# Histopathological Alterations of Rabbit Haemorrhagic Disease Virus in Native Egyptian Breed

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**Abstract**

Rabbit hemorrhagic disease (RHD) is a highly contagious disease of domestic and wild rabbits' species caused by a lagovirus belonging to the Caliciviridae family. RHD is characterized by acute liver necrosis and high mortality rate. The aim of this study was directed to recognize and describe RHDV (type 2) in naturally and experimentally infected rabbits, describing the histopathological alterations in liver, spleen, lungs and kidney in various Egyptian governorates during the period from January 2019 to May 2022. Nineteen suspected liver samples were collected from outbreaks in nine governorates. Three strains out of ten positive liver samples were proved for RHD virus by hemagglutination test and reverse transcriptase polymerase chain reaction. Kafr Sheikh strain, Sohag strain and Damiatta strain were inspected to study the pathological lesions associated with RHDV infection in naturally and experimentally infected rabbits.

**Keywords:** RHDV, RHDV type2, Caliciviridae Virus, histopathological changes, lagovirus

## Introduction

RHD, or rabbit hemorrhagic disease, has been threatening populations of European rabbits for more than 3 decades. It affects domestic and wild rabbits, and it is extremely infectious and lethal. The etiological agent of this disease is rabbit hemorrhagic disease virus (RHDV), a member of the family

Caliciviridae within the genus Lagovirus ***(Abrantes et al., 2012).***
Caliciviruses are spherical, single-stranded RNA viruses without an envelope that have a positively polarized genome. ***(Magouz et al., 2019).***
RHDV includes two genotypes, RHDV-GI.1 and RHDV2-GI.2 ***(Abodalal et al., 2021).*** RHDV1 classical causes an acute or hyperacute illness in adult rabbits that is marked by fulminant liver failure and hemorrhagic diathesis. It was initially identified in China in 1984 (***Liu et al., 1984)***. RHDV2, in contrast, affects rabbits younger than 4–8 weeks old and has been linked to various clinical outcomes as well as a much wider host range. It was initially discovered in France in 2010. ***(Le Gall-Recule et al., 2013)***
RHD was originally identified in Egypt after a sudden, very lethal outbreak among rabbits in the spring of 1991 in Sharkia Province, and it quickly spread throughout the majority of the governorates with severe morbidity and death ***(Salem and El Ballal, 1992).*** Massive mortalities that were verified to be RHDV2 positive in 2018 were reported in vaccinated rabbit flocks from several districts of Egypt ***(Abodalal and Tahoon, 2020).*** The primary cell type for RHDV replication is the hepatocyte. RHDV can bind to HBGAs that are expressed on the mucosa of the upper respiratory and digestive tracts of rabbits, ***(Ruvoën-Clouet et al., 2000).***
The characteristic clinical signs of RHD are described by fever, depression, dyspnea, as well as neurological symptoms (convulsions, ataxia, and paralysis of legs) that are observed just before animal death. ***(Magouz et al., 2019).***
Pathological investigation plays a significant role in recognition of viral infection in Rabbit diseases ***(Hamed et al., 2013)***. Disseminated intravascular coagulation (DIC) and necrotizing hepatitis lesions cause extensive circulation malfunction that results in death. ***(Marcato et al., 1991)***
Clinical signs observations, post-mortem examination, histological lesions, HA and HI tests and EM examination the most methods used in Diagnosis of RHD. ***(Li et al., 2023).*** The prevention and control strategies rely predominantly upon using of adequate preventive inactivated vaccine accompanied by adoption of strictly hygienic measures. There is no specific treatment of the disease.
The current study aimed to identify and characterize lesions of RHDV (type 2) in naturally and experimentally infected rabbits, tracing the histopathological changes in different organs.

## Material and Methods

### Sampling collection

In period between 2019 and 2022 a total nineteen herds of native breed

rabbits from nine provinces were inspected for RHDV infection. Three suspected liver samples represented each province were submitted for RHD clinical symptoms and post mortem lesions and samples for virus identification, experimental infection and histopathological examination.

**Identification of RHD Virus in rabbit's organs**

Nineteen liver samples were collected and prepared for RHDV isolation according to ***(Magouz et al., 2019).*** Liver samples were identified positive for RHDV by hemagglutination and hemagglutination inhibition test according to ***(Magouz et al., 2019).*** Ten liver samples out of nineteen were proved positive for RHDV using RT PCR according to ***(Magouz et al., 2019).*** Kafr Sheikh, Damiatta and Sohag strains were selected for experimentally infection and histopathological scoring in liver, lung, spleen and kidney according to ***(Bancroft and Layton, 2013)***

**Rabbits for experimental RHDV infection**

Thirty-three susceptible native breed rabbits were used for experimental infection with liver homogenate of rabbits with confirmed RHDV type 2. Each isolates represented by 3 rabbits and 3 were kept as uninfected control. Rabbits were inoculated intramuscularly with 1 mL of 10% liver homogenate with HA titer of 2 log 8/ml according to ***(Ismail et al., 2017).***

**Histopathological examination**

From each rabbit naturally and experimentally infected with isolates Kafr Sheikh2020 RHDV2 OP716873, Damiatta2020 RHDV2 OP716874 and Sohag2022 RHDV1 OP716875, four samples of liver, spleen, lung and kidney were taken and fixed in 10% buffered formalin solution for histopathological examination according to ***(Bancroft and Layton, 2013)***

**Result**

**Clinical features of RHDV in naturally infected rabbits.**

According to data shown in table 1, RHDV can result in a greater death rate in nursing kittens than in adults. Rabbits that were naturally infected with the Damiatta, Kafer Sheikh, and Sohag strains had significant mortalities ranging from 30% to 90%. High fever, anorexia, and severe respiratory and neurological manifestations are illness symptoms. Oral hemorrhages and red, foamy nasal discharges are observed. Lacrimation, ocular hemorrhages, epistaxis, and cyanosis are all evident (Fig. 1).

**Gross lesions and clinical findings of RHDV in experimentally infected Rabbits**

When compared to control negative animals, the most obvious and persistent indications of RHDV were an increased incidence of hepatic hemorrhages and a

congested or enlarged spleen (Fig. 2, 6). Additionally, the liver was enlarged, friable, and brown in color (Fig. 2). Slight comparable differences in clinical symptoms were found among rabbits infected with Kafer Sheikh, Damiatta and Sohag strain (Table 2). In contrast to the Sohag strain and the non-inoculated control animals, the gall bladder of animals infected with the Kafer Sheikh and Damiatta strains displayed enlargement, congestion, and hemorrhagic blood filled their cavity (Fig. 2).

The Kafer Sheikh and Damiatta strain-infected rabbits' lungs and tracheas displayed congestion, hyperemia, pulmonary edema, intra-alveolar hemorrhages, and spotted dark red petechial hemorrhage on the surface (Fig. 3). The tracheal cavity was also filled with bloody exudate.

The kidneys are swollen, congested, hyperemic, and have black spots on their surface due to tubular degeneration (Fig. 4). The bladder was badly affected by the colored urine (Fig. 5). The spleen was hyperemic, significantly enlarged (splenomegaly), and stained dark red in color (Fig. 6).

**Histopathological findings of RHDV in naturally and experimentally infected rabbits**

The histopathological results in our research showed a clear difference in the severity and distribution of lesions in rabbits experimentally infected with different RHDV Egyptian strains. These differences were observed in rabbits euthanized at 24hr and 48hr after infection than the rabbits were euthanized or died later. Significant lesions with variable scores were seen in the liver, spleen, lung and kidney of animals infected with Kafer Sheikh and Damiatta strains, but was less severe in rabbit infected with Sohag strain (Table3).

When compared to the un-infected control, the liver lesions of rabbits naturally and artificially injected with RHDV displayed centrilobular necrosis of hepatocytes and mononuclear cell infiltration (Figs. 7 and 8). Hepatocyte can also have an empty or pyknotic nucleus (Fig. 9). Spleen of control animal showing normal red pulp and white pulp (Fig. 10). Spleen of infected rabbit was moderately to severely congest and abundant, activated macrophages displaying active phagocytosis were seen throughout the red pulp compared to non-infected control (Fig. 11). Lung of control rabbit showing normal bronchiolar and alveolar tissues (Fig. 12). Lung of infected rabbit showing severe pulmonary congestion of alveolar capillaries, atelectasis and infiltration of mononuclear cells including histocytes and macrophages (Fig. 13). Lung of infected rabbit showing congestion of alveolar capillaries, oedema and perivascular infiltration of mononuclear cells includes lymphocytes (Fig. 14). Kidney of control rabbit showing normal renal glomeruli and tubules (Fig. 15).

Kidney of infected rabbit showing cortical congestion of the renal capillaries and severe degenerative and necrotic changes within the renal tubular epithelium (Fig. 16).

Kidney of infected rabbit showing medullary necrotic changes within the renal tubular epithelium and congestion of the renal capillaries (Fig. 17).

**Table (1)**: *Clinical presentation of RHDV in naturally infected Rabbits*

| **Clinical signs** | **Sohag strain** | **Damiatta strain** | **Kafr Sheikh strain** |
|---|---|---|---|
| **Breed** | Native breed | Native breed | Foreign cross breed |
| Mortality % of suckling | 90 | 62.5 | 30 |
| Mortality % of weaning | 82.5 | 54 | 46.6 |
| Mortalities of Growing | 53.3 | 41.6 | 35 |
| Mortality % of adult | 47.5 | 45 | 20 |
| Fever | +++ | +++ | ++ |
| Anorexia, collapse, lethargy | +++ | +++ | ++ |
| Sudden death | suckling (25) | suckling (17), weanig12 | - |
| Epistaxis | +++ | +++ | ++ |
| Hemorrhages from mouth | ++ | ++ | + |
| Haemorrhage of eye | + | + | - |
| Incoordination | +++ | +++ | ++ |
| Respiratory distress, dyspnea | +++ | +++ | ++ |
| Bloody Diarrhea | ++ | ++ | + |

**Table (2):** *Gross lesions of experimentally infected rabbits with Egyptian RHDV strains.*

| **Organ** | **Gross lesions** | **Sohag strain** | **Damiatta strain** | **Kafr Sheikh strain** |
|---|---|---|---|---|
| **Liver** | Enlargment | ++++ | +++ | ++ |
| | Hemorrhages | ++++ | ++++ | ++ |
| | Bloody,large gall bladder | ++++ | +++ | ++ |
| **Lung** | Pulmonary odema | ++ | ++ | - |
| | Spoted dark red color | +++ | ++ | ++ |
| | Intralveolr hemorrha | ++ | ++ | + |
| | Intratracheal hemorr | ++ | + | + |
| | Congesion,hyperemia | +++ | ++ | + |
| **Spleen** | Spleenomegaly | ++++ | ++++ | +++ |
| | Spoted dark red color | + | ++ | + |
| | Hypremia | ++ | ++ | ++ |
| | Congestion | ++ | ++ | ++ |
| **Kidney** | Enlargment | ++ | ++ | + |
| | Congesion, hypremic | ++ | ++ | ++ |
| | Hemorrhages | + | + | - |
| | Tubular degeneration | + | - | - |
| | Spoted dark red color | +++ | + | - |

**Table (3):** *Scores of histopathological changes in organs of rabbits experimentally infected with RHDV*

| Organ | Gross lesions | Sohag strain | Damiatta strain | Kafr Sheikh strain |
|---|---|---|---|---|
| **Liver** | Multifocal necrosis | ++++ | +++ | +++ |
| | Sinisoidal hypremia | ++++ | ++++ | ++++ |
| | Hepatocell dissociati | ++++ | +++ | ++ |
| | Granulocytes infilter | ++++ | +++ | ++ |
| | Hemosidrosis | ++ | ++ | - |
| **Lung** | Alveolar odema | ++++ | ++++ | - |
| | Hypremia | ++++ | ++++ | +++ |
| | Intralveolr hemorrha | +++ | +++ | ++ |
| | Desquamation of cell | ++ | + | + |
| | Venus dilatation | ++ | ++ | + |
| | Arterial constriction | + | + | - |
| | Interstitial necrosis | + | + | + |
| **Spleen** | Fibrin in red pulp | ++ | ++ | + |
| | Lymphocytosis | + | ++ | + |
| | Pyknosis | + | + | - |
| | White pulp necrosis | ++ | ++ | ++ |
| **Kidney** | Cortex hyperemia | ++ | ++ | + |
| | Protein cast | + | + | - |
| | Tubular degeneration | + | + | + |
| | Glomelular thrombi | + | - | - |
| | Glomlular necrosis | ++ | + | + |

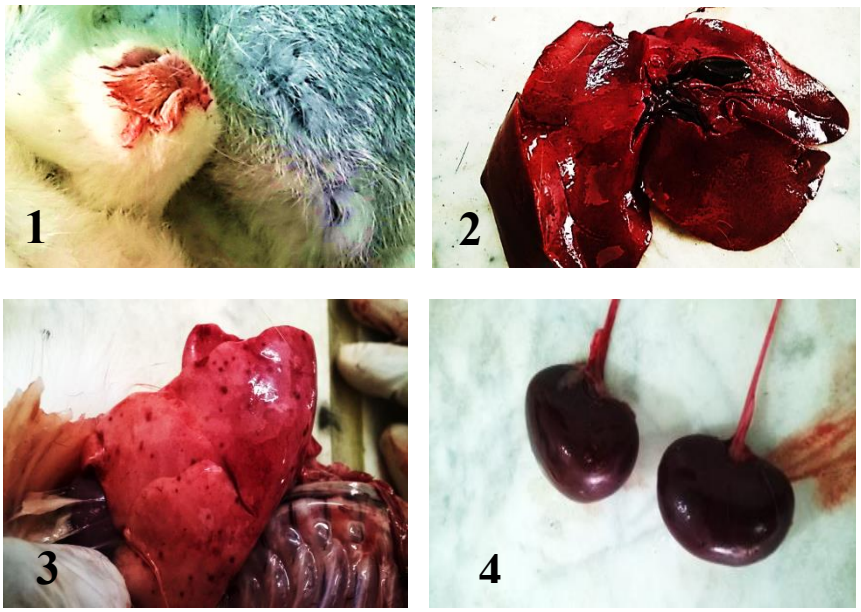


**Fig. (1):** Nasal hemorrhage in cross breed rabbits naturally infected with RHDV**.**

**Fig. (2):** Enlarged, edematous and congested liver of rabbits experimentally infected with RHDV kafer sheikh strain, gall bladder is enlarged and filled with blood.
**Fig. (3):** Lung of rabbits experimentally infected with RHDV Damiatta strain showed hyperemia, congestion, pulmonary edema and red spotted petechial hemorrhages on lung surface. Trachea is inflamed and filled with blood.
**Fig. (4):** Kidney of rabbits experimentally infected with RHDV Damiatta strain showed edematous and congestion. Red spotted petechial hemorrhages on its surface, ureters inflamed and filled with blood.



**Fig. (5):** Urinary bladder of rabbits experimentally infected with RHDV Kafr Sheikh Strain showing enlargement, inflamed and filled with yellowish urine.
**Fig. (6):** Spleen of rabbits experimentally infected with RHDV Kafer Sheikh strain, showed congestion, enlarged about 5 time than normal size and hemorrhagic inflammation in the entire organ.

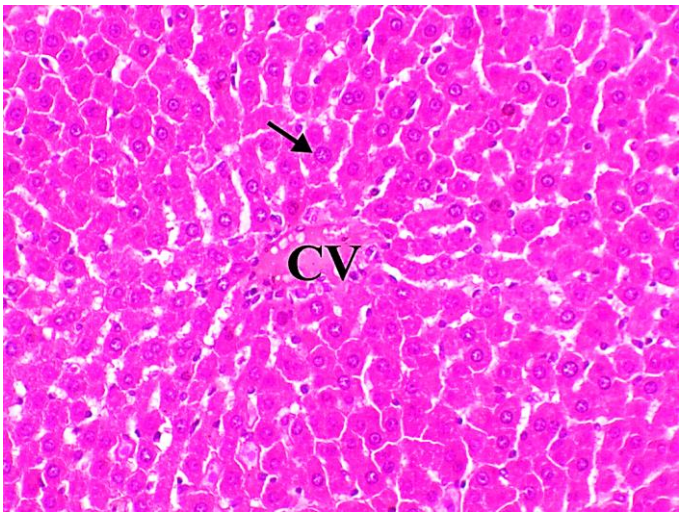


**Fig. (7).** Liver of control rabbit showing normal hepatocytes arranged in cords (arrow) around the central vein (CV), H&E, X200, bar= 50 µm.

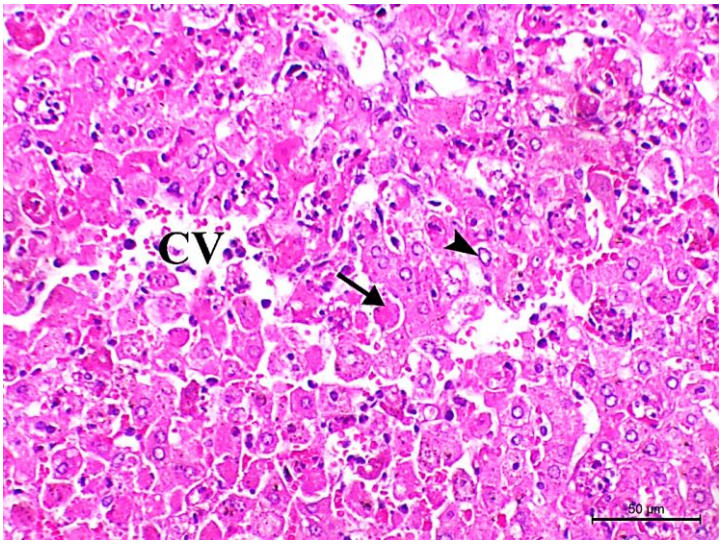


**Fig. (8).** Liver of rabbit showing centrilobular which extending to the whole hepatic lobules including the periportal area (arrow) with empty nucleus (arrowhead) (CV indicates central vein), H&E, X200, bar= 50 µm.

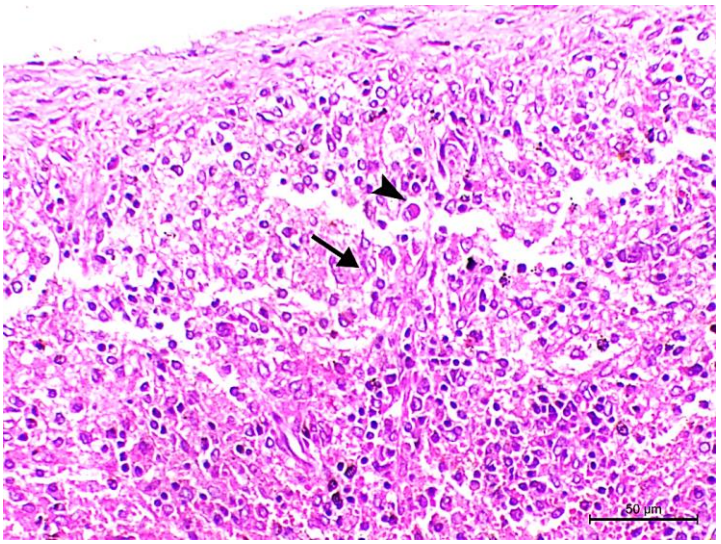


**Fig. (9).** Liver infected with RHDV showing subcapsular necrosis associated with marked mononuclear cells infiltration including histocytes (arrow), lymphocytes and plasma cells (arrowhead), H&E, X200, bar= 50 µm.

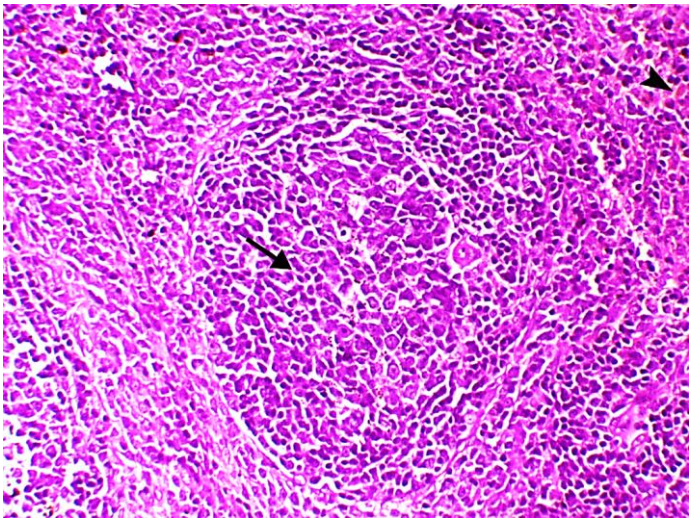

**Fig. (10).** Spleen of control animal showing normal red pulp and white pulp (arrowhead and arrow respectively), H&E, X200, bar= 50 µm.

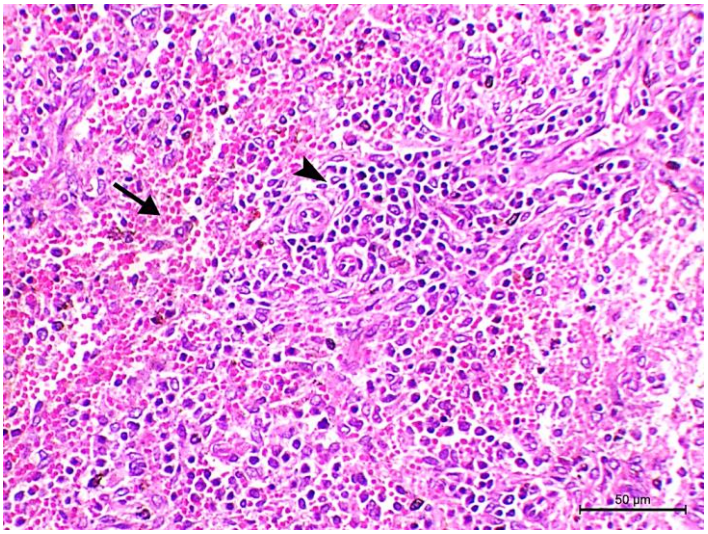


**Fig. (11).** Spleen showing severe congestion of the red pulp (arrow) and marked lymphoid depletion (arrowhead), H&E, X200, bar= 50 µm.

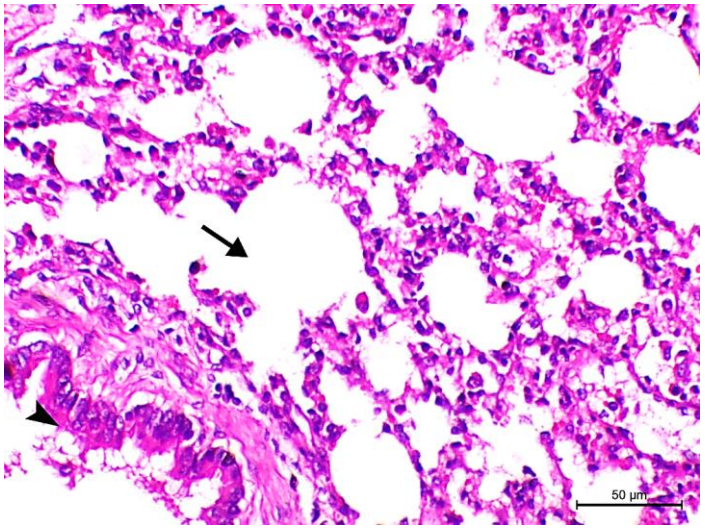


**Fig. (12).** Lung of control animal showing normal bronchiolar and alveolar tissues (arrow and arrowhead respectively), H&E, X200, bar= 50 µm.

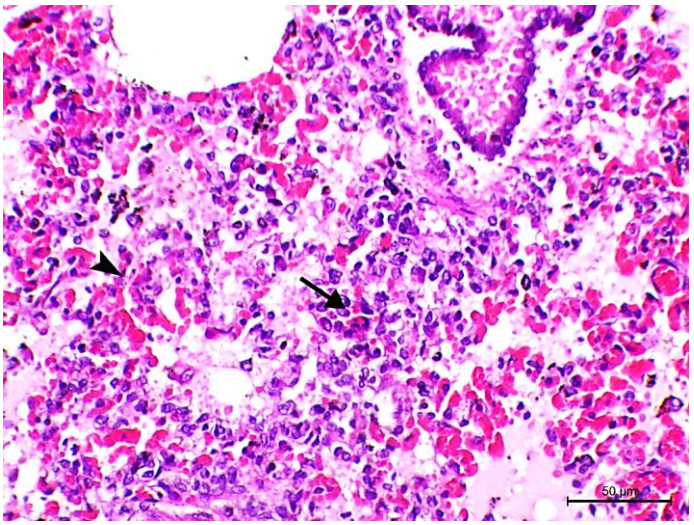


Fig. (**13**). Lung showing severe pulmonary congestion of alveolar capillaries (arrowhead), atelectasis and infiltration of mononuclear cells including histocytes and macrophages (arrow), H&E, X200, bar= 50 µm.

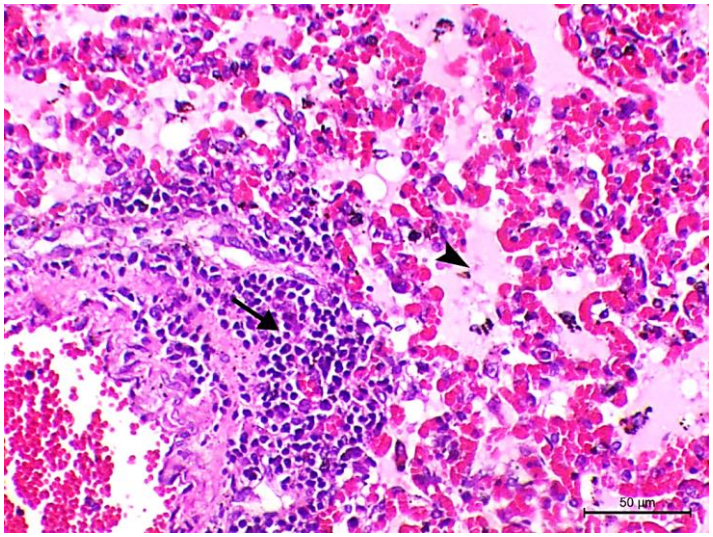


**Fig. (14).** Lung showing congestion of alveolar capillaries, oedema (arrowhead) and perivascular infiltration of mononuclear cells including lymphocytes (arrow), H&E, X200, bar= 50 µm.

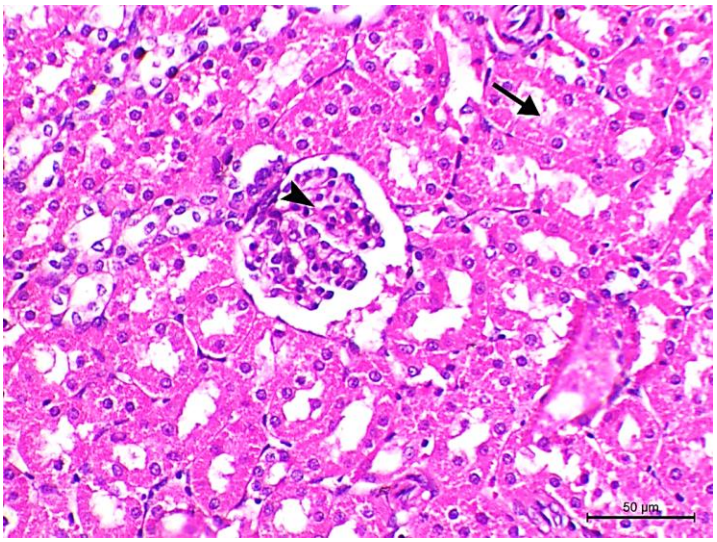


**Fig. (15).** Kidney of control animal showing normal renal glomeruli and tubules (arrowhead and arrow respectively), H&E, X200, bar= 50 µm.

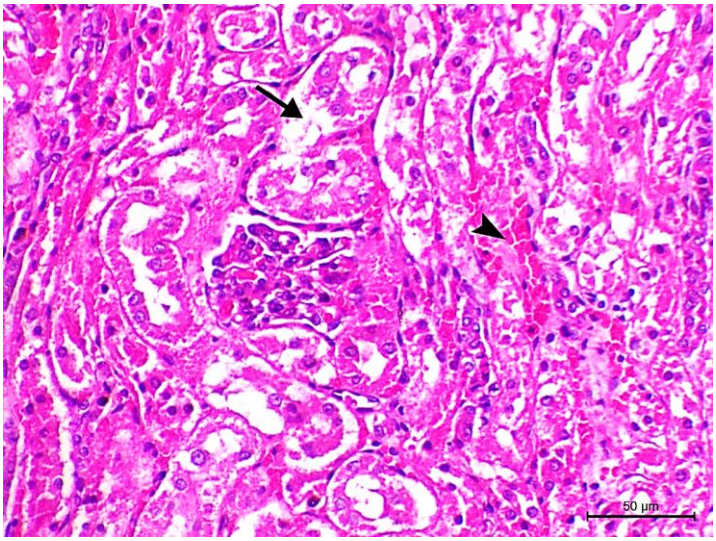


**Fig. (16).** Kidney showing cortical congestion of the renal capillaries (arrowhead) and severe degenerative and necrotic changes within the renal tubular epithelium (arrow), H&E, X200, bar= 50 µm.

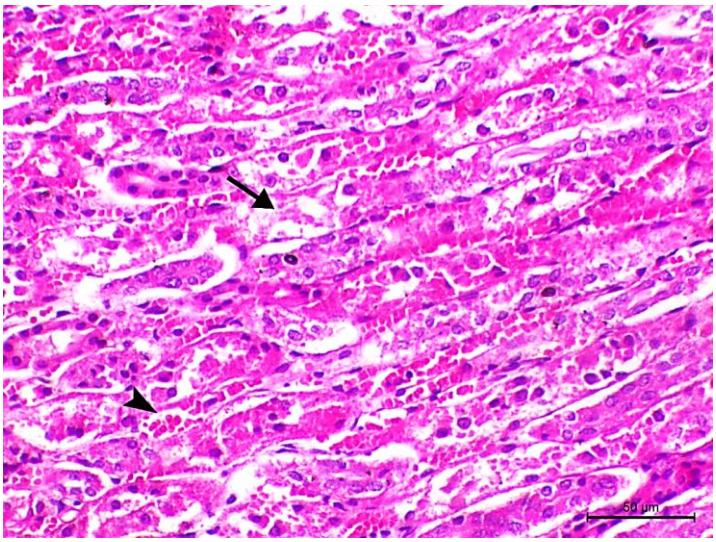


**Fig. (17).** Kidney showing medullary necrotic changes within the renal tubular epithelium (arrow) and congestion of the renal capillaries (arrowhead), H&E, X200, bar= 50 µm.

**Discussion**

RHD is a viral illness that affects both wild and domestic rabbits that is deadly, extremely infectious, and marked by high death rates. Due to high mortalities and considerable

losses in the production of meat and fur, the illness threatens the rabbit industry in Egypt and has a significant economic impact ***(Elsayed et al., 2023).*** Understanding the RHDV management strategy and updating the locally circulating strains utilized for vaccine manufacturing in Egypt were the main objectives of our investigation. In order to do this, RHDV in naturally and experimentally infected rabbits should be identified, characterized and describing Histopathological alterations.

Mortality rates for the rabbits under research varied from 30% to 90%. These results are in agreement with those from ***(Le Gall-Reculé et al., 2013)*** who noted mortality rates of up to 50% for kittens that were involved in RHD mortality events caused by RHDV- GI.2.

RHDV symptoms included a high fever, anorexia, lethargy, and the abrupt death of some nursing animals. These symptoms are indicative of the acute type, which is followed by death within 48-72 hours after infection. These findings are inconsistent with a previous study that found the clinical presentations of per acute, acute and chronic types of the disease are difficult to differentiate because the case histories lacked sufficient detail due to the criterion of sudden or unexpected death ***(Lavazza and Capucci, 2008)***.

The most notable symptoms of RHD included epistaxis and oral hemorrhages. Some animals that had subacute illness types showed milder clinical signs, the same findings were mentioned by ***(Greeno et al., 1996)***. The rabbit coagulation system disturbance may be the cause of bleeding from the nose and mouth. Coagulation cascade is stimulated by DIC, the first event in RHDV pathogenesis. ***(Ueda et al., 1992)***.

Hemorrhages, congestion in the liver, and spleen were found to be the most notable and consistent findings in our study's gross pathological lesions of RHDV. These data are parallel to results of ***(Anna Semerjyan et al., 2019*** *and* ***Julia et al., 2021)***. Infected rabbits' liver and spleen displayed classic symptoms such as enlargement, congestion, and hemorrhagic blood filling their cavity. These findings were in line with that obtained by ***(Abrantes et al., 2012)*** who stated that liver, lung and spleen consider the main target organs of RHDV and acute hepatitis because of liver cell loss as the result of RHDV-induced apoptosis and splenomegaly ***(Harcourt-Brown et al., 2020)***.

Hemorrhagic inflammation and congestions in liver, spleen, lungs and kidneys in our work may be due to massive disseminated intravascular coagulation (DIC) which is usually the cause of death ***(Ueda et al., 1992)***, and depletion of both B and T lymphocytes in the liver and the spleen accompanies the disease and accounts for an

impairment of the immune response ***(Marques et al., 2010).***

Results of histopathology in our work exhibited a clear difference in severity and distribution of lesions in rabbits experimentally infected with different Egyptian strains of RHDV, these difference showed in euthanized rabbits at 24hr and 48 hrs post infection than rabbits euthanized or died later. Liver lesion showed centrilobular necrosis of hepatocytes and mononuclear cell infiltration compared to an uninfected control. Hepatocytes may also show pyknotic or empty nucleus. These results are accordance with the discoveries of ***(Neimanis et al., 2018)***, in experimentally infected rabbits focused on the liver with degenerative changes. Generally, the mechanism of cell death is due to necrosis or apoptosis ***(Kerr et al., 1972)***, necrosis results from severe sudden injury and leads to consecutive inflammatory response. Conversely, apoptosis, proceeds following a cellular suicide program involving active gene expression in response to physiological or pathological signals ***(Vaux and Strasser, 1996)***, and resulting in activation of an intracellular proteases cascade ***(Alnemri, 1997).*** In previous studies about pathogenesis of RHDV infection, liver tissue destruction has been previously depicted as necrosis and apoptosis which leads to DNA fragmentation ***(Park et al., 1995).*** Apoptotic cell death with substantial cell loss and tissue destruction, recommended that apoptosis may play a central role in pathogenesis and may lead to the major pathologic changes and contribute to the rapid progression of this disease. Spleen of infected rabbits was moderately to severely congested, hemorrhagic and abundant, activated macrophages displaying active phagocytosis were seen throughout the red pulp compared to non-infected control. Other authors have reported the same results in liver, spleen, lung and kidneys who have stated that cell apoptosis is a procoagulant activity and constitute an initial event in RHDV pathogenesis stimulating the coagulation cascade ***(Greeno et al., 1996)*** and disseminated intravascular coagulopathy ***(Ueda et al., 1992).*** In comparison to the non-infected control, the pulmonary lesions were pulmonary congestion and edema, which were accompanied by somewhat higher numbers of intra-alveolar macrophages. These data are consistent with the findings of ***(Harcourt-Brown et al., 2020).*** Rabbits that had been experimentally injected with RHDV and developed renal lesions died quickly within 24 hours. In comparison to an uninfected control, glomeruli were substantially congested, occasionally accompanied by hemorrhage, and many fibrin thrombi were seen in both

glomerular capillaries and surrounding small arteries. These results were consistent with those of ***(Capucci et al., 2017),*** who observed the same pathological alterations in kidneys of rabbits that had been experimentally infected with RHDV and located RHDV antigen in the cortex and medulla of infected rabbits by immunohistochemistry.

Cortical and medullary tubular degeneration existed with epithelial degeneration and necrosis in dispersed tubules. These results support the theory of ***(Julia et al., 2021)*** that apoptosis and disseminated intravascular coagulopathy constitute the first events in the pathogenesis of RHDV and may play a crucial role in the progression of this disease, which is demonstrative for acute tubular nephrosis.

## Conclusions

It is appropriate to note that Histopathology plays a significant part in the accurate diagnosis of the RHD virus and has determined that the RHDV negatively affects the liver, spleen, lungs, and kidneys and causes severe mortalities.

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# التغيرات النسجية المرضية لفيروس المرض النزفي في الأرانب في السلالات المصرية الأصلية

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## الملخص العربي

مرض النزف الدموي الفيروسي في الأرانب (RHD) هو مرض شديد العدوى يصيب أنواع الأرانب المحلية والبرية ويسببه فيروس اللاجو التابع لعائلة كاليسي فيردي. ويهدد المرض صناعة الأرانب وله تأثير اقتصادي كبير بسبب الخسائر الكبيرة في إنتاج اللحوم والفراء.

يتميز مرض النزف الدموي الفيروسي في الأرانب بإلتهاب الكبد ومعدل وفيات عالية. تهدف هذه الدراسة إلى التعرف على ووصف فيروس النزف الدموي في الارانب (النوع الثانيRHDV2 ) في الأرانب المصابة طبيعيًا وتجريبيًا، وتتبع التغيرات النسيجية المرضية في الاعضاء الحيويه مثل الكبد والطحال والرئتين والكلى في مختلف المحافظات المصرية خلال الفترة من يناير 2019 إلى مايو 2022. وتم جمع عينات الكبد المشتبه بها من حالات التفشي التي حدثت في تسع محافظات مصريه. تم إثبات وجود ثلاث سلالات من أصل عشر عينات كبد إيجابية لفيروس النزف الدموي في الارانب عن طريق اختبار التلازن الدموي وتفاعل البلمره المتسلسل المسبوق بعمليه النسخ العكسي. تم فحص سلالة كفر الشيخ وسلالة سوهاج وسلالة دمياط لدراسة الآفات المرضية المصاحبة للإصابة بفيروس النزف الدموي في الأرانب المصابة طبيعياً وتجريبياً.