Kocatepe Vet J. (2023):16(3):450-458 DOI: 10.30607/kvj. 1336381

What Is the Latest Status of Cats' Health in Hatay (Türkiye) Province Following the SARS-COV 2 Pandemic?

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ABSTRACT

The current study focused on the latest status of gastrointestinal, urinary tract, and hepatobiliary diseases, which might be induced by stress in cats following the SARS-CoV-2 pandemic in Hatay province in Türkiye. The study looked at postpandemic (June 2021–June 2022) diagnosis data of cats (n:147) with gastrointestinal, urinary tract, and hepatobiliary diseases, admitted to Hatay Mustafa Kemal University Veterinary Health, Practice, and Research Center. The average age of the cats admitted to the clinic was 33.04±2.77 months in post-pandemic period. The ages of the cats diagnosed with gastrointestinal, urinary tract and hepatobiliary diseases were 27.78±4.33, 38.04±3.95, and 40.12±6.27, respectively. The cat breeds commonly brought to the clinic following the pandemic were Tabby, Mix, British shorthair, Persian, and Scottish fold-ear, respectively. There were no breed and sex difference for diseases diagnosed in post-pandemic duration. Distributions of gastrointestinal, urinary, and hepatobiliary diseases were determined as 51.0% (n=75), 37.4% (n=55), and 11.6% (n=17), respectively. Gastroenteritis (n=30, 40%), gastritis (n=13, 17.33%), and unconfirmed and suspected Feline inflammatory bowel disease (n=10, 13.33%) are more diagnosed digestive system diseases. Cystitis (n=30, 54.54%) and hemorrhagic cystitis (n=18, 32.72%) were commonly diagnosed in urinary diseases. Besides, cholangiohepatitis was commonly diagnosed either alone (n=7, 41.17%) or accompanied by hepatic lipidosis (n=4, 23.52%) or cholecystitis (n=3, 17.65%) in cats following the pandemic. Consequentially, although the restrictions implemented during the pandemic and causing stress on cats were ended, it was concluded that the chronic impacts of stress on cats, especially in terms of gastrointestinal system diseases, may continue following the pandemic.

Keywords: Cat, gastrointestinal disorders, post-pandemic, SARS-CoV-2, stress

SARS-COV 2 Pandemisi Sonrası Hatay (Türkiye) İlinde Kedilerin Son Sağlık Durumu Nedir?

ÖΖ

Bu çalışma, Türkiye'nin Hatay ilinde SARS-CoV-2 pandemisi sonrası kedilerde stresin tetikleyebileceği gastrointestinal, idrar yolu ve hepatobiliyer hastalıkların son durumuna odaklanmıştır. Çalışmada Hatay Mustafa Kemal Üniversitesi Veteriner Sağlık, Uygulama ve Araştırma Merkezi'ne başvuran gastrointestinal, idrar yolları ve hepatobilier hastalıkları olan kedilerin post-pandemik (Haziran 2021-Haziran 2022) tanı verilerine (n:147) bakılmıştır. Pandemi sonrası kliniğe başvuran kedilerin ortalama yaşı 33.04±2.77 aydı. Gastrointestinal, idrar yolu ve hepatobiliyer hastalık tanısı konulan kedilerin yaşları sırasıyla 27.78±4.33, 38.04±3.95 ve 40.12±6.27 idi. Pandeminin ardından kliniğe yaygın olarak getirilen kedi ırkları sırasıyla Tekir, Melez, British shorthair, İran ve Scottish fold-ear idi. Pandemi sonrası dönemde teshis edilen hastalıklar için ırk ve cinsiyet farkı yoktu. Pandemi sonrası gastrointestinal, üriner ve hepatobiliyer hastalıkların dağılımları sırasıyla %51,0 (n=75), %37,4 (n=55) ve %11,6 (n=17) olarak belirlendi. Gastroenterit (n=30, %40), gastrit (n=13, %17,33) ve Feline yangısal barsak hastalığı şüpheli (n=10, %13,33) hastalıklar en yaygın teşhis edilen sindirim sistemi hastalıkları idi. Sistit (n=30, %54.54) ve hemorajik sistit (n=18, %32.72) yaygın olarak teşhis edilen hastalıklar idi. Ayrıca, kolanjiyohepatit, pandemi sonrasında kedilerde sıklıkla tek başına (n=7, %41, 17) veya hepatik lipidoz (n=4, 1, 17) veya %23,52) ya da kolesistit (n=3, %17,65) ile birlikte teşhis edilmiş olgulardı. Sonuç olarak, pandemi döneminde uygulanan ve kediler üzerinde strese neden olan kısıtlamalara son verilmiş olsa da, pandemi sonrasında özellikle gastrointestinal sistem hastalıkları açısından stresin kediler üzerindeki kronik etkilerinin devam ediyor olabileceği kanısına varıldı. Anahtar Kelimeler: Gastrointestinal Bozukluklar; Kedi; Post-Pandemi; SARS-CoV-2; Stres

To cite this article: Köse S.İ. Sağkan Öztürk A. Uyanık G. Ertürk A. Durgut R. What Is The Latest Status Of Cats' Health In Hatay (Türkiye) Province Following The SARS-COV 2 Pandemic? Kocatepe Vet J. (2023):16(3):450-458

Submission: 02.08.2023 Accepted: 27.09.2023 Published Online: 29.09.2023

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Cats have gained popularity as pets because they are considered "low-maintenance" or "independent" animals (Lue et al. 2008, Rodan 2016). In today's lifestyle, generally, people have a long working time as opposed to time spent at home and live in cramped buildings (Lue et al. 2008, Horwitz and Rodan 2018). Therefore, cats, being easy to care for, seem to be a suitable candidate as a companion animal in this lifestyle (Lue et al. 2008, Rodan 2016). Because of environmental factors, cat-cat interactions or cathuman interactions, some cats may be sensitive to an indoor lifestyle (Buffington 2002, Adamelli et al. 2005, Rodan and Heath 2016). And this lifestyle for cats may cause some health problems (Buffington, 2002). The behavior of cats is affected by individual variations between cats during socialization with uncommon people in unfamiliar surroundings (Bernstein 2007). Cats usually prefer to communicate with their owners by meowing, rubbing, purring, and wagging their tails to demand food, but they spend the majority of their time post-meal grooming and less time interacting with their owners (Bradshaw and Cook 1996, Bernstein 2007). Cats prefer to spend time alone after meals. However, owners may interact more with their cats during the post-meal period. Owners, unaware of this cats' behavior, may need to increase own mental health outcomes, such as alleviating stress, enhancing social communication, and overcoming difficulties (Shoesmith et al. 2021).

Stress is used to describe deleterious or unpleasant stimuli that bring about behavioral and psychological changes (Moberg and Mench 2000). Stressors in domestic animals include physical stressors, social stressors caused by interactions with other members of the same species, and stressors that occur as a result of human interaction (Moberg and Mench 2000, Amat et al. 2016). If the animal is subjected to long-term stress that exceeds its capacity for adaptation, its welfare will suffer (Broom and Johnson 1993, Moberg and Mench 2000, Amat et al. 2016). Owners, on the other hand, may complain of stress-related behavioral changes in their animals, and finally, relinquishment for cats and dogs may be involved (Edney 1998, Amat et al. 2016). Sharing a house with other animals and the change in the owner's environment are shown to be important causes of behavioral changes in cats that result in relinquishment (Salman et al. 2000, Casey et al. 2009). Crowded life, sudden and unexpected changes (Keeling and Jensen 2002), environmental changes, inadequate or excessive human-cat relations (Stella et al. 2013, Amat et al. 2016), new individual participation in the environment, and changes in daily routine all come to the fore as stress factors in cats (Stella et al. 2011, Amat et al. 2016). Sickness behavior in cats exposed to stressful conditions is

possible (Stella et al. 2011). Gastrointestinal symptoms (diarrhea, lack of appetite, low-high water

intake), physical symptoms (reduced activity, lethargy, somnolence, increased pain-like behaviors, reduced grooming), and mental symptoms (decreased social interactions, aggression) may be observed as sickness behaviors (Buffington 2011, Stella et al. 2011, Stella et al. 2013, Ropski et al., 2023). Sickness behaviors have been reported to be responses to adverse environmental events, such as the physical and behavioral response to infection, that are well established in the animal species studied (Stella et al. The production of pro-inflammatory 2011). cytokines, immunological activation, emotional state alterations, and pathological pain have been related to psychological stressors (Stella et al. 2011, Stella et al. 2013). Thus, sickness behaviors can be generated by the body's central (psychological) and peripheral (infection) channels (Keeling and Jensen 2002, Stella et al. 2011). The stress reaction may result in the formation of a new infection or the reactivation of an existing one as a result of a decrease in immune system function (Keeling and Jensen 2002, Amat et al. 2016). Consequently, stress seems to be a critical connection between the environment, behavioral problems, and disease (Keeling and Jensen 2002). Herewith, although behavioral issues in cats are assumed to be individual, stress from the owner and the surroundings is frequently disregarded (Keeling and Jensen 2002, Jensen et al. 2020).

The severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2), which broke out approximately four years ago in late December 2019 and was named Coronavirus disease 2019 (COVID-19), caused a new pandemic all over the world (Wang et al. 2020, World Health Organization 2020). In order to limit the spread of the disease during the pandemic process, various restrictions and measures (such as social isolation, travel restrictions, closure of educational institutions, and remote work) were implemented all over the world (Seker et al. 2020, Islam et al. 2021). Following the first case notification on March 11, 2020, quarantine measures (such as flexible working hours and curfews) were strictly implemented in Türkiye as well as all over the world (Maden 2020, Seker et al. 2020). It was obvious that both cats and humans were exposed to stress thanks to quarantine measures during the pandemic (Shoesmith et al. 2021, Köse et al. 2022). When the stressful situation ends, induction of the sympathetic nervous system by the adrenal medulla disappears, but the endocrine effect of the stress response may be continued (Buffington 2002, Keser 2018). In this study, considering the endocrine effect of the stress response, it was hypothesized that stress-related diseases may continue following the pandemic. Based on this, in this study, the post-pandemic status of gastrointestinal system

diseases, which were observed to increase especially during the pandemic (Köse et al. 2022), and hepatobiliary and urinary system diseases, which may also be stress-related, were aimed to analyze.

MATERIALS and METHODS

Materials

The data from July 2021, the date when restrictions were ended in Türkiye (Republic of Türkiye Ministry of Interior 2021), to July 2022 were examined. Herewith, a total of 147 diagnosis data of cats admitted to the Department of Internal Medicine Clinic of Hatay Mustafa Kemal University Veterinary Health, Practice, and Research Center comprised the materials of this study. These data included gastrointestinal, hepatobiliary, and urinary system diseases in cats that could be caused by stress (Rodan 2016, Rodan and Heath 2016).

Methods

Initial admission of cats with urinary disorders, complete blood count (CBC) (MS4S, Melet Schloesing Laboratoires, Osny, France) and blood chemistry analysis (BC) (Chem200, Gesan Production S.R.L. Campobello Di Mazara, Italy), ultrasound (USG) (ESAOTE Pie Medical Aquila, Czech Republic) and radiographic imaging (RI) (Regius Σ II, Konica Minolta, Tokyo, Japan) were used for diagnosis. The diagnosis of cystitis, hemorrhagic cystitis, feline urinary syndrome, and urolithiasis was performed in cats as described previously (Köse et al. 2022). Diagnosis of cystitis with urolithiasis was performed with together evaluation of ultrasound imaging (UI) (thickening of the bladder wall, the bladder's fullness, existence of urolith in bladder), stick test of urine (MEDPA, Türkiye) (observation of reaction for leukocyte, protein, or nitrite in addition to pH and SpG levels), microscopic examination of urine sediment (casts, crystalluria, and the presence of WBC), and blood works (CBC and BC). In the urine works (stick and microscopy) of cats with urinary symptoms, hemorrhagic cystitis with urolithiasis was diagnosed if RBC and erythrocyte were present in addition to evidence of cystitis and urolithiasis. The diagnosis of urethral obstruction was made by determining the strain during urinary catheterization. Acute renal failure was diagnosed according to clinical signalments (anuria, vomiting, weakness), laboratory analysis (blood works and urinalysis), and especially UI (presence renal enlargement). In order to diagnose gastrointestinal and hepatobiliary problems in cats, blood works (CBC and BC), imaging techniques (UI and RI), and stool examination (including microscopy and rapid tests, etc.) were carried out as described by authors (Köse et al. 2022). Besides, for the diagnosis of hepatobiliary disorders, serum chemistry (alteration in enzyme, blood urea nitrogen and creatinine levels), and liver ultrasound imaging to determine structural

and parenchymal changings were especially used as described previously (Köse et al. 2022).

Evaluation of data

Patient registries and patient monitoring software (EVET, Hasvet, Türkiye) were investigated for the purpose of gathering data. The data belonging to the period between July 2021, when normalization was announced (Republic of Türkiye Ministry of Interior 2021) to July 2022 were accepted as post-pandemic period.

Statistical Analysis

For categorical variables, descriptive statistics were presented as frequencies and percentages, and for continuous variables, as arithmetic means and standard errors. Fisher's Exact Test was used to compare the distributions of categorical variables among subgroups due to the existence of zero cells and a small number of observed and predicted values in cells. To evaluate the difference in the average age of the cats diagnosed in the post-pandemic period, one-way ANOVA test was used. All statistical analyses were performed using SPSS 26.0 (IBM Corp., Armonk, NY), and p<0.05 was considered statistically significant.

RESULTS

The average age (mean±SEM) of the cats was 33.04±2.77 months in the post-pandemic period. In this period, gastrointestinal, urinary, and hepatobiliary diseases were diagnosed in cats at 51.0% (n=75), 37.4% (n=55), and 11.6% (n=17), respectively (Table 1). The monthly ages of the cats diagnosed with gastrointestinal, urinary, and hepatobiliary diseases were 27.78±4.33, 38.04±3.95, and 40.12±6.27, respectively. The difference was not detected in the average ages of cats diagnosed in the post-pandemic period (F=1.925 (df:2), p=0.150). There was no sex difference in urinary (X2=8.214, p=0.252), gastrointestinal (X2=4.766, p=0.596), or hepatobiliary (X2=4.995, p=0.484) diseases diagnosed in the cats admitted to internal medicine clinic following the pandemic (Table 1). It was determined that the cat breeds commonly brought to the clinic as patient and diagnosed in the post-pandemic period were tabby, mixed, British shorthair, Persian, and Scottish foldear, respectively. It was also found that there was no statistical difference (X2=28.732 (df:26), p=0.181) between the cat breeds that presented to the clinic in terms of gastrointestinal, urinary, and hepatobiliary diseases (Table 2). Commonly diagnosed digestive system diseases in cats admitted with gastrointestinal symptoms were gastroenteritis (n=30, 40%), gastritis (n=13, 17.33%), and unconfirmed and suspected Feline inflammatory bowel disease (n=10, 13.33%), respectively (Table 1). On the other hand, in urinary system diseases, cystitis (n=30, 54.54%) and hemorrhagic cystitis (n=18, 32.72%) were commonly

diagnosed (Table 1). Interestingly, in hepatobiliary diseases, it was determined that cholangiohepatitis was commonly diagnosed either alone (n=7, 41.17%) or accompanied by hepatic lipidosis (n=4, 23.52%) or

cholecystitis (n=3, 17.65%) in the cats admitted to internal medicine clinic following the pandemic (Table 1).

Table 1. Gender difference in gastrointestinal, urinary and hepatobiliary diseases in cats diagnosed following pandemic.

		Gender (n)		T- +-1
		Female	Male	Total
Gastrointestinal Diagnosis	Gastritis	5	8	13
	Gastroenteritis	15	15	30
	Enteritis	5	3	8
	Hemorrhagic Gastroenteritis	2	3	5
	Colitis	1	4	5
	Constipation	2	2	4
	FIBD*	7	3	10
	P value	0.596		75
Urinary Diagnosis	Hemorrhagic Cystitis	3	15	18
	Cystitis	11	19	30
	FUS	1	0	1
	Urolithiasis	0	2	2
	Cystitis with Urolithiasis	1	0	1
	Acute Renal Failure	0	1	1
	Hemorrhagic Cystitis with Urolithiasis	0	1	1
	Urethral Obstruction	0	1	1
	P value	0.252		55
Hepatobiliary Diagnosis	Hepatic Lipidosis	1	0	1
	Cholangiohepatitis	2	5	7
	Cholangiohepatitis & Cholecystitis	1	2	3
	Cholangiohepatitis & Hepatic Lipidosis	1	3	4
	Cholestasis	1	0	1
	Cholecystitis	1	0	1
	P value	0.484		17

Table 2. Difference* in breed prevalence in disease diagnosis.

		Diagnosis				
		Urinary	Gastrointestinal	Hepatobiliary	Total	
	Tabby	25	40	6	71	
	Mix	6	11	3	20	
Breeds	British Shorthair	6	9	1	16	
	Scottish Fold Ear	2	6	1	9	
	Tuxedo	2	0	1	3	
	Ankara	1	3	0	4	
	Bombay	3	0	0	3	
	Siamese	1	1	1	3	
	Van	2	0	1	3	
	Persian	3	4	3	10	
	Exotic Shorthair	1	0	0	1	
	Norwegian Forest	1	0	0	1	
	Russian Blue	2	0	0	2	
	Ragdoll	0	1	0	1	
otal		55	75	17	147	

DISCUSSIONS

All over the world, various pandemics, such as the Black Death, cholera, swine flu, and Middle East respiratory syndrome coronavirus, have been recorded (Huremović 2019, Piret and Boivin 2021). The SARS-COV-2 pandemic, which was effective all over the world and was first reported in Wuhan, China in 2019 (Wang et al. 2020, World Health Organization 2020), has been effective in Türkiye for more than a year (Maden 2020, Şeker et al. 2020, Republic of Türkiye Ministry of Interior 2021). With the goal of stopping the spread of the disease throughout the pandemic phase, various limitations and procedures (such as social separation, limitations on travel, closing of educational organizations, and faraway employment) have been put in place in Türkiye as well as all over the world (Maden 2020, Şeker et al. 2020, Islam et al. 2021).

In the studies on human-animal interactions (Wood et al. 2015, Bowen et al. 2020), it is informed that companion animals provide social support for people in overcoming challenges, especially during a time when the majority of people are facing similar environmental and social issues like the SARS-COV-2 pandemic. Pet animals can nonetheless suffer the unfavorable effects of a duration of home restriction; the quality of life of cats and dogs is greatly affected by the features of their physical and social surroundings, as well as the owners' habits and lifestyle, all of which would be significantly altered during quarantine measures (Bowen et al. 2020, Fatjó and Bowen 2020).

Cats are the most popular pets in many countries, and Türkiye is among the top 10 of these (Batson 2008, Rodan and Heath 2016). But, during the pandemic, interest in pets and spending time with cats at home indirectly decreased or increased, contrary to normal days, because of quarantine measures and restrictions implemented in Türkiye. So, it may be stressful for cats to have their regular routines changed (Moberg and Mench 2000, Amat et al. 2016, Horwitz and Rodan 2018, Köse et al. 2022). Under stressful conditions, the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system (SNS) are stimulated by environmental stressors. After this stimulation, corticosteroids are released from the adrenal cortex, which interact with ACTH released from the pituitary gland, into the blood stream (Buffington 2011, Amat et al. 2016, Keser 2018, Köse et al. 2022). The HPA axis has an impact that lasts longer in the body due to its endocrine effects (Buffington 2002, Keser 2018, Köse et al. 2022). Chronic distress may occur due to strong, prolonged, or severe stressors (Hargrave 2015, Horwitz and Rodan 2018). Thereby, stress may cause a variety of behavioral and mental issues, as well as new diseases or the recurrence of old infections in cats (Enck and

Holtmann 1992, Tanaka et al. 2012, Amat et al. 2016, Köse et al. 2022). A number of gastrointestinal issues

(vomiting, diarrhea, etc.), urinary problems like idiopathic cystitis, and some hepatobiliary diseases (hepatic lipidosis, cholangitis, etc.) may occur in cats due to stress (Enck and Holtmann 1992, Buffington 2011, Tanaka et al. 2012, Amat et al. 2016).

Gastrointestinal disease may be brought on by chronic distress (Horwitz and Rodan 2018, Köse et al. 2022). Compared to the previous study of the authors (Köse et al. 2022), the present study showed that gastrointestinal diseases, especially gastroenteritis, enteritis, and hemorrhagic gastroenteritis, were continuing to relatively increase in also postpandemic season, except gastritis. Different from the previous study of the authors (Köse et al. 2022), feline inflammatory bowel disease (suspected but unconfirmed), colitis, and constipation stand out as new diagnoses (Figure 1). Mast cell activation, degranulation, and colonic mucin depletion can all be caused by stress. Additionally, stress increases one's vulnerability to colonic inflammation (Rakesh et al. 2005). On the other hands, intestinal activities may be affected by stress factors (external or intestinalrelated), which may lead to an alteration in the intestinal microbiota and a deterioration in the intestinal barrier (Enck and Holtmann 1992, Köse et al. 2022). The onset of gastrointestinal diseases, especially colitis, constipation, and inflammatory bowel disease in cats in the post-pandemic period, might be related to colonic mucin depletion, increasing vulnerability to colonic inflammation, an alteration in the intestinal microbiota, and a deterioration in the intestinal barrier.

Acute or chronic stress are both possible (Amat et al. 2016, Horwitz and Rodan 2018, Köse et al. 2022). And cats may experience urinary disorders under prolonged distress as opposed to acute stress (Horwitz and Rodan 2018, Köse et al. 2022). In the previous study of the authors (Köse et al. 2022), they did not detect a statistical difference between the number of pre-pandemic and pandemic period urinary diagnoses in cats. On the other hand, in the present study, the number of major urinary disease diagnoses (Figure 2), which are cystitis and hemorrhagic cystitis, is seen approximately equal to sum of the number of diagnosed in pre-pandemic and pandemic period reported in the previous study of authors (Köse et al. 2022). In addition, the other diagnoses, which are the same as those diagnosed in the pre-pandemic and pandemic periods, were also observed at similar levels following the pandemic. In light of these findings, it is suspected that this relative increase in cystitis and hemorrhagic cystitis following the pandemic may be resulted from the endocrine effects of stress in cats.

Under stressful conditions, cats may tend to develop hepatic disease, including hepatic lipidosis and cholangiohepatitis, but the mechanism of this process cannot be definitively explained (Amat et al. 2016, Kuzi et al. 2017, Köse et al. 2022). One approach to this issue suggests that a decrease in appetite or anorexia may develop due to chronic distress, and rapid weight loss resulting in hepatic disorders including cholangitis, cholangiohepatitis, hepatitis, and hepatic lipidosis may easily occur following this process (Rutgers 1998, Köse et al. 2022). Lack of glucuronyl transferase, inability to synthesize arginine, and a propensity for hepatic fat buildup, bacterial overload, small intestinal shortness, and anatomical characteristics all predispose to the development of liver disease in cats (Rutgers 1998, Cerná et al. 2020, Köse et al. 2022). In the previous study of the authors (Köse et al. 2022), it was reported that the number of cholangiohepatitis cases observed in the pandemic was relatively higher than in the pre-pandemic. But this increase in cholangiohepatitis was not found to be significant. In the present study, the total number of cholangiohepatitis cases observed (Figure 3) was closely similar to the previous study's data related to

the pandemic (Köse et al. 2022). But, in the present study, cholangiohepatitis was diagnosed either alone (n:7) or accompanied by hepatic lipidosis (n:4) or cholecystitis (n:3) (Figure 3). These comorbidities in hepatobiliary disease may be related to the recurrence of previous diseases due to chronic distress in addition to a new one following the pandemic.

The pandemic is reported as a serious stress factor for both people and cats (Wood et al. 2015, Bowen et al. 2020, Fatjó and Bowen 2020, Shoesmith et al. 2021). Before and during the pandemic, diseases that may be caused by stress were examined in the previous study (Köse et al., 2022), and it was determined that there was an increase in gastroenteritis in cats during the pandemic. In the presented study, it was hypothesized that stress-related diseases in cats may continue after the pandemic period. Since the diagnoses made in cats after the pandemic period were only examined and analyzed retrospectively in this study, the factors regarding stress (blood cortisol level, clinical observations of stress, etc.) are not present. This may be the limiting factor of the study.

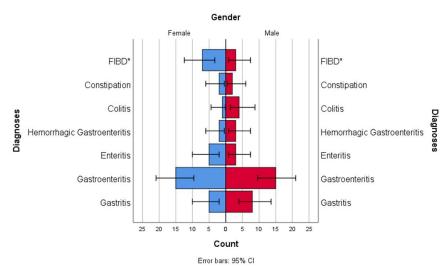
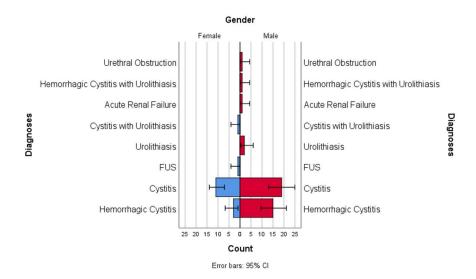


Figure 1: Gastrointestinal diagnosis distributions





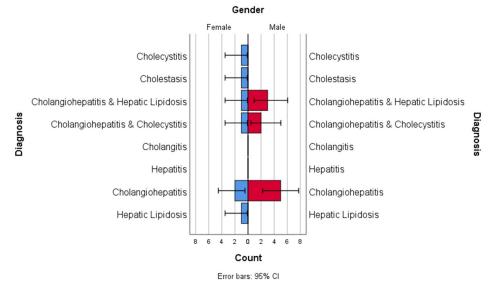


Figure 3: Hepatobiliary diagnosis distributions

CONCLUSION

It is obvious that the daily routine may change due to official quarantine measures, and this may result in stress for both cats and people. Although it is not certain, it is concluded that the cats may have suffered from chronic distress, lasting since the days of the pandemic in Hatay (Türkiye) province. Starting at this point, it is not underestimated that acute stress or chronic distress may have negative effects on cat welfare. Measures, such as environmental enrichment, to relieve stress affecting cats may be implemented. In addition, further comprehensive case-controlling studies, including cat-human and cat-environment relationships, should be conducted for the evaluation of stress-related diseases in cats.

Conflict of interest: The authors have no conflicts of interest to report.

Funding: The authors received no financial support for the research, authorship, and/or publication of this article.

Authors' Contributions: SİK contributed to the project idea, design and execution of the study. GU and AE contributed to the acquisition of data. SİK analyzed the data. SİK drafted and wrote the manuscript. ASÖ and RD reviewed the manuscript critically. All authors have read and approved the finalized manuscript.

Ethical Approval: Retrospective data from patient registries and client-monitoring software were used in this project. So, this study is not subject to the permission of HADYEK in accordance with the "Regulation on Working Procedures and Principles of Animal Experiments Ethics Committees" 8 (k). The data, information and documents presented in this

article were obtained within the framework of academic and ethical rules.

Acknowledgment: We would like to thank MSc students Gizem Şeyma Bölük, Hindreen Mohammed Radhi, and Büşra Talan for their assistance with the clinical examination and case application. In addition, this work is dedicated to our colleagues and friends, Dr. Pınar Ambarcıoğlu Kısaçam, Dr. Mehmet Ali Kısaçam, Dr. Erhan Tek, and Assoc. Prof. İbrahim Ozan Tekeli, who died in a devastating earthquake tragedy in Türkiye on February 6, 2023, and we wish them eternal peace in paradise.

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