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Research Article

Outcomes of Treatment of Cats with Effusive Feline Infectious Peritonitis Using Parenterally Administered Remdesivir with Two Different Maintenance Dose Concentrations

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Abstract

The emergence of antiviral drugs against human coronavirus offers a promising approach for treating progressive and fatal feline infectious peritonitis (FIP). This study aims to evaluate the effectiveness of remdesivir in treating effusive FIP and to compare the lower and upper maintenance doses. Sixteen cats suffering from effusive FIP were randomly assigned to two treatment groups, eight cats in each group. Both groups (A) and (B) were treated with the same initial dose of 10-12 mg/kg body weight by IV route for the first 3 days, while for maintenance dose, group (A) was treated with a lower limit of 5-6 mg/kg body weight and group (B) was treated with upper limit 10-12 mg/kg body weight by SC route till day 84. The overall survival rate was 87.5%. Two cats (one from each group) died within the first 48 h of the treatment protocol. The recurrence rate excluding the two dead cats was 14.28% for group A; one case had disease recurrence, while there was no case recurrence in group B; no significant difference was observed between the two treatment groups in recurrence rate ($P<0.05$). At the end of the treatment period, all 14 surviving cats had normalized clinicopathological findings and disease remission. The lower maintenance dose of remdesivir is as effective as the upper dose.

Keywords: Antiviral, Effusive FIP, Feline coronavirus, Survival rate, Treatment doses

Introduction

FIPV (feline infectious peritonitis virus) is a virulent biotype of feline coronavirus (FCoV) that causes feline infectious peritonitis (FIP), a highly fatal disease with a worldwide distribution affecting both wild and domestic felines of different ages, usually at the age of 3 months to 2 years [1,2].

FIP has two well-recognized clinical forms: effusive (wet) and non-effusive (dry). The main clinical presentation of the effusive form is abdominal distension with fluid, and the accumulated fluid is more likely yellow in color with high protein content; the fluid also accumulates in the pleura resulting in dyspnea. The non-effusive form is less common and chronic form; it causes granulomatous lesions in internal organs such as the liver, kidney, intestine, and lymph nodes. Ocular and central nervous symptoms such as ataxia and coordination are more likely in cats suffering from the non-effusive form [3-5].

Diagnosis of FIP remains a challenge in veterinary practices; clinical signs combined with various diagnostic techniques may be helpful for the diagnosis of FIP in living animals. Ante-mortem definitive diagnosis is particularly significant following the development of effective antiviral drugs against FIP [6]. Nonspecific clinical signs make the diagnosis of FIP embarrassing especially in case of dry form; while in wet form presence of typical effusions ascites and pleural effusions improve the diagnostic procedure and some simple helpful and rapid test as Rivalta's test can be done on effusive fluids [7].

The distinctive histopathological changes and the immunohistochemical technique of the affected tissues remain the gold standard methods for diagnosis of FIP, but it's usually performed after post-mortem examination [6,7]. Many laboratory diagnostic techniques can not differentiate between the two pathotypes of FCoV: feline enteric coronavirus (FECV) and FIPV; however, there is a great difference in virulence between the two pathotypes. FECV is a highly prevalent contagious infection, even though it's usually asymptomatic or may only cause mild diarrhea in some cases [5,6]. FIPV emerged as a result of, different mutations that occurred in the avirulent biotype (FECV); mutations lead to changes in the viral tropism from enterocytes to monocyte immune cells, causing severe disseminated systemic disease [2,3,8].

FIP was considered a highly fatal disease the median survival period without treatment is only eight to nine days instead of using some immunomodulatory agents; these drugs only increase the survival time of diseased cats without complete recovery [4,9]. Recently, the development of some antiviral drugs as "GS 441524" an antiviral medication that acts as a nucleoside analog, and its prodrug remdesivir (GS-5734), which were developed to treat human corona viruses SARS-CoV-1 and SARS-CoV-2 which causes COVID-19 pandemic, have given highly encouraging results with high recovery rates in experimentally and naturally infected cats with FIP [10-13].

Remdesivir (GS-5734) is a broad-spectrum antiviral drug with a small molecule that acts particularly against RNA viruses, including *Coronaviridae;* it interferes with the viral genome replication process [11]. Remdesivir is evaluated in many studies to treat different forms of FIP [1,13]. The recommended dose of remdesivir for treatment of FIP varies significantly between different studies from 5-30 mg/kg body weight depending on the treatment phase (initial or maintenance), FIP form (effusive or dry), presence of ocular or nervous signs, route of administration parenteral method by IV or SC routes or orally (low bioavailability requires high doses), and the study protocol [1,7,11-13].

There are some studies investigating FIP in Africa and the Middle East countries, including Egypt [14-16]. Our study was conducted to spotlight on the common clinical and clinicopathological findings of effusive FIP, evaluate the efficacy of remdesivir in effusive FIP treatment, and compare the efficacy of two different maintenance dose concentrations of remdesivir in effusive FIP treatment.

Material and Methods

Ethical Approval

The Institutional Animal Care and Use Committee of the Faculty of Veterinary Medicine Cairo University (Vet. CU. IACUC) with code number (Vet CU131020241022) approved all the methods of animal handling and sampling included in this study.

Study Design and Inclusion Criteria

Cats with a highly suspected diagnosis of effusive FIP were recruited for this single-centered prospective randomized treatment trial. All of the included diseased cats in treatment procedures were client-owned cats; the study was established without control untreated or placebo group as the untreated group is unethical because untreated FIP is a fatal disease.

Suspected animals were admitted to the small animal clinic of referral teaching veterinary hospital at the Faculty of Veterinary Medicine, Cairo University. Cats that suffered from effusive FIP form were identified from January 2023 to March 2024.

Case data and physical examination: patient signalment, vital parameters (body temperature, respiratory rate, and heart heart) and clinical signs (general health conditions, presence of body cavities effusions, and other clinical signs) were recorded for each case.

Sample collection and analysis: blood sample collection during the animal examination was performed on the plain tube for blood biochemistry and EDTA tube for CBC at zero weeks and 12 weeks of treatment. Body cavity centesis and collection of effusive fluid in sterile containers as a sample for Rivalta's test, detection of protein concentration, and other biochemical analyses were performed during the physical examination of suspected cases.

Imaging: X-rays and ultrasonography were performed on each examined animal for detection and assessment of different body cavity effusions.

Inclusion criteria for treatment procedures:

Inclusion criteria used for diagnosis of FIP cases to be subjected to treatment procedure were defined as highly suspected cases of FIP [13,17] by the following criteria:

1. Clinical signs: typical effusions (ascites +/- pleural and pericardial effusions).

2. Characteristic high proteinaceous effusive fluid (>35 g/L) with positive Rivalta's test [17,18].

3. Decrease in albumin globulin ratio (A/G ratio) with cut of point <0.6 [1,8].

4. Presence of ≥3 other clinicopathological findings such as pyrexia, anemia, lymphopenia, neutrophilia, hyperbilirubinemia, hypoalbuminemia, and hypergammaglobulinemia [1,8,12].

5. Negative test results for feline immunodeficiency virus (FIV) and feline leukemia virus (FeLV) infection. A SNAP

Combo FeLV Ag/FIV Antibody rapid immunoassay (Product Code 502A.02, IDEXX laboratories) was performed for each serum sample according to the manufacturer's instructions to detect feline leukemia virus (FeLV) antigen and feline immunodeficiency virus (FIV) antibodies in feline serum [1,8].

Treatment Procedures and Protocol

The drug used: remdesivir - Eva Pharma Egypt (20 mL vial containing 100 mg remdesivir) for parenteral administration (I/V or S/C).

Treatment regimen: all diagnosed cats with FIP were initially treated for the first three days of therapy at a dose of remdesivir (10-12 mg/kg diluted to 10 mL with saline and given over 10 minutes) by intravenous route as loading dose to speed up the antiviral efficacy. The treatment regime was then changed to the subcutaneous route with a maintenance doses [12] illustrated in *(Table 1)*. The treated cats were randomly selected for either group (A) or group (B); the treatment period lasted for 84 days.

Table 1. *Treatment regime: doses concentration, method of administration, and treatment groups*

Groups	Treatment Regime and Dose Concentrations	
	Initial Dose (every 24 h for 3 days, IV)	**Maintenance Doses (every 24 h from day 4 to day 84, SC)**
Group (A)	10-12 mg/kg body weight	5-6 mg/kg body weight
Group (B)		10-12 mg/kg body weight

Treated cases follow-up: veterinarians examined and evaluated cats weekly for the first month of treatment, then monthly until the end of the treatment period, and for another three months of follow-up of treated cases. Clinical follow-ups of cases and monitoring animal's body weight to adjust the drug dose were done by patient owners, caretakers, and veterinarians.

Study Outcomes and Statistical Analysis

Study outcomes were evaluated as primary outcomes, including survival rate, disease remission (complete resolution of clinical signs such as pyrexia, lethargy, and body cavity effusions) [19], and recurrence rate during 84 days of treatment and 3 months of follow-up and the progression and normalization of clinical and clinicopathological findings as a secondary outcome. For evaluation of liver and kidney function ALT, ALP, and creatinine were measured pre and post-treatment.

Pearson's Chi-squared test was performed to test whether there is a statistically significant difference in the recurrence rate between the two treatment groups (A and B) ($P<0.05$).

An independent sample T-test was used to test for the difference between both groups before treatment and the difference between both groups after the treatment among each studied hematological and serum parameter. A one-way analysis of variance (ANOVA) was used to test the effect of the two treatment protocols (groups A and B) on the studied hematological and serum parameters. The Shapiro-Wilk test was utilized for normality analysis of the variables, and Levene's test was used to evaluate the homogeneity of variance. Parametric statistical tests were used for analyzing data with a normal distribution, and if there were significant differences, the least significant difference (LSD) test was used for post-hoc analysis. Otherwise, the non-parametric tests were used for the data that was not distributed normally. Data were presented as the mean ± standard error (SE). Statistical significance was set at $P<0.05$. All analyses were performed with SPSS® version 20.

Results

Animals

Of 31 suspected effusive cases suffering from ascites and other body cavity effusions on physical examination and imaging, sixteen cases (16/31) are considered highly suspected cases of FIP (n=16) according to the study inclusions criteria and owners' approval to be included in the treatment procedures.

Demographic character of included animals: according to sex (10 males and six females), according to age (14 cats <2 years and two cats >2 years), and according to breed (8 Persian, 4 mixed, and four domestic short hair). The different recorded clinical and clinicopathological findings of the 16 included cats are illustrated in *(Table 2)*, body cavities effusions (mainly ascites *(Fig. 1-A,B)*, lethargy, inappetence, and pyrexia were the most common clinical findings in examined cases. All included cats are Rivalta's test positive *(Fig. 1-C,D)* and feline immunodeficiency virus (FIV) and feline leukemia virus (FeLV) rapid commercial test negative. X-Ray imaging and ultrasonographic examination reveals different body cavities effusions *(Fig. 2, Fig. 3-A,C)*.

Primary Outcome of the Study

The survival rate from the beginning till the end of the treatment protocol (84 days) and 3 months of follow-up is 87.5%; one cat from each group A and B died within 48 h from the beginning of the treatment regime. The survival rate after 48 h from the beginning of the treatment regime reaches 100%. All the surviving 14 cats had disease remission by the end of the treatment period. In group (A) receiving the lower dose of remdesivir 5-6 mg/kg body weight as a maintenance dose, one case had disease recurrence after ending the treatment regime by

Table 2. *Number and percent of included cats with different clinical and clinicopathological findings*	
Clinicopathological Finding	**Number and Percent of Cats**
Lethargy	15/16 (93.75%)
Pyrexia	13/16 (51.25%)
Labored breathing and tachypnea	10/16 (62.5%)
Tachycardia and cardiac arrhythmia	5/16 (31.25%)
Inappetence	15/16 (93.75%)
Abdominal distension	16/16 (100%)
Peritoneal effusions	16/16 (100%)
Thoracic effusions	4/16 (25%)
Pericardial effusions	2/16 (12.5%)
Anemia	8/16 (50%)
Lymphopenia	8/16 (50%)
Neutrophilia	9/16 (56.25%)
Hyperbilirubinemia	8/16 (50%)
Hypoalbuminemia	9/16 (56.25%)
Hypergammaglobulinemia	11/16 (68.75%)
A/G ratio (< 0.6)	16/16 (100%)
ALT	3/16 (18.75%)
ALP	1/16 (6.25%)
Creatinine	2/16 (12.5%)
Protein content (>35g/L) of effusive fluid	16/16 (100%)

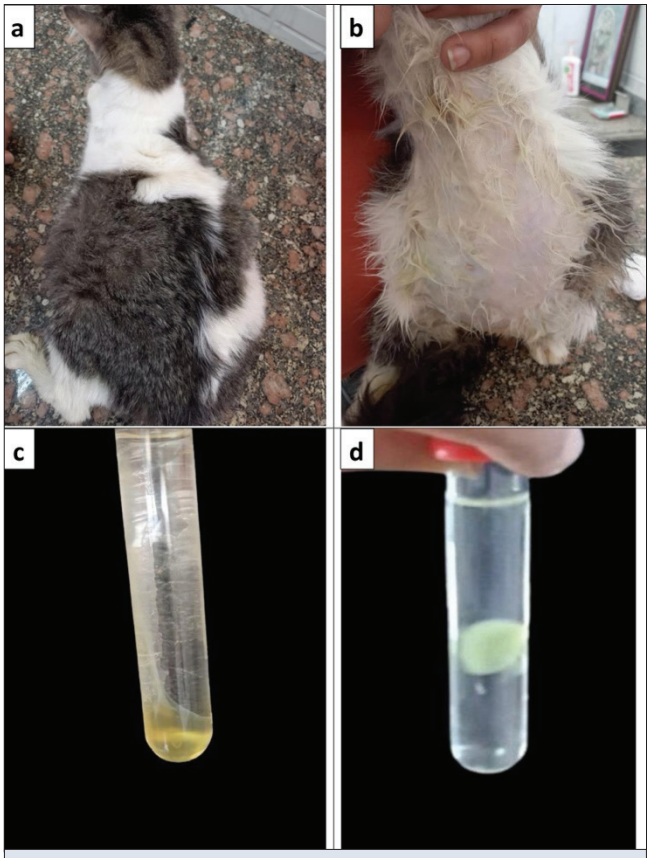

Fig 1. a, b- five months old cat suffering from abdominal distension (ascites); **c, d**- positive Rivalta's test, note the drops of the examined fluids retain its shape

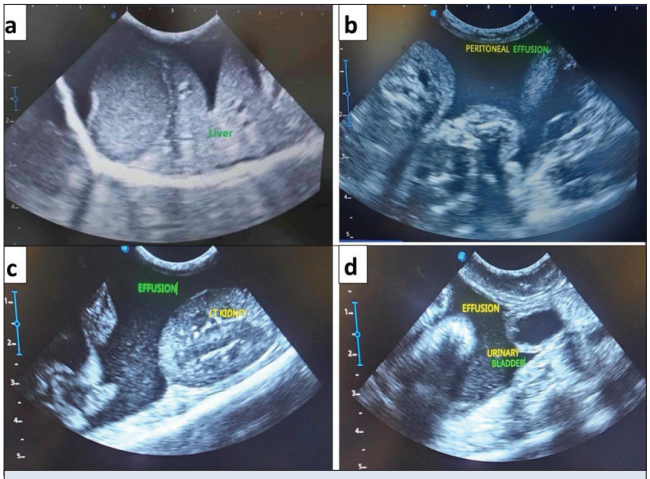

Fig 2. Ultrasonic imaging of cats suffering from effusive FIP; **a**- one years old Persian cat suffering from peritoneal perihepatic effusions; **b, c, d**- one and half years old DSH cat suffer from abdominal effusions, **b**- peritoneal effusions, **c**- peritoneal effusions around kidney, **d**- effusions in pelvis cavity around the urinary bladder

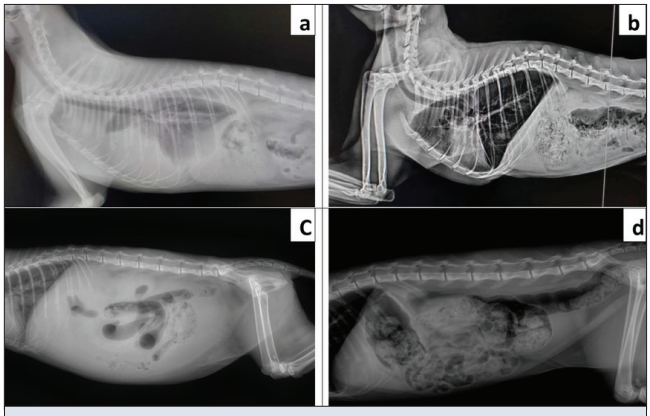

Fig 3. X-Ray imaging of cats suffering from effusive FIP; **a, b**- one year old Persian cat suffer from pleural and peritoneal effusions a- pre-treatment, **b**- 15 days post-treatment; **c, d**- eight months old DSH suffer from severe peritoneal effusions; **c**- pre-treatment, **d**- 15 days post treatment

10 days with the appearance of few amounts of peritoneal effusions and pyrexia.

The overall recurrence rate for surviving cats was 7.14% (1/14); the recurrence rate was 14.29% (1/7) in group (A) while, in group (B), no detected recurrence cases (0/7). No significant difference in disease recurrence between the two groups was detected at $P<0.05$. No another recurrent cases were reported until the date of paper submission.

Secondary Outcome of the Study

Obvious clinical improvement was observed in all of the 14 cats survived during the study, the. The main clinical signs improved within short period after starting the

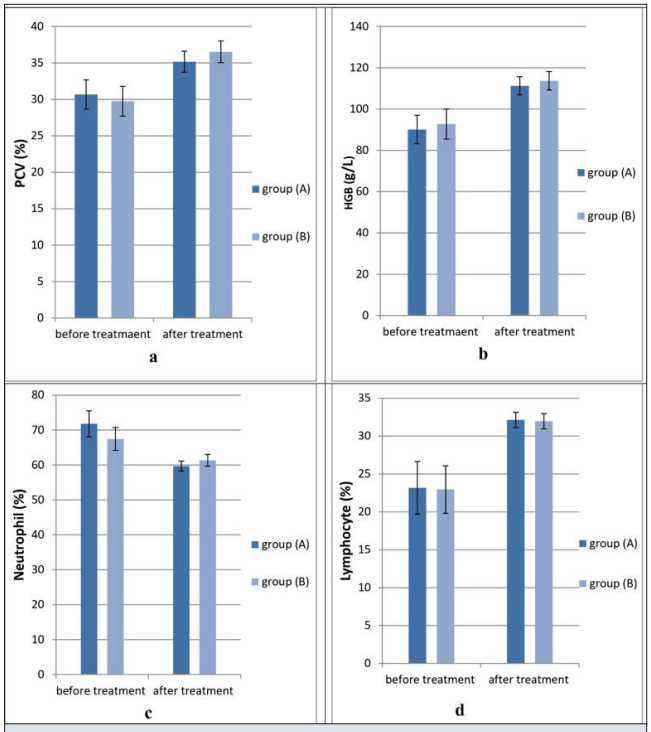

Fig 4. Hematology findings of group A and group B before and after treatment; bars represent the values in mean and bar-lines represent the standard error, P value at <0.05. **a**- PCV, **b**- HGB, **c**- neutrophils, **d**- lymphocyte

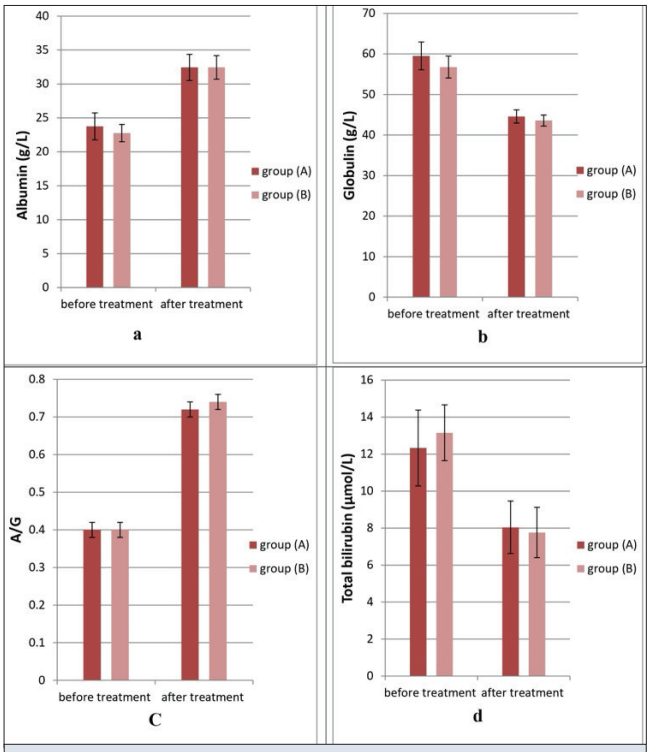

Fig 5. Biochemical findings of group A and group B before and after treatment; bars represent the values in mean and bar-lines represent the standard error; **a**- Albumin, **b**- Globulin, **c**- A/G ratio **d**- Total bilirubin

treatment protocol; pyrexia resolved in a mean of 8 days, effusions resolved in a mean of 14 days *(Fig. 3-B,D)*, and improvement of lethargy and return to normal activity occurred in a mean of 20 days.

Clinicopathological finding results analyses using one-way ANOVA of both groups before and after treatment were illustrated in *(Fig. 4, Fig. 5)*. A non-significant difference between both groups before and after treatment for almost all studied variables was detected at P<0.05. For hematological findings, PCV and HGB increased markedly after treatment in group B compared to groups A and B before treatment. Neutrophils decreased significantly in both groups after treatment compared to before treatment, while lymphocytes showed a significant increase after treatment in both groups. Regarding blood biochemistry findings, albumin and A/G ratio showed a significant increase after treatment in groups A and B; however, globulin revealed a marked decrease after treatment in groups A and B. Total bilirubin decreased obviously in group B after treatment compared to before treatment. All of the evaluated clinicopathological findings were improved toward their standard values at the end of the treatment period.

Clinicopathological finding related to liver and kidney function test such as ALT, ALP and creatinine were also improved toward their standard value at the end of treatment period.

Discussion

FIP was considered a progressive fatal disease with unfavorable prognosis [20]; the development of antiviral drugs for the treatment of human corona viruses gives a new hope for effective FIP treatment and lifesaving. In many countries, treatment of FIP is still limited; many veterinarians still use unlicensed and unregistered antiviral drugs in their countries for the treatment of FIP [22-24]. Remdesivir, a widely used drug for COVID-19, was evaluated in many studies for treating FIP in cats. The effusive form is the common clinical form of FIP; the recommended maintenance dose of remdesivir for effusive FIP form in cats ranged from 5-6 mg/kg body weight to 12 mg/kg body weight [12,24].

The main primary outcome of this treatment study using parenteral remdesivir is the survival rate; the survival rate in this randomized treatment study was 87.5% overall from the beginning of the treatment regime and reached 100% after 48 h from the beginning of the treatment regime, our finding is similar to previous study investigated the treatment of FIP in Sydney [12] with parenteral administration of remdesivir with or without transition administration of GS-441524, the overall survival rate from the beginning of treatment regime was 86% and after 48 h from start of treatment regime reach 96% and also agree with a retrospective study performed from 2020-2022 [13] illustrated that at completion of initial treatment

period by injectable remdesivir or oral GS-441524, 88.6% of treated cats were alive.

Our finding is not similar to a previous blinded study to treat effusive FIP, which indicated that the survival rate of oral remdesivir from the start of the treatment protocol to the end of the study was 77% [1], the authors attributed the lower survival rate to the medical condition of the included animal, which may be severely compromised at the start of antiviral treatment. Moreover, it may be related to dose adjustment of oral remdesivir and its bioavailability after oral administration.

Another important primary outcome of the study is disease recurrence and relapsing of the clinical signs recorded in treating FIP with various antiviral drugs. The overall relapsing rate in this study was 1/14 (7.14%) after excluding the two dead cats; this finding is nearly similar to the previous study [13], which recorded the recurrence rate of FIP after treatment by remdesivir or GS-441524 as (6.6%) and disagreed with the previous study [12], which recorded recurrence rate of the remdesivir treatment as 25%, the authors attributed the higher recurrence to unwilling remdesivir dose drop due to the increase in the animal's body weight during the treatment period and also disagree with Cosaro et al.[1] who recorded no recurrence rate however, one of the nine survived cats showed seizures after disease remission and was suspected to had the nervous manifestation of FIP but not confirmed after euthanization.

The secondary outcome of the treatment study is the clinical and clinicopathological changes that occur with antiviral treatment of FIP; the disease remission depends on the resolution of clinical signs and normalization of clinicopathological findings. The main clinical signs of effusive FIP in this study are pyrexia, body cavity effusions, and lethargy resolving in a mean period of 8, 14, and 20 days, respectively; this finding is consistent with a previous study [12] that reported quick and clear improvement of clinical signs and the median time for resolution of pyrexia and effusions by 7 and 9.5 days respectively. These findings disagree with the prior study [1], which reported that the effusions take 6 weeks to resolve in all surviving cats treated with oral remdesivir, and this is attributed to the study protocol of the treated animals as they only evaluated at three visits (0, 6,16 weeks).

Clinicopathological findings mostly take longer than clinical signs to normalize again and reach normal reference values; even though the average time for normalization of these values can not be detected in this study due to the absence of follow-up sampling and testing. One limitation of this study is that the evaluation of hematology and blood biochemistry was only done twice during the study: once before starting the treatment and once at the end of the treatment course on day 84.

All clinicopathological findings were adjusted toward their normal values after 84 days of treatment by parenteral remdesivir. One of the most clinicopathological findings used for the diagnosis of FIP is the A/G ratio; hyperglobulinemia with or without hypoalbuminemia leads to a decrease in the A/G ratio [25,26]. Our findings showed normalization in the value of albumin by an increase in the mean value by 9 g/L, reduction in the mean value of globulin by 14 g/L, and an increase in the mean value of A/G ratio by 0.3; these findings are nearly consistent with other studies [12,13] that recorded normalization in values of albumin, globulin and A/G ratio after treatment with remdesivir or GS-441524 or both, even though Cosaro et al.[1] reported that one cat still had elevated globulin level at 16 weeks of the treatment protocol, but they attributed this to other concurrent infections with gingivostomatitis and upper respiratory infection.

The selection of a cutoff point <0.6 for the A/G ratio in this study is to reach adequate specificity (87%), sensitivity (75%) and positive predictive value (95%), while selection of lower cutoff point will adversely lower the sensitivity reaching 50% [18].

In this randomized prospective centric study, we compare the efficacy of a low recommended maintenance dose (5-6 mg/kg body weight) of remdesivir in group (A) to higher maintenance dose (12 mg/kg body weight) of remdesivir in group (B) to treat effusive FIP.

In the consideration that the effusive FIP form without ocular or nervous signs is mostly less severe form; the study aims to determine whether the lower limit dose of remdesivir is as effective as the upper limit dose. Using the lower maintenance dose limit will significantly reduce the cost of treatment. The cost of the treatment regime of FIP, which usually takes 3 months or more, is still challenging to many patient owners, especially in developing countries as remdesivir is considered an expensive drug, particularly the available parenteral form.

In this study, the survival rates for both groups A and B were similar from the beginning of the study to 6 months including three months of follow-up (87.5%) and after 48 hrs. from the beginning of the treatment protocol (100%). Although the recurrence rate in group (A) receiving the lower dose was 1/7 (14.28%) and there were no recurrence cases in group (B), statistically no significant difference was detected between the two groups in recurrence rate.

There is no statistically significant difference in almost all clinicopathological findings between the two treatment groups, especially the A/G ratio, which is critical for the diagnosis of effusive FIP. Even though the

included animals in the study were randomly assigned to two treatment groups, no statistical differences were found in clinicopathological characteristics between the two groups. This may be related to the fact that all of the included animals were suffering from the same disease form of effusive FIP without ocular or nervous manifestation and were nearly similar in disease severity at the time of inclusion.

Another limitation of the study is that all included cats are considered highly suspected cases of effusive FIP due to the lack of confirmatory diagnostic tests, especially the gold standard test in effusive FIP in living animals' immunocytochemistry on effusive fluid instead of immunohistochemistry tissue biopsy [27,28], which requires special specific labs and professional technicians.

However, many previous treatment studies [13,29] for FIP include highly suspected cases of FIP in their study protocol and inclusion criteria. Furthermore, some studies [1,8,12] depend on the detection of FCoV RNA by PCR in body cavity effusions as a main test in the study inclusion criteria, which have variable sensitivity (72-100%) and specificity (83-100%) [6]. The combination of characteristic clinical signs of body effusions, distinctive effusive fluid with high protein content (positive Rivalta's test), low A/G ratio, and other clinicopathological findings without detecting any other relevant health disorders enhanced effusive FIP diagnosis, more over the response of most treated cases to remdesivir without any other specific treatment make the diagnosis more rationale.

The drug side effects in this study are related to the method of administration by subcutaneous injection as pain and discomfort; the same side effects reported previously [12,30,31]; registered and licensed oral remdesivir to be used in cats is highly recommended to overcome side effects related to the method of administration, be easily applied, and decrease the cost of therapy. However, no follow-up blood and biochemical analysis was performed in this study, and the clinicopathological findings evaluation depends on pre and post-treatment analyses; no clinically relevant adverse events showed by treated animals suspect liver or other organ insufficiency require further blood and biochemical analysis during treatment protocol or discontinued of treatment protocol.

In conclusion, remdesivir is effective in effusive FIP treatment without signs of nervous or eye manifestations with a high survival rate, especially for cats that survive the first 48 h of the treatment regime. Low-maintenance doses of remdesivir are as effective as high doses with a non-significant recurrence rate. Oral registered and licensed remdesivir is required to be used in animals with convenient concentration. It may be more cost-effective and easily administrated to avoid adverse side effects of injectable remdesivir. Additional future studies are essential to compare the efficacy of different antiviral drugs in FIP therapy. A rapid, reliable, and simple confirmatory test for FIP diagnosis is highly required.

Declarations

Availability of Data and Materials: The data illustrated in this study is available upon request from the corresponding author (E.S.)

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Ethical Approval: The Institutional Animal Care and Use Committee of the Faculty of Veterinary Medicine Cairo University (Vet. CU. IACUC) with code number (Vet CU131020241022) approved all the methods of animal handling and sampling included in this study.

Conflict of Interest: The authors declare that there is no conflict of interest

Declaration of Generative Artificial Intelligence (AI): The authors declare that the article and/or tables and figures were not written/created by AI and AI-assisted technologies.

Author's Contributions: Conceptualization, E.S. and A.Z.; methodology, E.S. and M. S.; investigation, A.Z. and E.S.; formal analysis M. S. and E.S.; writing-review & editing, all the authors. All authors have read and agreed to the published version of the manuscript.

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