occurs only rarely, various infections can trigger a pancreatitis (1,16,17). Trauma, such as high-rise-syndrome in cats, as well as minimally invasive and surgical interventions are among the risk factors for cats developing pancreatitis (3). Ischemia induced pancreatitis can develop due to anaesthesia associated hypotension or other conditions causing a decreased blood supply of the pancreas (1,5).

Certain diseases seem to affect cats more often in connection with pancreatitis. These include diabetes mellitus, chronic enteropathies, hepatic lipidosis, cholangitis, nephritis, and immune-mediated haemolytic anaemia (1,18–21). It is still unknown if these are potential risk factors for developing pancreatitis or not (1,20,22).

2.5 Forms of Pancreatitis

Histopathology represents the only diagnostic tool which, can differ between acute and chronic pancreatitis. Biopsy is only rarely performed, the most histologic changes originate from necropsy material (1,5,23).

2.5.1 Acute Pancreatitis

Acute pancreatitis (AP) affects mostly the pancreatic interstitial and adipose tissue, while the ducts and the centrilobular tissues do not show signs of inflammation in the beginning of the disease.

Histologically acute pancreatitis is marked by neutrophilic cells, edema and necrosis. The necrosis often spreads over the adjoining adipose and mesenchymal tissue. Also, an overlap of AP and chronic pancreatitis (CP) is possible (2).

2.5.2 Chronic Pancreatitis

CP is characterised by lymphocytic invasion, fibrosis and acinar atrophy. An interstitial oedema can also occur. Also, an overlap of AP and CP is possible (2). Fibrosis can extend through the interlobular septa and even spread into the lobules. Periductal fibrosis can cause local stenosis and cysts (1).

Depending on the progression of the disease, the pancreatitis can result in a mild form or develop severe complications (2).

2.6 Clinical Signs

The majority of cats do not show any specific symptoms. Anorexia, lethargy, dehydration and vomiting are the most frequent clinical signs. Abdominal pain is one of the leading signs for pancreatitis in dogs. The evaluation of abdominal pain in cats can be very difficult, therefore clinicians often fail to recognize it. The type and the severity of the pancreatitis cannot be differentiated based on the clinical appearance (2).

Table 1 - Common Historical and Clinical Signs of Pancreatitis in Cats from three separate studies

Clinical Sign	**Study**				**Total**	**Overall Prevalence**
	Stockhaus et al.	*Ferreri et al (ANP)*	*Ferreri et al (CP)*	*Hill & Winkle*		
Number of cats	33	30	33	40	136	
Inappetence	32 (97%)	19 (63%)	23 (70%)	39 (98%)	113	83%
Lethargy	33 (100%)	15 (50%)	17 (52%)	40 (100%)	105	77%
Dehydration	24 (73%)	10 (33%)	17 (52%)	37 (93%)	88	65%
Vomiting	18 (55%)	13 (43%)	13 (39%)	14 (35%)	58	43%
Icterus	6 (18%)	5 (16%)	8 (24%)	21 (53%)	40	29%
Weight loss	3 (9%)	12 (40%)	7 (21%)	NS	22	16%
Abdominal pain	17 (52%)	NS	NS	10 (25%)		

Table 1 shows the clinical signs of pancreatitis which are collected from three different studies. Cats from one study (Ferreri et al. 2) are subdivided into acute necrotizing (ANP, n=30) and chronic nonsuppurative (CP, n=33) pancreatitis. NS= Not specified Overall prevalence is rounded to the nearest whole percentage volume. (3)

2.7 Laboratory Findings

Acute and chronic pancreatitis cannot be differentiated by any laboratory result. Complete blood count and serum biochemical profile is usually performed (4). Cats with pancreatitis often show abnormalities in the number of Leukocytes (46%), a change of haemoconcentration (2). Some patients also tend to have higher liver enzymes and total bilirubin. Also, hypoglycaemia has been reported in 10-64% of the cases. Hypocalcaemia (32-61%) and hypokalaemia (56%) have also been found more frequently in cats with pancreatitis (2,4).

Serum creatinine, blood urea nitrogen (BUN), and symmetric dimethylarginine (SDMA) concentrations can be increased due to dehydratation or either chronic or acute renal failure. Azotemia can be a sign of progression (1).

Hypocalcaemia often correlates with a more severe stage of the pancreatitis and can be a valuable indicator for more aggressive treatment. A change of biochemical parameters such as increased levels of liver enzymes, bilirubin or abnormal concentrations of electrolytes can be caused by common comorbidities such as hepatic lipidosis and diabetes mellitus. The diagnosis of frequent comorbidities plays a major role in the arrangement of the therapy (3).

2.8 Diagnostic Imaging

X-rays of cats with an acute pancreatitis can show abnormalities like reduced abdominal contrast, dilatation of bowel loops and pleural effusion. Unfortunately, these radiographic changes are non-specific and only show a poor sensitivity for pancreatitis. Also, there are no characteristics for radiographic imaging for cats suffering from a chronic pancreatitis. Therefore, x-rays are not the method of choice for diagnosing pancreatitis (3).

Abdominal ultrasound is the gold standard of the imaging techniques when it comes to pancreatitis. Unfortunately, it is only of limited value for the diagnoses because it is nor specific nor sensitive for the inflammation of the pancreas. The sensitivity of abdominal ultrasound for diagnosing a pancreatitis range from 11 – 69% and highly depends on the experience and expertise of the ultra-sonographer, as well es the quality of the ultrasonic device. Still, it is recommended to rule out other diseases (4).

Changes in the pancreatic thickness, margination, echogenicity of the peripancreatic fat and the pancreas itself, as well es the dilatation of the pancreatic duct or the small bowel can be detected with ultrasonography in cats with pancreatitis. Low echogenicity is the result of necrosis of the parenchyma or a mass effect. High echogenicity is caused by fibrosis or the necrosis of the peripancreatic fat (24).

2.9 Cytology

Aspirates of an acute inflamed pancreas are highly cellular and characterised by neutrophilic cells, which show a different degree of degeneration. The background is usually marked by amorphous, necrotic material, which can as well contain refractile crystalline structures (1,25).

The occurrence of dysplastic cells makes it difficult to differentiate between primary pancreatitis and an inflamed pancreatic carcinoma, although this kind of neoplasia is only rarely seen in cats (1,26–28).

Chronic pancreatitis often results in a low cellularity aspirate (1,27). If the sampling is successful, the cell population consists out of lymphocytes, plasma cells and sporadically neutrophils.

Because of the possibility of a focal inflammation, an absence of inflammatory cells does not exclude an acute nor a chronic pancreatitis (1,27,28).

2.10 Histopathology

Histopathology presents the gold standard for diagnosing pancreatitis in cats (1,2,5). A scoring system was designed, because no detailed guideline for histopathologic changes and their interpretation can be found in the current literature (5).

Table 2 - Semiquantitative histopathology scoring system

	Acute pancreatitis		**Chronic pancreatitis**		
	Acute suppurative pancreatitis	**Acute necrotising pancreatitis**			
Lesion	*Inflammation, neutrophilic*	*Edema and fat necrosis*	*Inflammation, lymphocytic/mononuclear*	*Fibrosis*	*Cystic degeneration*
Score 0	/	/	No or only isolated lymphocytes or erratic small nests of lymphocytes	/	/
Score 1	Mild infiltration (<25% of the parenchyma affected)	Mild (<25% of the parenchyma affected)	Mild mononuclear infiltrate (<25% of the parenchyma affected)	Mild thickening of septa or multifocal areas of mild interstitial fibrosis (<15% of the parenchyma affected)	≤3 cysts
Score 2	Moderate infiltration (25%-50% of the parenchyma affected)	Moderate (25%-50% of the parenchyma affected)	Moderate mononuclear infiltrate (25%-50% of the parenchyma affected)	Moderate thickening of most septa (15%-30% of the parenchyma affected)	4-5 cysts
Score 3	Severe infiltration (>50% of the parenchyma affected)	Severe (>50% of the parenchyma affected	Severe mononuclear infiltration (>50% of the parenchyma affected)	Severe thickening of all septa, dissecting the lobules (>30% of the parenchyma affected)	≥6 cysts
Disease index	**Total score: 1-2 mild AP, 3-4 moderate AP, 5-6 severe AP**		**Total score: 1-2 mild AP, 3-4 moderate AP, 5-6 severe AP**		

Table 2 visualizes the semiquantitative histopathology scoring system for pancreatitis in cats (1,5)

Biopsy is only rarely performed and only indicated for cats with severe pancreatitis. Unfortunately, exactly these patients cannot be undertaken anaesthesia. Also results have a poor impact on the further therapy. (4)

2.11 Pancreas Specific Diagnostic Tests

Unspecific clinical signs, the lack of sensitivity in diagnostic imaging and the biopsy as a rather invasive diagnostic method, make it hard to detect pancreatitis. Because of that finding a sensitive, specific and minimally invasive diagnostic tool is of great interest. The following paragraphs describe the most used tests.

2.11.1 Lipase and Amylase

Not only pancreatic tissue but also the gastric mucosa and the hepatic parenchyma, as well es many other organs can lead to an increased level of amylase and lipase. (Simpson et al. 2001) Because of lack of sensitivity, neither lipase nor amylase is recommended for the diagnose of feline pancreatitis (23,29).

2.11.2 Feline Pancreatic Lipase Immunoreactivity (fPLI)

Feline pancreatic lipase immunoreactivity (fPLI) is a species-specific immunoassay that measures the pancreatic lipase and allows to rule out or diagnose feline pancreatitis. Unlike the traditional analysis like lipase or amylase, fPLI is specific for the pancreas lipase activity and is not affected by the increase of Lipase in any other organ (such as the stomach, duodenum). The traditional catalytic assays have a poor clinical specificity (30). Until now the Feline pancreatic lipase immunoreactivity is believed to be the best available test (30,31).

The test is available as a qualitative SNAP-fPLI for in-house measurements to exclude a pancreatitis and as a quantitative Specific fPLI assay (30).

2.11.3 DGGR-Lipase

The DGGR assay is a colometric catalytic assay based on the use of 1,2-o-dilauryl-rac-glycero-3-glutaric acid-(6′-methylresorufin) ester as a substrate for pancreatic lipase activity (9).

Because DGGR is not only hydrolysed by pancreatic tissue, the specificity of the DGGR assay is questionable (32).

One study showed that cats with kidney disease have a signific higher DGGR-Lipase than healthy cats. However, most of the results were within the reference range and therefore not clinically relevant (33).

Nonetheless the DGGR assay seems to be a valuable method compared to the fPLI. Specificity and sensitivity were not significantly different. Sensitivity and specificity were 48% and 63% for DGGR-Lipase (cut-off, 26 U/L) and 57% and 63% for Spec fPL (>5.3 µg/L) (31).

2.11.4 Serum Feline Trypsin-Like Immunoreactivity (fTLI)

Trypsin-like immunoreactivity is measured using a species-specific immunoassay. It detects trypsinogen and trypsin, which are produced by the pancreatic acinar cells.

Chronic pancreatitis can lead to pancreatic atrophy and therefore an exocrine pancreatic insufficiency. Exocrine pancreatic insufficiency is characterized by a decreased secretion of digestive enzymes and ultimately leads to decreased TLI levels (1). On the other hand, acute pancreatitis can be associated with an increased level of TLI (1,34).

Also, chronic enteropathies, gastrointestinal lymphoma and an increased glomerular filtration rate can cause rising TLI levels (1,6).

However feline trypsin-like immunoreactivity (fTLI) could not be associated with clinical signs, nor the histopathologic diagnosis of cats with pancreatitis and is therefore not a valuable method for the diagnostics (1,34).

3 Materials and Methods

3.1 Study Design

The study includes 805 cases of cats and 1149 measurements of the DGGR-Lipase values. 888 of the measurements were rated as negative, 261 as positive. Only the first DGGR value in the specified time period was evaluated in this study. After the exclusion of multiple measurements, the number of cases with an increased DGGR-Lipase was limited to 179. 8 patients were retrospectively excluded since no history data was available.

All patients were examined at the Small Animal Hospital of the University of Veterinary Medicine in Vienna in between May 2017 and May 2019. The study includes cats from different breed, sex, age and weight.

Based on the levels of the DGGR-Lipase as well as the clinical examination, laboratory results, diagnostic imaging and pathological examinations, the cats were divided into two groups.

Group 1 includes 58 cats with increased DGGR-Lipase levels that were confirmed by a clinical examination and further diagnostic methods.

Group 2 includes 70 patients with increased DGGR-Lipase levels and contrary results of the clinical examination as well as the ultrasound and further diagnostics.

The rest of the cats were excluded from further evaluation due to a lack of clinical records.

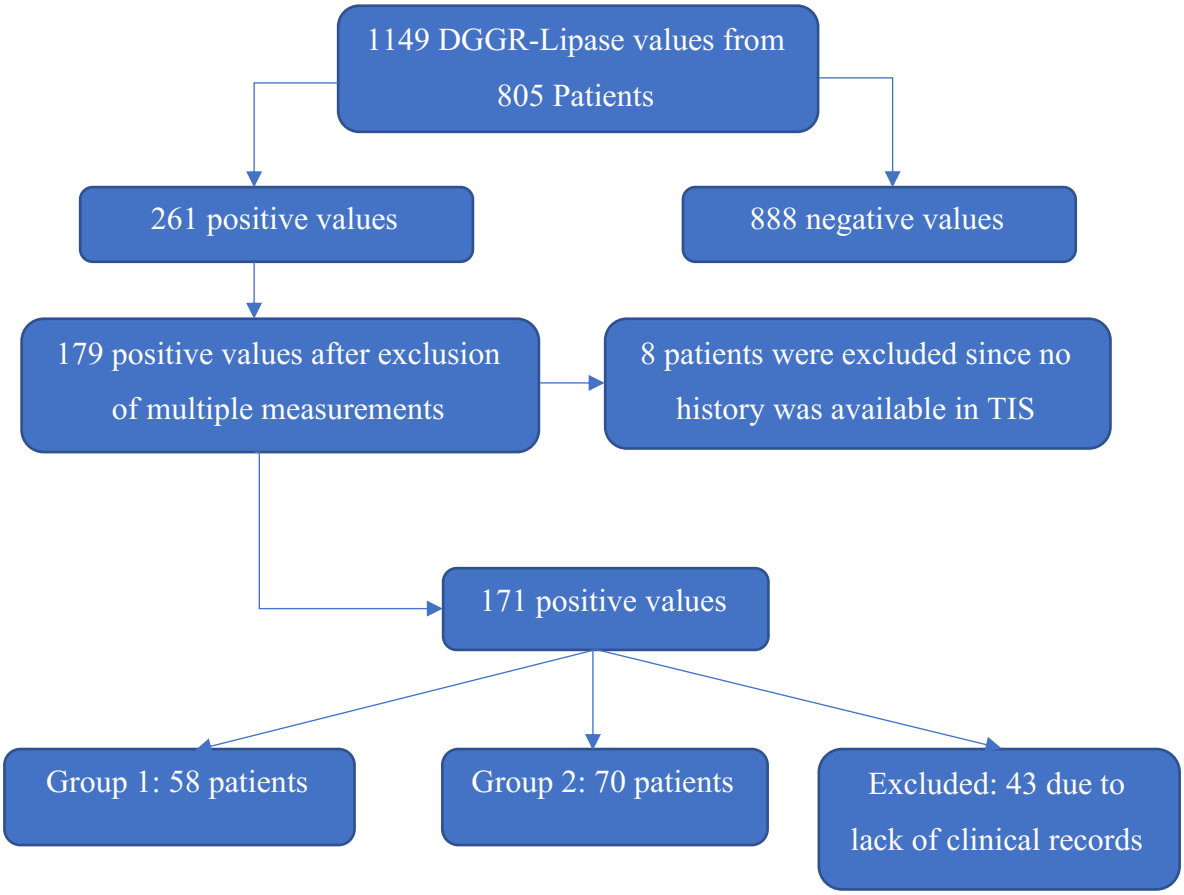

Figure 1 - Grouping of the Cats

Figure 1 shows the grouping of the patients. In total 171 cats were chosen to be part of this study. 58 patients were admitted to group 1. Group 2 consists out of 70 patients. 43 patients were excluded, due to lack of clinical records.

3.2 Inclusion Criteria

The inclusion criteria were based on an abnormal serum concentration of the DGGR-Lipase. All 171 patients had an equal or higher DGGR-Lipase than 30 U/L. Only the first increased level of DGGR-Lipase in the specified period was evaluated. The clinical examination, diagnostic imaging, laboratory results and further examinations like FNA and Biopsy of the pancreas were considered as well.

The most common clinical signs according to literature (3) such as Inappetence, lethargy, dehydration, vomiting, icterus, weight loss, diarrhea and abdominal pain were evaluated

retrospectively for each patient. The associated clinical examination was done within 24 hours prior or after the blood sampling for the DGGR Lipase. The examinations were performed by clinicians of the Animal Hospital of the University of Veterinary Medicine in Vienna. Further, the patient's history was checked for any pre-existing illnesses.

For the diagnostic imaging, a special emphasis was laid upon the ultrasonographic evaluation of the abdomen, and more specifically the pancreas. The examination was always done by radiologists of the Department of Diagnostic Imaging at the University of Veterinary Medicine Vienna. The closest possible ultrasonographic examination to the blood samples for the DGGR Lipase was evaluated. The same applies to the few CT scans that were included.

Further clinical blood count and blood chemistry parameters were examined simultaneously to the DGGR-Lipase levels. The clinical blood count included parameters such as neutrophil cells/µl and erythrocytes/10^6. For the blood chemistry an increase of the liver enzymes such as the ALT, AP and GGT, as well as blood glucose levels were taken into consideration. For some cases a SNAP-fPLI was performed, in these cases the results were also taken into account. The reference values set for healthy cats, are under 100 U/L for the ALT, under 30 U/L for the AP and under 3 U/L for the GGT. Additionally, it was also examined if the patients had shown an electrolyte imbalance, which is expressed as an increase or decrease of kalium, calcium or glucose.

In some cases, more invasive methods like FNA or Biopsy of the pancreas were performed for further diagnostic security. The FNA and the Biopsy took place under general anesthesia, done by anesthetists of the University of Veterinary Medicine Vienna. The samples were either taken by clinicians of the surgery department or the clinical unit for diagnostic imaging. Some of the biopsies were collected postmortem by the department of pathology.

3.3 Statistical Analysis

The statistical analysis relied on a descriptive approach. For the DGGR-Lipase a chi-square test was performed including the Jarque-Bera Test to evaluate the normal distribution of the values. A Mann-Whitney-U Test was performed to evaluate differences regarding de DGGR-Lipase values between group 1 and group 2.

4 Results

4.1 DGGR-Lipase

In group 1 58 DGGR-Lipase values were evaluated. The median was 66.50 U/L. The mean value was 158.62 U/L with a standard deviation of 262.90 U/L. The Jarque-Bera test was 106.29 with a significant chi-square test with a $p < 0.01$. Therefore, the values were not normally distributed.

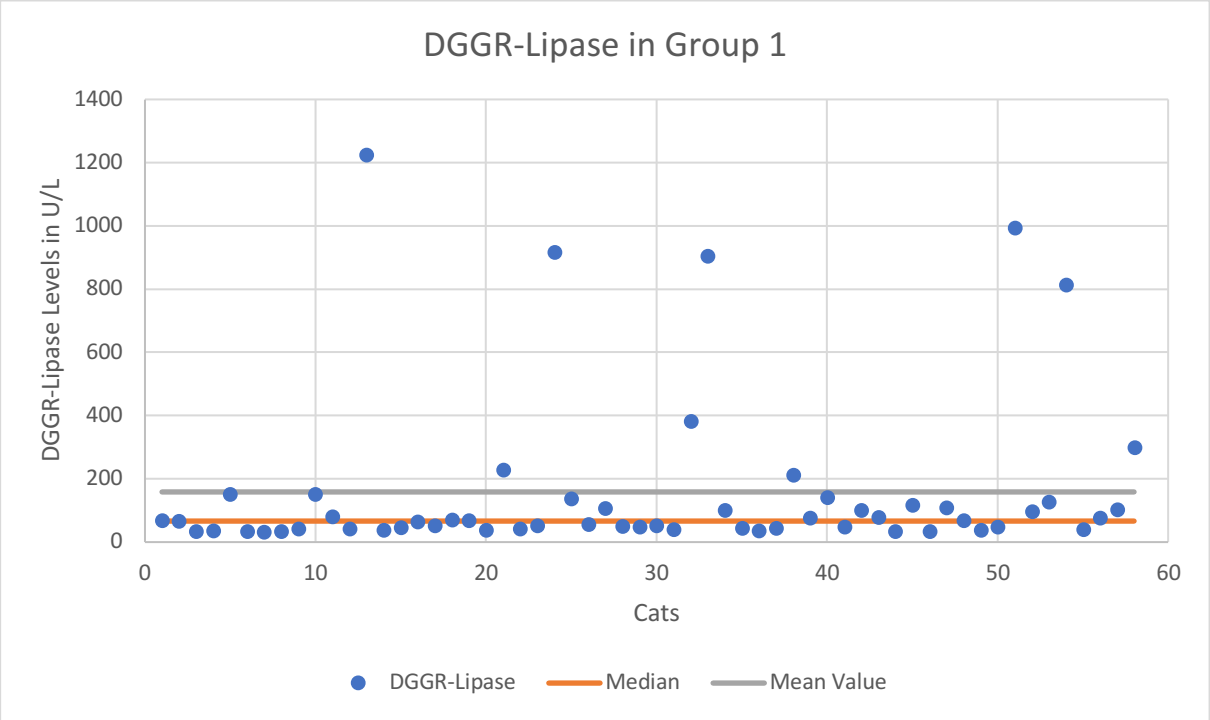

Figure 2 - DGGR-Lipase Levels in Group 1

Figure 2 shows the DGGR-Lipase levels in group 1. The median within this group was 66.50 U/L. The mean value was 158.62 U/L.

In group 2 70 DGGR-Lipase values were evaluated. The median was 48.00 U/L. Meanwhile the mean value was 71.21 U/L and the standard deviation was 105.61 U/L. As well as in group 1 the values were not normally distributed. This was also evaluated with the Jarque-Bera Test.

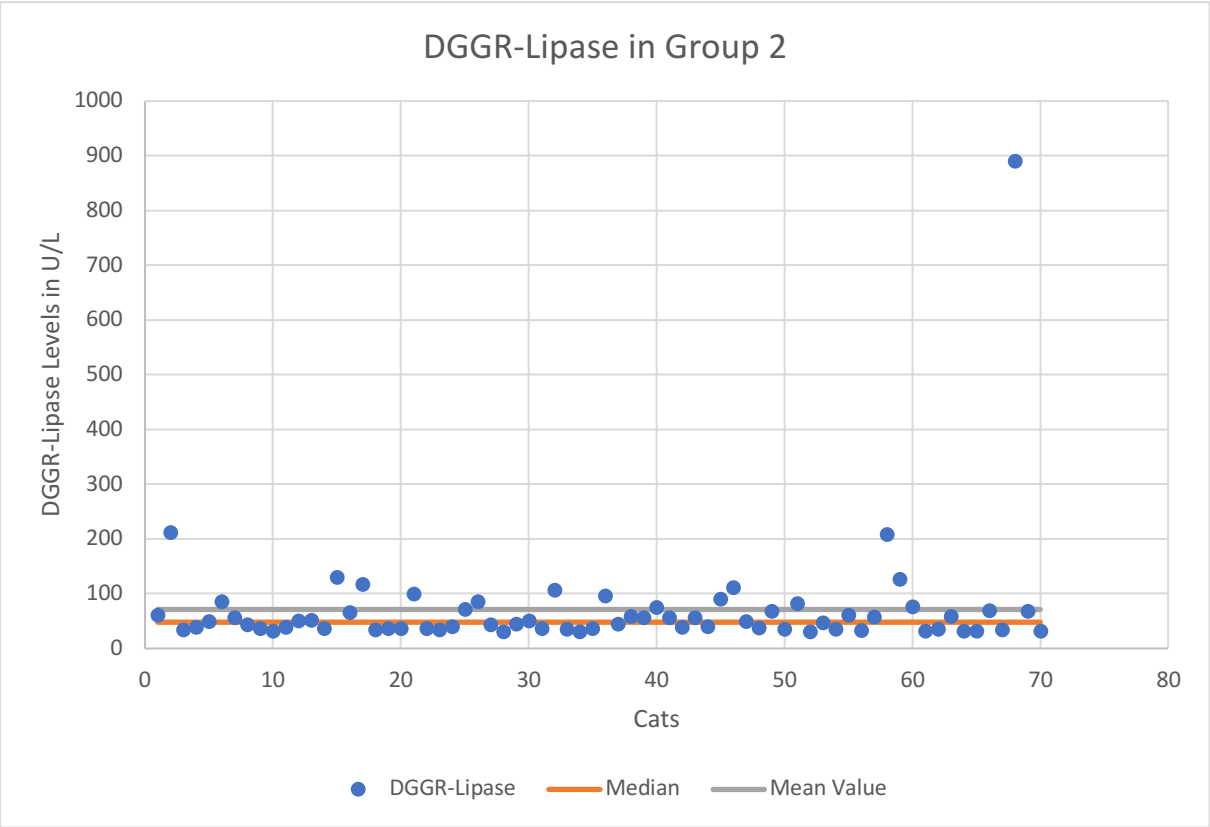

Figure 3 - DGGR-Lipase Levels in Group 2

Figure 3 shows the DGGR-Lipase levels in group 2. The median was 48.00 U/L, while the mean value was 71.21 U/L.

The DGGR-Lipase levels in between the two groups differed significantly in the Mann-Whitney U test with a p-value of 0.01.

Table 3 - Mann-Whitney U Test for the DGGR-Lipase

	Rank sum	Count	U-Statistic
Group 1	4280	58	2569
Group 2	3976	70	1491
EU	2030		
s2	43645		
s	208,91		
z1	2,58		
z2	-2,58		
p	<0.01		

Table 3 shows the results of the Mann-Whitney U Test

4.2 Clinical Examination

Table 4 - Comparison of clinical examination parameters between the two groups

Clinical examination				
Clinical signs	Group 1		Group 2	
	Total numbers	*Percentage (%)*	*Total numbers*	*Percentage (%)*
Inappetence	49/58	84.48	45/70	64.29
Lethargy	38/58	65.52	34/70	48.57
Dehydration	48/58	82.76	47/70	67.14
Vomiting	29/58	50.00	28/70	40.00
Icterus	5/58	8.62	10/70	14.29
Weight loss	25/58	43.10	17/70	24.29
Diarrhea	14/58	24.14	14/70	20.00
Abdominal Pain	20/58	34.48	10/70	14.29

Table 3 shows the comparison of the evaluated clinical parameters between group 1 and group 2. The represented clinical signs are the most common symtoms of pancreatitis in cats according to literature (3)

For each patient clinical signs, including inappetence, lethargy, dehydration, vomiting, icterus, weight loss, diarrhea and abdominal pain were retrospectively evaluated and compared in between the two groups. Group 1 showed a tendency of suffering more commonly from clinical signs than group 2. Only icterus and diarrhea seemed to occur more frequently in group 2.

The two most occurring clinical signs in both groups were inappetence and dehydration. 49/58 (84.48 %) of the patients in group 1 were presented with inappetence, in comparison 45/70 (64,29 %) of the cats in group 2 suffered from inappetence. The second most common clinical sign in group 1 was dehydration with 48/58 (82.76 %) of the patients being affected. 47/70 (67.14 %) of the patients in group 2 were presented with dehydration.

38/58 (65.52 %) of the patients in group 1 showed lethargy during the evaluation period, whereas only 34/70 (48.57 %) of group 2 were presented as lethargic.

Vomiting applied to 29/58 (50.00 %) of the patients in group 1 and to 28/70 (40.00 %) of the cats in group 2. Directly followed by weight-loss, which was found in 25/58 (43.10 %) participants in group 1 and in 17/70 (24.29 %) in group 2.

20/58 (34.48 %) patients in group 1 suffered from abdominal pain. In group 2 abdominal pain was only diagnosed in 10/70 (14.29 %) cats.

14/58 (24.14 %) patients of group 1 and 14/70 (20.00 %) in group 2 were presented with diarrhea.

Icterus however affected only 5/58 (8.62 %) cats in group 1. Otherwise, 10/70 (14.29 %) patients in group 2 showed clinical signs of an icterus.

4.3 Diagnostic Imaging

All patients in group 1 underwent an abdominal ultrasound. In 56/58 (96.55 %) patients ultrasonographic changes which were compatible with the diagnosis of pancreatitis could be evaluated.

In group 2 66/70 (94.29 %) cats underwent an abdominal ultrasound. Only 13/66 (19.69 %) showed ultrasonographic changes that were suspicious of pancreatitis. Further 2 cats in group 2 even had a CT-scan with no suspicion of pancreatitis.

4.4 Histopathology and SNAP- fPLI

Table 5 - Further diagnostic methodes

Method	Group 1		Group 2	
	Total numbers	*Percent (%)*	*Total numbers*	*Percent (%)*
Biopsy	3/58	5.17	0/70	0
FNA	8/58	13.79	1/70	1.43
SNAP-fPLI	9/58	15.52	2/70	2.86

Table 4 shows further diagnostic methods and the number of patients they have been used in group 1 and group 2

Biopsy was performed in 3/58 (5.17 %) patients in group 1. FNA was done in 8/58 (13.79 5) of cats in group 1 and 1/70 (1.43 %) of participants in group 2. The patient who underwent FNA in group 2 had no cytological signs of pancreatitis. Except for 1 all the patients who underwent

biopsy or FNA in group 1 showed cytologic changes that were compatible with the diagnosis of pancreatitis.

A SNAP-fPLI was performed in 9/58 (15.52%) in group 1 and 2/70 (2.86%) in group 2 to secure the pancreatitis diagnose additionally. In group 1 all SNAP-fPLI tests confirmed the suspicion of pancreatitis. In group 2 the SNAP-fPLI helped to rule out the suspicion of pancreatitis in 1 cat and the other cat was tested false positive.

4.5 Pre-existing illnesses

With 96.55 % most of the patients in group 1 suffered from additional diseases. All the participants, who were admitted to group 2 were diagnosed with another illness.

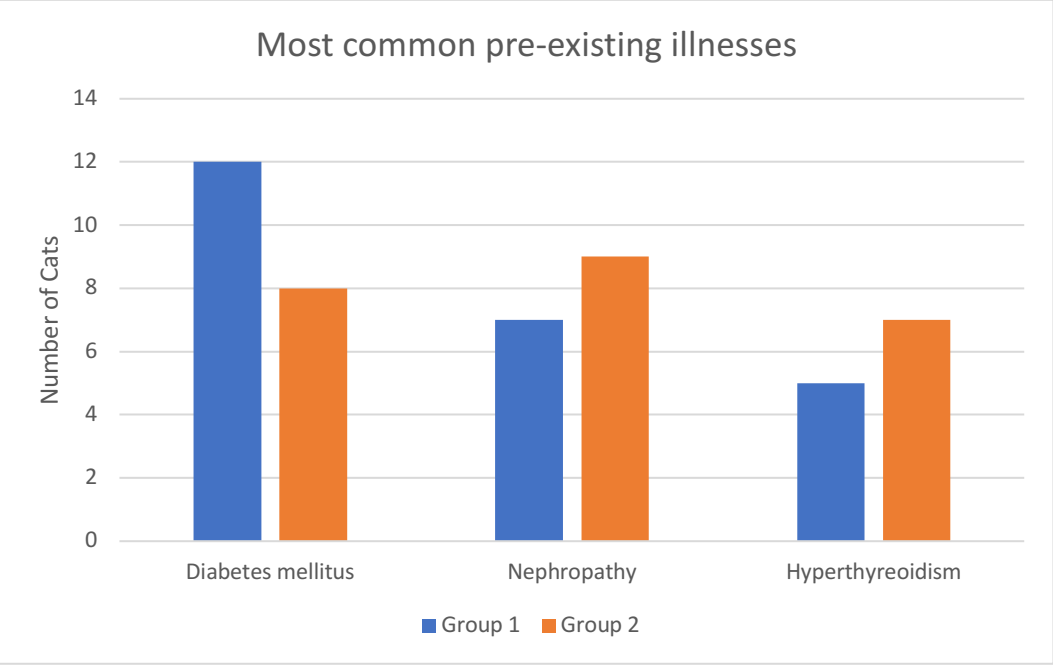

Figure 4 - Comparison of the 3 most common pre-existing illnesses in our study population

Figure 4 shows the graphs of patients who have been suffering from Diabetes mellitus, Nephropathy and Hyperthyroidism in group 1 and group 2

Table 6 - Most common pre-existing illnesses

Most common pre-existing illnesses						
Groups	Diabetes		Nephropathy		Hyperthyroidism	
	Total numbers	Percent (%)	Total numbers	Percent (%)	Total numbers	Percent (%)
Group 1	12/58	20.69	7/58	12.07	5/58	8.62
Group 2	8/70	11.43	9/70	12.86	7/70	10.00

Table 5 shows the numbers of patients who have been suffering from Diabetes mellitus, Nephropathy and Hyperthyroidism in group 1 and group 2

12/58 (20.69 %) cats in group 1 were previously diagnosed with diabetes mellitus. In comparison 8/70 (11.43%) cats in group 2 suffered from diabetes mellitus.

The second most common illness was a kidney disfunction. 7 out of 58 (12.07%) patients in the group 1 had a nephropathy. 9 out of 70 (12.86 %) patients in group 2 were diagnosed with a nephropathy before entering the study.

Only 5 out of 58 (8.62 %) cats in group 1 were having hyperthyroidism at the time of examination. In contrast 7 out of 70 (10.00 %) patients of group 2 were suffering from hyperthyroidism.

5 Discussion

The hypothesis was that the DGGR-Lipase may not be used as a single diagnosing tool for pancreatitis in cats.

The aim of this study was to examine if the DGGR-Lipase is a useful and reliable diagnostic tool in cats suffering from pancreatitis with and without additional diseases.

The DGGR-Levels between the two groups showed a significant difference with a p-value of 0.01. Nevertheless, it is important to mention that most of the evaluated patients were put into group 2 (70 cats) compared to group 1 (58 cats). Therefore, the diagnosis of pancreatitis was declined after further investigation. Maybe another cut-off value for the DGGR-Lipase would be a suitable choice and may show better sensitivity, but further studies are necessary to prove that hypothesis. Another explanation may be, that the DGGR-Lipase is influenced by additional diseases.

Although there are no pancreatitis specific clinical signs, studies have shown that inappetence, lethargy, dehydration, vomiting, icterus, weight loss, diarrhea, and abdominal pain occur more often in cats with pancreatitis. Regarding the high number of patients with pre-existing illnesses, it was not surprising that the participants of group 1 as well as the ones of group 2 were having additional diseases.

However, there was a trend that patients in group 1 suffered more often and more severely from clinical symptoms than those in group 2. Nonetheless, all the frequently occurring symptoms, unlike in human medicine, are nonspecific. In human patients, abdominal pain is one of the leading signs of pancreatitis. It is unknown if cats experience less pain or are just less likely to show it. Experts assume that under recognition is the main reason for the low number of cats suffering from abdominal pain (1).

Ultrasonography was the most applied imaging method. In the group 1, 56/58 (96.66 %) of the ultrasound results were pancreatitis suspicious. Only 13/66 (19.69 %) of the undergone ultrasounds in group 2 were indicating pancreatitis. Studies have shown that success is highly dependent on the experience and expertise of the ultra-sonographer, as well as the quality of the ultrasonic device (4). The CT examination was rarely performed and plays a minor role in pancreatitis diagnostics.

A biopsy of the pancreas is still the gold standard for diagnosing pancreatitis. However, it was only performed on 3 cats in group 1. FNA was performed in 8 cats in group 1 and 1 cat in group

2. Except for one all the biopsies and FNAs in group 1 turned out positive. None of the cats in group 2 had histopathological changes suspicious of pancreatitis. The one who was an exception was diagnosed with a pancreas lymphoma but with suspicion of secondary pancreatitis, diagnosed through clinical examination as well as an ultrasound. Although biopsy represents the gold standard in diagnostics, it requires general anesthesia and a patient who fulfills all the criteria for it, as well as trained specialists and suitable equipment. All these requirements lead to a small number of cases where these diagnostics are applied.

The SNAP-fPLI seemed to be a reliable additional diagnostic tool for pancreatitis in cats as all the performed tests turned out positive in group 1. In group 2 only 2 tests were performed, and 1 turned out false positive.

Since 56/58 (96.55 %) patients of group 1 and 70/70 (100%) of group 2 were presented with pre-existing conditions, a precise clinical exam, as well as further diagnostics, were of great importance to rule out or confirm the diagnosis of pancreatitis. The three most common pre-existing diseases in our study were diabetes mellitus with 12/58 (20.69 %) patients in group 1 and 8/70 (11.43 %) in group 2. Nephropathy with 7/58 (12.07 %) cats in group 1 and 9/70 (12.86 %) in group 2. The third most common condition was hyperthyroidism, which occurred in 5/58 (8.62 %) participants in group 1 and 7/70 (10.00 %) in group 2. It remains unknown whether these diseases develop primarily or secondarily to pancreatitis, or if they exist independently from each other.

DGGR is not only released by the pancreatic lipase, but also produced by the hepatic and lipoprotein lipase. Recent studies imply, that the specificity of the DGGR-Lipase could be influenced by the secretion of these extra pancreatic lipases (32).

With 20.69 %, nearly twice as many cats from group 1 were pre-diagnosed with diabetes mellitus in comparison to group 2. The high number of cases may originate from long term damage to pancreatic tissue through CP that result in pancreatitis.

There is a correlation between elevated DGGR-Lipase levels and kidney disease. But the values in that study were nonetheless all in the reference interval (32). If other diseases have more influence on the DGGR-Lipase levels remains unknown.

In summary, a clinical exam, blood work, and abdominal ultrasonography are the least diagnostics to rule out other conditions and to form the suspected diagnosis of pancreatitis. An additional DGGR-Lipase may be a reliable diagnostic method to confirm the suspicion.

However, the results should be interpreted with caution, because the DGGR-Lipase is not meant to be used as a sole diagnostic method and may also be influenced by other diseases.

6 Summary

Pancreatitis is defined as an inflammation of the pancreas. The inflammation can cause mild to severe symptoms, even life-threatening conditions are possible. Especially pancreatitis in cats has been underestimated in the past decades. Although the overall awareness about pancreatitis has risen, diagnostics and therapy remain very challenging (1).

This study includes 805 cases of cats and 1149 measurements of DGGR-Lipase values. 888 of the measurements were rated as negative, 261 as positive. After the exclusion of multiple measurements, as well as cases with a lack of clinical data, the number of cases with an increased DGGR-Lipase was limited to 171. All of them were examined at the Animal Hospital of the University of Veterinary Medicine in Vienna in between 01, May 2017 and the 01, May 2019. The participants were divided into two groups depending on their DGGR-Lipase levels as well as the clinical examination, laboratory results, diagnostic imaging and pathological examinations.

The statistical analysis relied heavily on a descriptive approach. As no control groups were included in this thesis, this was the only possible option.

We took a close look at the DGGR-Lipase levels in group 1 and group 2, the co or pre-existing illnesses, the diagnostic methods and the clinical exam.

The influence of pre-existing diseases on the value of the DGGR-Lipase could not be clarified in this study. The high number of cats with additional conditions make this issue even more interesting. Hopefully, more detailed prospective studies can provide us with reliable results.

The DGGR-Lipase seems to be a reliable method to diagnose pancreatitis, but only in addition to further diagnostics methods. High levels of DGGR-Lipase correlate with a greater risk of pancreatitis. Additional investigations are necessary to make a clear statement about the value of the DGGR-Lipase as a tool for diagnosing pancreatitis.

7 Zusammenfassung

Als Pankreatitis bezeichnet man eine Entzündung der Bauchspeicheldrüse. Die Entzündung kann leichte bis schwere Symptome verursachen und sogar lebensbedrohliche Zustände hervorrufen. Die Bedeutung der Pankreatitis als Erkrankung der Katzen wurde in den letzten Jahrzehnten deutlich unterschätzt. Trotz des deutlichen wissenschaftlichen Fortschrittes verbleiben die Diagnostik und Therapie sehr herausfordernd. (1)

Diese Studie umfasst 805 Fälle von Katzen und 1149 Messungen von DGGR-Lipase Werten. 888 der Messungen wurden als negativ bewertet, 261 als positiv. Nach Ausschluss von Mehrfachmessungen sowie Fällen mit fehlenden klinischen Daten wurde die Zahl der Fälle mit erhöhter DGGR-Lipase auf 171 begrenzt. Alle Untersuchungen wurden auf der Veterinärmedizinischen Universität Wien zwischen dem 01.05.2017 und dem 01.05.2019 durchgeführt. Die Teilnehmer wurden je nach DGGR-Lipasespiegel sowie klinischer Untersuchung, Laborergebnissen, bildgebender Diagnostik und pathologischen Untersuchungen in zwei Gruppen eingeteilt.

Die statistische Analyse stützte sich stark auf einen deskriptiven Ansatz. Da in dieser Arbeit keine Kontrollgruppen eingeschlossen wurden, war dies die einzig mögliche Option.

Wir haben uns abschließend die DGGR-Lipase-Werte in der Gruppe 1 und Gruppe 2, die Begleit- oder Vorerkrankungen, die diagnostischen Methoden und die klinische Untersuchung angesehen.

Der Einfluss von Vorerkrankungen auf den Wert der DGGR-Lipase konnte in dieser Studie nicht geklärt werden. Die hohe Anzahl an Katzen mit Zusatzerkrankungen macht diese Fragestellung noch interessanter, weswegen hoffentlich detailliertere prospektive Studien uns in der Zukunft verlässliche Ergebnisse liefern können.

Die DGGR-Lipase scheint eine zuverlässige Methode zur Diagnose einer Pankreatitis zu sein, jedoch nur in Ergänzung zu weiteren diagnostischen Verfahren. Hohe Konzentrationen der DGGR-Lipase korrelieren mit einem größeren Pankreatitis-Risiko. Um eine verlässliche Aussage über den Stellenwert der DGGR-Lipase als Diagnostikmethode treffen zu können, sind weitere Untersuchungen notwendig.

8 Appendix

Table 7 - Chi-square test group 1

Chi-square Test regarding normal distribution in group 1	
Sample skewness	2.88
Sample kurtosis	7.43
Count	58.00
JB Test	106.29
p-value	**8,32*E-24**

Table 8 - Chi-sqaure test group 2

Chi-Quadrat Test regarding normal distribution in group 2	
Sample skewness	7.01
Sample kurtosis	54.10
Count	70.00
JB Test	658.86
p-value	**8,52*E-144**

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