Comparative Medicine
Copyright 2023
by the American Association for Laboratory Animal Science

Vol 73, No 1
February 2023
Pages 58–71

Overview

Comparison of Cardiovascular Pathology in Animal Models of SARS-CoV-2 Infection: Recommendations Regarding Standardization of Research Methods

Kathleen Gabrielson,[1] Stephanie Myers,[2] Jena Yi,[1] Edward Gabrielson,[3] and Isabel A Jimenez[1]

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged as the viral pathogen that led to the global COVID-19 pandemic that began in late 2019. Because SARS-CoV-2 primarily causes a respiratory disease, much research conducted to date has focused on the respiratory system. However, SARS-CoV-2 infection also affects other organ systems, including the cardiovascular system. In this critical analysis of published data, we evaluate the evidence of cardiovascular pathology in human patients and animals. Overall, we find that the presence or absence of cardiovascular pathology is reported infrequently in both human autopsy studies and animal models of SARS-CoV-2 infection. Moreover, in those studies that have reported cardiovascular pathology, we identified issues in their design and execution that reduce confidence in the conclusions regarding SARS-CoV-2 infection as a cause of significant cardiovascular pathology. Throughout this overview, we expand on these limitations and provide recommendations to ensure a high level of scientific rigor and reproducibility.

Abbreviations: ACE2, angiotensin-converting enzyme 2; COVID-19, 2019 Coronavirus Disease; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

DOI: 10.30802/AALAS-CM-22-000095

Introduction to the Virus and the Pandemic

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a positive-sense, single-stranded, enveloped RNA virus that emerged as a human pathogen in late 2019. In March 2020, the World Health Organization declared a global state of emergency for the 2019 Coronavirus Disease (COVID-19) pandemic, which has since resulted in an estimated 18.2 million deaths worldwide.[36] Like the majority of emerging infectious diseases affecting human populations in recent history, SARS-CoV-2 is thought to have originated in wildlife.[61] This emergence may have been precipitated by the progressive blurring of human–wildlife–domestic animal interfaces resulting from progressive urbanization, deforestation, disruption of wildlife habitats, and wildlife trafficking.[38,143] Without intervention, these factors are poised to contribute to the emergence of future zoonotic disease.

Submitted: 16 Aug 2022. Revision requested: 04 Oct 2022. Accepted: 06 Jan 2023.
[1]Department of Molecular and Comparative Pathobiology, The Johns Hopkins University School of Medicine, Baltimore, Maryland; [2]School of Veterinary Medicine, Texas Tech University, Amarillo, Texas; and [3]Department of Pathology, The Johns Hopkins University School of Medicine, Baltimore, Maryland
**Corresponding author. Email: kgabriel@jhmi.edu*

Pathogenesis of a virus and the consequential lesions depend on the location and expression of host proteins that the virus uses to enter the cell. SARS-CoV-2 enters the host cell via viral spike-protein–mediated fusion at the host's angiotensin-converting enzyme 2 (ACE2) receptor. The ACE2 receptor is highly expressed in the respiratory tract, myocardium and arterial smooth muscle, gastrointestinal tract, and kidney, paralleling the organ systems affected by the virus.[14] Disease severity in patients with COVID-19 ranges from asymptomatic to critically ill, although the majority of cases are considered mild.[78] Fever, coughing, respiratory difficulty, loss of smell, muscle aches, fatigue, nausea, vomiting, headaches, and diarrhea are common presenting signs of acute COVID-19 infection.[14] A subset of patients—particularly those with comorbidities including advanced age, obesity, hypertension, and diabetes mellitus—commonly develop more severe clinical manifestations, including acute respiratory distress syndrome and multiorgan failure.[78] Immune response dysregulation is thought to contribute to the more severe pathogenesis responses in COVID-19, with systemic inflammation and exaggerated proinflammatory cytokine production playing a role in the development of coagulopathy, vasculitis, and multiorgan damage.[60,74,95,154]

Pathology of Cardiovascular Disease in Humans with SARS-CoV-2 Infection

This review of SARS-CoV-2 infections focuses on published data from human patient and animal studies that probe effects on the cardiovascular system. According to clinical criteria (for example, elevated serum levels of troponin I, ECG or echocardiography findings), the incidence of cardiac injury among COVID-19 patients ranges from 15% to 42%, depending on patient factors.[53] Moreover, cardiac injury is a documented risk factor for in-hospital mortality among COVID-19 patients.[129] Other viruses, including influenza viruses, also are associated with cardiac events, such as arrythmias,[28] and viral infections in general should be viewed as having the potential to exacerbate preexisting cardiac disease.

With regard to the incidence of the SARS-CoV-2 virus infecting cells in the heart, one study of 39 patients who died from COVID-19 found that 61.5% were RT-PCR positive for SARS-CoV-2 RNA in cardiac tissue.[91] However, the investigators could not rule out the possibility that the virus was within the vascular space (viremia) and not within the heart interstitial cells. Similar frequencies of cardiac involvement have been reported in patients who had clinically recovered from COVID-19, with 78% of patients having cardiac inflammation on MRI at time of testing.[115] However, these MRI findings were not confirmed by biopsy.

Cardiovascular disease is one of the most common prior comorbidities reported in patients with COVID-19 infection, and cardiovascular disease increases susceptibility to severe clinical disease with COVID-19,[45,132] implicating the heart as a target—either directly or indirectly—in severe SARS-CoV-2 cases. More specifically, SARS-CoV-2 infection has been associated with acute myocarditis, with the CDC reporting that patients with COVID-19 had nearly 16 times higher risk for myocarditis.[16] In addition, young men vaccinated with SARS-CoV-2 mRNA vaccines have a higher incidence of myocarditis.[77] However, relatively few published cases of COVID-19–associated acute myocarditis were confirmed by autopsy.[24,31,52,80,109,120]

Although various clinical studies have suggested that heart injury is a common complication of COVID-19,[4,49,70,101,121,129,164] autopsy studies assessing COVID-induced cardiac disease have been ambiguous with regard to the incidence and types of cardiac injury in patients with COVID-19, and differ in both methodology and criteria for diagnosis.[10,42,63,66,80,91,116] In particular, variation in the criteria used to render a diagnosis of myocarditis prevents a consensus regarding the frequency of this type of cardiac injury in SARS-CoV-2–infected patients.

Myocarditis is generally defined as the presence of an inflammatory infiltrate with adjacent cardiomyocyte injury (myocyte degeneration or necrosis). Viral infections of the heart are usually associated with a lymphocyte-predominant inflammatory infiltrate.[87] However, in the absence of known infection, hearts of many elderly patients also contain scattered small collections of tissue lymphocytes without evidence for myocardial injury. Thus, the histologic presence of small aggregates of lymphocytes alone is insufficient for the diagnosis of myocarditis.[9] Beyond lymphocytic inflammation, autopsy studies of some hearts from patients who died of COVID-19 have revealed microthrombi and inflammation, but necrosis has not commonly been reported.[63,93] In contrast with the high frequency of myocarditis diagnosed based on clinical criteria, if more rigorous criteria are used to diagnose myocarditis (inflammatory infiltrate in conjunction with the presence of myocyte necrosis), the true prevalence of myocarditis is likely relatively low (< 2%). Correlating pathologic findings and clinical data suggests that myocarditis is an uncommon cause of death in patients who die of COVID-19.[24,31,52,80,109,120] However, because the available literature has not used standardized terminology or methods for diagnosis, additional rigorous autopsy studies might reveal subsets of COVID-19-affected patients who do die as a result of myocarditis and provide insight into this apparently uncommon consequence of COVID-19 infection and its risk factors.

Overview of Spontaneous and Experimental Models of SARS-CoV-2 Infection in Animals

Early in the pandemic, many research facilities worldwide were temporarily shut down, while those that remained operational were focused on SARS-CoV-2. Thus, a great deal of research effort pivoted to SARS-CoV-2 studies. At the time of the writing of this manuscript, a PubMed search using the keyword 'SARS-CoV-2' yielded 207,458 publications. This intensive research effort has led to timely establishment of animal models for SARS-CoV-2. These models provided critical insights into SARS-CoV-2 pathogenesis, which were key to the development of appropriate outbreak management and biocontainment strategies, and for investigating therapeutic and preventative measures, including vaccine development.[161]

Animal models of COVID-19 infection show significant species variation in susceptibility to infection, clinical presentation, viral shedding, and transmission potential. For example, differences in ACE2 receptor structure between animal species determine host susceptibility to SARS-CoV-2 viral entry into cells.[163] Animal models are important both for understanding the pathogenesis and sequelae of COVID-19 infection and for addressing the applicability of research findings in various animals to the human situation.

Mice (*Mus musculus*) are one of the most common animals used in biomedical research[68] due to their well-characterized genome and molecular pathways, and the availability of commercial diagnostic reagents and standardized protocols in mice. However, due to differences in the structure of the murine ACE2 receptor, mice are not naturally susceptible to COVID-19 infection. Mouse-adapted viral strains of SARS-CoV-2 have been developed through a variety of techniques, including genomic (host and virus) modification and viral transfection, thus allowing mice to be utilized as an animal model for COVID-19 infection.[5,40,163] However, in order to study natural infection, researchers have also developed non-transgenic models using other animal species.[30,130]

Rather than mice, golden (Syrian) hamsters (*Mesocricetus auratus*) have emerged as the leading non-transgenic model for studying COVID-19 pathogenesis, due to the natural susceptibility of this species to SARS-CoV-2 infection.[26,58,72,131] In golden hamsters, overt respiratory signs are typically absent, and the primary clinical signs are weight loss, hunched posture, squinting, and lethargy. These clinical signs typically resolve after several days and the infection is cleared, with virus undetectable by 5 to 7 d after inoculation. Gross and histopathologic features of respiratory tract inflammation and pulmonary pathology in hamsters mirror the findings in mild to moderate human cases of COVID-19,[26,58,72,86,103,108,131] making golden hamsters a useful and reproducible model for research studies. The Roborovski dwarf hamster (*Phodopus roborovskii*)

also shares the same susceptibility to infection after intranasal inoculation,[162] but the dwarf hamster is reported to develop clinical respiratory signs and more prominent alveolar damage and microthrombi.[146] In addition, an inbred hamster substrain, SH101, was recently reported to develop lesions in the brain and liver, thus making this strain a good potential model for COVID-19 systemic disease.[162]

Various nonhuman primate (NHP) species with an ACE2 receptor conformation similar to that of humans are also susceptible to SARS-CoV-2 infection.[163] Given this susceptibility, as well as anatomic and physiologic similarities to humans, NHPs are important large animal models for COVID-19. Rhesus macaques (*Macaca mulatta*),[27,105,126,158] cynomolgus macaques (*Macaca fascicularis*),[108,112,147] African green monkeys (*Chlorocebus sabaeus*),[155] pigtail macaques (*Macaca nemestrina*), and squirrel monkeys (*Saimiri* spp.) have all been used to study SARS-CoV-2 pathogenesis.[55] However, despite the development of pulmonary lesions in some species, cardiovascular lesions have rarely been reported, and NHP inconsistently show clinical signs.[96,104,118,126,130,155] Differential susceptibility of Old World and New World primates has also been reported, with rhesus macaques appearing more susceptible than cynomolgus macaques.[92]

Natural and experimental SARS-CoV-2 infections also occur in cats (*Felis catus*),[6,18,55,111] dogs (*Canis lupus familiaris*),[128,133] ferrets (*Mustela putorius furo*),[82,128] farmed American mink (*Neovison vison*),[43,64] rabbits (*Oryctolagus cuniculus*),[163] and other susceptible species.[127] In zoological collections, SARS-CoV-2 infection has been documented in large cats[69] and in Western lowland gorillas (*Gorilla gorilla gorilla*) at 2 zoos (San Diego Zoo[127] and Zoo Atlanta[165]). In addition, wild white-tailed deer (*Odocoileus virginianus*) are also susceptible to SARS-CoV-2 infection.[34,62,65,94,110,139] In domestic cats and dogs, myocarditis has been well documented clinically in association with natural SARS-CoV-2 infection, as diagnosed through the presence of acute onset of clinical signs of congestive heart failure, ECG abnormalities, echocardiogram findings, and elevated cardiac troponin I in animals without a prior history of cardiac disease.[29,46] In contrast, little data is available regarding the incidence of cardiac pathology associated with natural SARS-CoV-2 infections in other animal species.

Evaluation of Cardiovascular Pathology in Experimental SARS-CoV-2 Infections

Given the clinical evidence suggesting that the cardiovascular system may be involved during SARS-CoV-2 infections, we conducted a literature review of animal-based studies of COVID-19 to evaluated the effect of infection on the development of cardiovascular pathology. Few SARS-CoV-2 studies in animals have focused primarily on the cardiovascular system. Of those that did address the cardiovascular system, few concluded that cardiovascular pathology was present. Moreover, our review identified limitations in the methodology and interpretations of the animal experiments that did report cardiovascular pathology in SARS-CoV-2 infections of animals. These limitations undermined our confidence in the extent of cardiovascular viral infectivity and subsequent cardiovascular lesions in animals. Misinterpretation in veterinary pathology is a common problem that has been reviewed elsewhere.[7,17,23,73,145,151] Here, we outline several components of the scientific investigation process that could be improved to increase the rigor and reproducibility of COVID-19 research using animals. In addition, throughout the remaining sections, we expand on some of these components, provide examples, and offer recommendations.

Increasing Rigor and Reproducibility in SARS-CoV-2 Infection in Animals: Common Problems and Examples

Lack of pathology expertise. One common problem is that research groups may not have consulted with veterinarians and pathologists in the evaluation of study design and study material. Including pathology experts with experience with background lesions of the examined species is critical for interpretation of pathology in animal models of SARS-CoV-2 infection. The veterinary pathology community is aware that myocarditis, necrosis, and fibrosis are background findings in macaques.[25,33] Myocardial lesions, such as degeneration and fibrosis, are also background findings in hamsters,[97] with myocardial inflammatory cell infiltrate observed as a background lesion in 6% of hamsters.[98] Experimental groups of hamsters and macaques should be large enough to provide a well-powered background lesion survey. Otherwise, background lesions may be misinterpreted as being caused by the etiologic agent being tested. For example, the authors of one study noted a left atrial thrombus in a golden hamster that died after SARS-CoV-2 infection[125] but failed to acknowledge the high spontaneous background incidence of atrial thrombi in this species.[97,98,125]

Importance of preparing high-quality figures and legends. The published figures in some reports of animals infected with SARS-CoV-2 are inadequate for critical evaluation, and cardiovascular pathology in particular is often difficult to interpret due to poor image quality. For example, one group reported that virus is present at 3 d after infection only in hearts of golden hamsters with positive RT-PCR findings, but negative for virus based on immunohistochemistry and in situ hybridization, with no positive viral signals at days 5, 7, 18, and 37 after infection.[135] In the legend and text, the authors described hearts as showing mild focal myocardial degeneration and inflammation compared with the normal control myocardium. However, the provided images showed no apparent cardiovascular lesions in either control or treated animals. Thus, the text and the legend—and ultimately the conclusions—did not accurately reflect the data shown in the figures. In another study, authors reported uniform lethality after experimental SARS-CoV-2 infection in so-called cardiomyopathic J2N-k golden hamsters. However, reporting of the pathology results and cause of death was inadequate, and further information was not given,[89] thus reducing confidence in these conclusions. In both examples, inappropriate conclusions were made with regard to pathologic findings, and the reviewers and editors apparently lacked the appropriate pathology expertise to evaluate the studies.

Does viral infectivity coincide with cardiovascular lesions? The majority of SARS-CoV-2 models do show that the virus is present in lung tissue at least one time point during the time course of the study. However, defining viral tropism based on tissue RT-PCR positivity is confounded in animals whose vessels have not been perfused, because virus from cells within the tissue cannot be differentiated from virus present only in the blood.[142] A more rigorous approach is to perfuse an animal with PBS to remove the blood cells from within vessels in organs before performing methods of viral identification such as RT-PCR analysis and genomic sequencing. Many reports have claimed to find viral tropism in a tissue based on evaluation of animals that were not perfused, thus preventing

determination of true organ infection.[21,56,57] Other methods of viral identification within organs can also be problematic. For example, positive immunohistochemistry labeling for virus was reported in the myocardium of a single rhesus macaque infected intratracheally, but the figure supporting this claim showed weak specific and high background staining.[39] In addition, the study did not illustrate or report myocarditis, cardiomyocyte degeneration or necrosis, thus calling into question conclusions regarding myocardial viral tropism in this one animal. Notably, clearly demonstrating the presence of virus within individual myocardial cells based on positive immunohistochemistry could constitute strong evidence of viral infectivity, even in the absence of cardiac pathology, providing that this was found in multiple animals.

Another example of inadequate documentation of virus infectivity is the description of cardiovascular lesions without demonstrating the presence of virus. In one study in rhesus macaques,[126] the authors reported varying levels of edema and inflammatory cell infiltration in multiple tissues, including the heart, on day 3 after inoculation, and diminished injury on day 6, but the figures provided do not match the descriptions and thus do not support the conclusions. Importantly, that particular study[126] provided no documentation of the presence of viral antigen or genome, and the authors failed to consider background inflammation. Another study in the golden hamster diagnosed myocarditis and myocardial microthrombi, but supporting figures were not included, nor was evidence of viral infection of the heart.[50] Demonstrating viral infectivity in an animal model at some point after inoculation should be a standard for all published work but is not always included. A rigorous experimental approach, following the guidelines of a modernized Koch's postulates (etiologic agent A causes lesion B) would include isolation or identification of virus from cells within the lesions that are attributed to the virus.

The current body of literature on SARS-CoV-2 in animals likewise does not sufficiently account for the pathogenicity concept of linking viral tissue tropism as either cause or effect of tissue injury by the virus. A question that should always be considered is whether observed lesions are caused by the virus itself, or whether the lesions are caused by a secondary biologic process, such as cytokine release syndrome (a phenomenon of hyper-inflammation involve elevation of various cytokines that is believed to contribute to increased myocardial oxygen consumption, endothelial dysfunction, and suppressed cardiac function).[102,141,159] Questions that should also be addressed in the literature are whether the virus present in the tissue with pathology, and whether the virus is present in a tissue in a feasible time frame for virus-induced cytopathology.

Confirmation of cardiac hypertrophy in SARS-CoV-2 infection studies. Cardiomyocyte cell death stresses the remaining cardiomyocytes of the heart pump. In response, surviving cardiomyocytes can become enlarged (that is, hypertrophic). Documentation of cardiac hypertrophy in the context of SARS-CoV-2 infection can therefore be used to support potential effects of the virus on the cardiovascular system. However, hypertrophy is common in aging animals and can be a background lesion, not caused by SARS-CoV-2 infection. A standard method used in cardiovascular research with rodents defines cardiac hypertrophy at necropsy by dividing the heart weight (in milligrams) by tibia length (in millimeters).[157] In NHP, heart weight as a proportion of body weight and myocyte cross-section measurements are used to assess hypertrophy. However, the heart weight:body weight ratio is not as accurate as heart weight:tibial length, given that body weight can vary due to the species, genetics, diet, and body condition. Thus, conclusions of heart hypertrophy in studies of SARS-CoV-2 infection that did not use the heart weight:tibial length method should be interpreted with caution, and overall changes in body weight should be evaluated as a potential confounder. According to the ventricular mass:body mass ratio, ventricular hypertrophy was present at 7 and 14 d after SARS-CoV-2 challenge in infected compared with unchallenged golden hamsters.[117] However, the authors did not correct for the fact that weight loss after SARS-CoV-2 infection is a consistent feature of the disease in this species, confounding their interpretation (that is, tibial length does not change despite weight loss).[26] This conclusion—that hearts develop hypertrophy after SARS-CoV-2 infection—is not supported by the data and was apparently a result of a misunderstanding of the experimental model.

Other methods also can lead to incorrect diagnosis of cardiac hypertrophy. Some studies have misinterpreted ratios of ventricular space to ventricle wall thickness based on the assumption that ventricular space reduction, as characterized by thickening of the ventricular wall and interventricular septum, implies hypertrophy.[117] However, the methods used to make these conclusions must be analyzed carefully. When a heart ceases to contract after euthanasia or natural death, it stops in either systole or diastole. Rigor mortis and fixation can affect these features of the heart. Due to this variability, scientists who are not experienced with anatomic pathology may interpret systole as heart hypertrophy or confuse a heart that stops in diastole with dilated cardiomyopathy.[124]

Determining chronicity of lesions in the cardiovascular system with SARS-CoV-2 infection. Because interstitial collagen deposition reflects prior or chronic inflammation in the heart, some studies use special stains to identify cardiac collagen deposition. For example, Masson trichrome staining has been used to identify perivascular collagen in a study of SARS-CoV-2 infection in golden hamsters, but the reported timeline of collagen deposition was not consistent with the acknowledged time course for collagen deposition after myocardial injury.[135]

When fibrosis is a component of a lesion, cardiomyocyte injury should also be assessed because it typically precedes fibrosis. Serum troponins are commonly used as biomarkers of cardiomyocyte damage, and troponin I is an excellent biomarker for cardiomyocyte damage in rodents and NHP.[11] Appropriate control subjects should always be used to determine the baseline levels of troponin release, but in at least one study in golden hamsters, troponin levels were compared only between treated and untreated infected animals, with no uninfected controls.[135] That particular study presented no evidence for viral infection of the heart, and intraluminal clotted blood in the heart of a hamster that recovered was misidentified as "mild focal myocardial degeneration" when compared with the normal control myocardium,[135] thus suggesting that a pathologist was not consulted for data interpretation.

Importance of differentiating vessel inflammation from leukocyte transmigration. In rodents, pulmonary arteries are easily delineated from pulmonary veins by the smooth muscle media of the arteries, in contrast to the cardiac (striated) muscle media of the pulmonary veins.[81] This morphology helps differentiate these vessels, which could be targets of inflammation or serve as a conduit for leukocytes to enter the lung during infection. Leukocyte entry into the lung from the bloodstream is important for combating infectious disease and is classically described as occurring via transmigration of leukocytes through the thin walls of capillaries and postcapillary venules.[1] Movement of

leukocytes through these vessels can be easily misinterpreted as inflammation.

The host response of leukocyte paving and transmigrating from small pulmonary arteries and veins to alveolar spaces is another important process that is an expected host response to infection in the lung parenchyma. In numerous published reports, this process of leukocyte paving and transmigration has been mischaracterized as vasculitis or "endothelialitis" (sometimes called "endothelitis"), despite the clear absence of viral antigen or genomic DNA in the affected vessels.[12,41,59,88,108,144]

Typical of most reports of so-called endothelialitis or vasculitis in golden hamsters, one of the most detailed investigations involved histology, immunohistochemistry, and transmission electron microscopy evaluated pulmonary vessels at 1, 3, 6, and 14 d after intranasal inoculation of hamsters with SARS-CoV-2.[3] The study reported that SARS-CoV-2 infected hamsters showed endothelial hypertrophy, endothelialitis, and vasculitis, with inflammation mainly consisting of macrophages with lower numbers of T-lymphocytes and neutrophils infiltrating the vascular walls and the perivascular region at 3 and 6 d after inoculation. The authors defined endothelial hypertrophy as endothelial cells bulging into the vascular lumen, endothelialitis as macrophages and lymphocytes directly beneath within or the endothelial cell layer, and vasculitis as inflammatory neutrophils, macrophages, and lymphocytes in small (< 100-µm diameter) and medium (100- to 200-µm diameter) vessels (artery or vein was not specified). Vasculitis was reported as early as 1 d after inoculation, peaking at 3 d, and "resolved" at 14 d.[3] However, our review of the provided images found no convincing evidence of an actual inflammatory process targeting the blood vessels in these hamsters; instead, the images were consistent with inflammatory cell movement through vessels walls and into the lung parenchyma during an infection. Pathologists vary on the diagnostic criteria used to differentiate vasculitis and leukocyte vascular transmigration. Providing the criteria for this diagnosis within the publication would allow readers to understand the rationale that supports this diagnosis, especially given the differences of opinions in this regard.

To differentiate between the process of normal transmigration of inflammatory cells from an infection with vasculitis, pathologists must consider the following questions: 1) does the response resolve? 2) does the response occur early after infection at a time when inflammatory cell recruitment to the lung is expected, and 3) do the vessels show a morphologic change at a later time point after viral infection? The previously mentioned report[3] included no descriptions or images of damage to the vessel walls, such as medial muscle cell necrosis, hemorrhage, or insudation of plasma proteins (fibrinoid necrosis). Moreover, positive medial immunostaining for complement, fibrin, or (hamster) immunoglobulin was not described, and later time points were not reported to show replacement fibroplasia, medial or intimal hypertrophy, or loss of elastic laminae. Rather, in this example,[3] the authors solely reported the complete disappearance of detectable pathologic changes at the end of the investigation period of 14 d after inoculation, when neither the vascular wall nor lumen showed significant numbers of inflammatory cells. Indeed, a transcriptomic study of SARS-CoV-2–infected hamster lungs found endothelial cell expression of chemoattractant chemokines, *Icam1*, and *Vcam1*,[106] thus supporting the fact that this transmigration process is part of the body's response to clear the infection, and vessels are left unharmed.

Another important point worth discussing is determining the causal relationship of virus infectivity in a cell and the cytopathic change in the cells that make up the vessel. In the study discussed earlier,[3] the authors noted a wide zone of absent immunostaining for SARS-CoV-2 nucleoprotein in and surrounding these vessels. Based on the Chapel Hill consensus conference on vasculitides:[75] the so-called inflamed vessels are clearly uninfected in this model,[3] therefore, this outcome cannot be considered an infectious vasculitis per se. Because the so-called inflammation is present at 24 to 72 h after inoculation, it cannot reasonably be interpreted as an adaptive immunity–mediated process, unless all of these hamsters uniformly had preexisting reactive B or T lymphocytes or both). Rather, a genuine autoimmune disease develops weeks after a viral trigger. Furthermore, any autoimmune vasculitis triggered by the virus would continue unabated in the absence of treatment after resolution of infection, given that these processes are not self-limited. Notably, in this example,[3] the virus was cleared, and no chronic lesions were ever found in vessels.

Not all descriptions SARS-CoV-2 infections of hamsters have described pulmonary endothelialitis or vasculitis.[26,48,114,119,131,135] A detailed ultrastructural study of the golden hamster SARS-CoV-2 model did not document viral infection of the endothelium or endothelial cell damage.[156] A number of papers with complete and thorough necropsy examinations of infected hamsters have likewise failed to note any systemic cardiovascular lesions.[26,103,131]

Similar vessel interpretations have been published regarding the pathology of NHP with SARS-CoV-2 infection. For example, endothelialitis was reported in 4 rhesus macaques infected with SARS-CoV-2[2] and in the lung endothelium of 4 Cambodian-origin cynomolgus and 4 Chinese-origin rhesus macaques, with mononuclear and neutrophil infiltrates in the intima of many vessels, vessel edema, and focal hemorrhage.[84] As for the hamster studies discussed above, these publications provided no evidence documenting viral targeting of the endothelium.

In contrast, pulmonary endothelialitis, vasculitis, and thromboemboli were not observed in a comparative review of SARS-CoV-2 lung lesions in 4 NHP species (rhesus macaques, pigtail macaques, African green monkeys, and squirrel monkeys).[32] Numerous other studies of SARS-CoV-2–infected rhesus, cynomolgus, and pigtail macaques; African green monkeys; and marmosets document absence of lesions or viral infection in the cardiovascular system, including pulmonary vessels.[15,19,37,76,92,99,104,105,118,123,137,149,150,152] Multiple studies of SARS-CoV-2 in ferrets similarly report no cardiovascular infection or lesions.[51,82,83,122,148,160]

Evidence of coagulopathies in SARS-CoV-2 animals. Viral infection of endothelial cells and inflammation of vessels are important in the pathogenesis of SARS-CoV-2. Coagulopathy is a logical result of these events. COVID-19–associated coagulopathy has been studied in human patients, with documented involvement of venous, arterial, and microvascular systems.[13] One human study proposed that hypercoagulability may enhance SARS-CoV-2 viral entry,[79] and thromboprophylaxis may improve outcomes for critically ill COVID-19 patients.[90] However, reports of thrombosis are rare in animal studies. Macroscopic or microscopic pulmonary thrombosis were absent in lung tissue from SARS-CoV-2 infected ferrets, and mass spectroscopy demonstrated stable plasma coagulation factors, suggesting that ferrets do not develop thrombotic sequela in response to SARS-CoV-2 infection.[85] Unfortunately, that study did not perform functional testing of coagulation (for example, prothrombin time, activated partial thromboplastin time).

A hamster study evaluating SARS-CoV-2 infectivity reported "virus infection-induced vasculitis," despite no detection of

viral antigen in the perivascular tissues or endothelium in the lungs of infected hamsters at any time point.[107] The authors did note a coagulopathy in infected hamsters, as determined by prolonged prothrombin times—based on human point-of-care strip tests that were not validated for use in hamsters—and by phosphotungstic acid–hematoxylin staining of the lung, without actual demonstration or reporting of any actual intravascular thrombi.[108] Salient details regarding blood collection (for example, site, anticoagulant) were not reported, and the collection of blood after cervical dislocation (and release of tissue factor) may be a confounding feature.

Recommendations

Since the start of the COVID-19 pandemic, a focus on SARS-CoV-2 research and the development of animal models has generated a large body of research that has undoubtedly contributed toward clinical benefits for COVID-19 patients. However, multiple opportunities remain to improve rigor and reproducibility in animal studies of SARS-CoV-2. Although clinical patient studies have demonstrated a concern for immune-mediated disease as a sequela of SARS-CoV-2 infection and subsequent development of vasculitis and coagulopathy, the current literature reveals sparse evidence of these pathologic changes in animals. We recommend the following practices for conducting and interpreting future studies of SARS-CoV-2 in animals (Table 1).

First and foremost, the scarcity of comparative pathologists has been a persistent issue.[44,138] The inclusion of veterinary pathologists in the design and analysis of animal-based COVID-19 research would ameliorate many of the concerns that we have addressed and would facilitate the implementation of many of our other recommendations. In addition, the inclusion of veterinary pathologists in comprehensive reviews of animal models would ensure that the literature is being appropriately interpreted with regards to the validity of pathologic findings (or lack thereof), which could influence the design of future studies.

Background lesions are histologic findings that, although abnormal, occur naturally in a particular species; familiarity with these lesions in the examined species is essential to avoid interpreting them as results of the experimental model. In addition, in initial studies, sample size must be maximized to the extent possible in order to allow determination of the level of background lesions and account for this potential confounding variable. For example, myocardial degeneration and fibrosis occur as background lesions in hamsters, whereas myocarditis, necrosis, and fibrosis are background lesions in macaques. Veterinary pathologists have unique training and familiarity with lesions in a variety of species, whereas physician pathologists or other MDs may lack sufficient experience with the species to recognize these findings, and may thus overinterpret or misinterpret the presence or significance of these lesions as related to infection. In species where background lesions have been previously characterized, historical controls can be used to reduce the number of animals used in a study. However, this requires that prior studies have rigorously evaluated and documented background lesions. On the other hand, diet and infectious disease prevalence could vary from year to year. Thus, controls should be included and evaluated at the same time as the experimental groups in order to control for environmental changes.

All investigators using animals in biomedical research should collaborate with a pathologist who has the appropriate expertise to provide interpretation of the histologic lesions and, where necessary, consult on the adequacy of the prior literature with regards to historical controls. Although veterinary pathologists with the appropriate experience are scarce and geographically dispersed,[8,22] resources are available to facilitate consultations and collaboration between the medical and veterinary research fields. Organizations such as the American College of Veterinary Pathologists may be contacted for assistance in locating a pathologist in your region (https://www.acvp.org). Furthermore, the Dean's Office at your regional veterinary or medical school may be able to provide suggestions regarding collaborating veterinarians and pathologists in the area. Some universities have core facilities for pathology and phenotyping animal models.

When reporting histopathologic lesions, authors should provide figures that clearly illustrate the findings, and these images must have adequate quality and resolution to allow readers to make their own interpretation. Figure legends must correspond to the lesions shown in the images. Ideally, images should contain visual aids (for example, arrowheads) that point out relevant lesions to readers. To ensure that the figure images and legends are appropriate, a veterinary pathologist should perform the histologic interpretation. Understandably, not every scientific journal will have a veterinary pathologist on the editorial staff or available to serve as a reviewer. Including a veterinary pathologist as an author reduces the likelihood of publication of inconsistent or inaccurate figures.

When cardiac hypertrophy is suspected, animals should be perfused with a potassium–cadmium chloride solution; this procedure will consistently stop the heart in diastole, thus facilitating comparison of hearts among treatment groups.[136] When this cannot be done, perfusion with PBS at least allows testing for SARS-CoV-2 viral genome in tissue samples without blood cell contamination. At necropsy, heart weights and tibia lengths should be recorded; the ratio of these parameters can then be used to assess the presence of cardiac hypertrophy across various treatment groups. After 48-h fixation in 10% buffered formalin, the heart should be sectioned at the midpapillary level, processed, paraffin-embedded, sectioned at 4 to 5 µm, and stained with either hematoxylin and eosin or with wheat germ agglutinin to outline the cardiomyocyte cross section. Microscopic evaluation of the heart can then be used to measure and compare cardiomyocyte cross sectional contours across treatment groups.[54]

When vascular lesions and microthrombi are reported, readers should be aware that microthrombi can occur after phlebotomy, venous catheter placement for anesthesia or euthanasia, following release of tissue factor associated with cervical dislocation, and with the use of euthanasia solution in NHP. It is important to recognize that the histologic presence of a thrombus does not necessarily mean that coagulopathy was present. Functional testing of coagulation (for example, prothrombin time, activated partial thromboplastin time, D dimers) should be included in studies with coagulopathy diagnoses to support or rule-out confounders that can cause thrombosis. In addition, the definitions of vasculitis and coagulopathy should be standardized. Reviewers and journal editors should be aware of these potential misunderstandings, particularly from authors without the background to understand the differences between vasculitis and the normal process of vessel transmigration. Editorial boards of journals should be expanded to include pathologists and veterinarians. In addition, funding agencies can organize workshops involving experts who can design a standardization scheme for infectious disease studies involving vessels and coagulopathy.

Table 1. Summary of recommendations related to research on cardiovascular pathology in animal models of SARS-CoV2 infections

Complications	Recommendations
The scarcity of comparative pathologists involved in the design and analysis of COVID-19 animal research models.	A veterinary pathologist should be included on the team of authors to provide expertise in the interpretation of pathologic findings from a comparative pathology background. The inclusion of veterinary pathologists in comprehensive reviews of animal models would ensure that the literature supports appropriate interpretation with regard to the validity of pathologic findings.
Animals have background (baseline) lesions that can occur naturally in a particular species. Background lesions must be identified and not misinterpreted as an outcome of the experimental model.	All investigators using animals in biomedical research should collaborate with a pathologist who has the appropriate expertise to interpret the histologic lesions. Organizations such as the American College of Veterinary Pathologists (https://www.acvp.org) may be contacted for assistance in locating a pathologist in your region. Furthermore, the Dean's Office at a regional veterinary or medical school can provide suggestions regarding collaborating veterinarians and pathologists in your area. In addition, sample size must be maximized whenever possible to determine the type and level of background lesions and account for this potential confounding variable.
Some publications that use SARS-CoV-2-inoculated animals provide low-resolution figures that may lack markers (for example, arrowheads), thereby interfering with critical evaluation by readers. Also, photomicrographs are not always consistent with the lesions described in the figure legends or the text.	When reporting histopathologic lesions, figures should be provided to illustrate the findings. These images have resolution sufficient to allow readers to make their own interpretation. Images should have visual aids (e.g., arrowheads) to indicate the relevant lesions. If possible, a veterinary pathologist should perform the histologic interpretation.
In many cases, conclusions of cardiac hypertrophy in experimental SARS-CoV-2 infection are inconsistent in methodology, calling into question the validity of the conclusions.	When cardiac hypertrophy is suspected, animals should undergo perfusion with a potassium–cadmium chloride solution; the heart will then consistently arrest in diastole, enabling consistent comparison of cardiac size between treatment groups. In addition, heart weights and tibia lengths should be recorded at necropsy; the ratio of these parameters can be used to assess for the presence of cardiac hypertrophy across different treatment groups. After 48-h of fixation in 10% buffered formalin, the heart should be sectioned at the midpapillary level, processed, paraffin-embedded, sectioned at 4 to 5 µm, and stained with either hematoxylin and eosin or with wheat germ agglutinin to outline the cardiomyocyte cross section.
Leukocyte transmigration can be confused for vasculitis on histopathologic evaluation. Vascular lesions and microthrombi are often misinterpreted or over-interpreted, and the definitions of vasculitis and coagulopathy lack standardization.	Involvement of a pathologist in the interpretation of histopathologic lesions would enhance appropriate differentiation of vasculitis and leukocyte transmigration. When vascular lesions and microthrombi are reported, authors should consider that microthrombi can also occur after phlebotomy, venous catheter placement, or the use of euthanasia solution. The histologic presence of a thrombus does not necessarily mean that coagulopathy was present. Functional testing of coagulation (for example, prothrombin time, activated partial thromboplastin time, D dimers) should be included in studies with coagulopathy diagnoses. In addition, the definitions of vasculitis and coagulopathy should be standardized. In the meantime, authors should provide definitions of vasculitis and coagulopathy in their publications.
Some animal models require a power analysis to determine the sample size needed to provide statistical significance for a pre-determined effect size and to allow determination of background pathology.	Whenever possible and feasible, a power analysis should be performed to determine the sample size needed for an adequately powered experiment. The incidence of background lesions should be considered in the power analysis.
Reproducibility of animal models can be complicated by inadequate reporting of methods, particularly with regard to scoring lesions.	Accurate and thorough details of the methods used, including systems used to score lesions, should always be reported to improve reproducibility.[161] Standard recommendations such as the ARRIVE (Animal Research: Reporting In Vivo Experiments) guidelines have been published to aid investigators.
The focus on lung pathology in animal studies of SARS-CoV-2 infection results in a lost opportunity for data collection in studies that fail to investigate the heart and vasculature. This failure makes it impossible to determine whether the lack of cardiac pathology in COVID-infected animals is due to the absence of this complication or lack of investigation.	The heart and vasculature (and perhaps other tissues) should be investigated (or at least retained for future evaluation) of histopathologic lesions and the presence of SARS-CoV-2 viral genome.
Failure to remove blood from the heart via vascular perfusion can confound the ability to differentiate the presence of the virus within cardiomyocytes compared with the blood cells within heart chambers. Molecular methods of detection of SARS-CoV-2 viral genomic DNA in tissue samples cannot be a reliable indicator of viral replication in those tissues where blood contamination is present.	Tissues should be processed after performing vascular perfusion to remove blood cell contamination. When potassium-cadmium chloride solution is not available, PBS perfusion should be performed. Vascular perfusion will enable detection of SARS-CoV-2 viral genome in tissue samples to be more representative of viral replication within those tissues. Molecular methods of SARS-CoV-2 detection in tissues should be correlated with histopathologic findings (for example evidence of viral replication within tissue). The methods of documenting viral tropism within tissues must be standardized.
Direct comparisons between the pathology findings of animals and humans are complicated by the variability in the time course of the disease in these populations.	The different time courses of infection between human and animal SARS-CoV-2 infection must be acknowledged as a potential confound of direct comparisons between species.

Whenever possible and feasible, we recommend performing a power analysis to accurately determine the sample size needed for an adequately powered experiment, and we propose that this analysis consider the incidence of background lesions.[47,140] We recognize that large animal models, such as macaques, require more resources and are associated with a greater financial overhead than other species, such that a large sample size may not be feasible. However, background pathology should still be acknowledged, and a board-certified veterinary pathologist (or a veterinary pathologist with sufficient experience) should consider background lesions when interpreting the pathology. Published guidelines for pathology review are available for various species, and may serve as a resource when the use of historical controls is to be considered.[11,20,35,67,71,124,134,153]

Accurate and thorough details of the methods, including scoring systems used for lesions, should be included to improve reproducibility.[100] Standard recommendations such as the ARRIVE (Animal Research: Reporting In Vivo Experiments) guidelines have been published to aid investigators in reporting necessary experimental conditions to ensure full transparency and replicability.[112,113]

In addition, the majority of SARS-CoV-2 animal models in the literature principally evaluate lung tissues. By failing to investigate the heart and vasculature or by inappropriately processing these tissues (for example, vascular perfusion), important biologic information is lost, making it impossible to determine whether the lack of cardiac pathology in animals infected with SARS-CoV-2 results from the absence of this condition, or from inadequate investigation and rigor. A similar principle exists with regard to standardizing the methods of documenting viral tissue tropism; for example, failure to remove blood from the heart via perfusion confounds the differentiation of viral presence in cardiomyocytes as opposed to its presence within blood cells in the heart chambers.

Finally, inherent issues exist in making direct comparisons between experimental findings from animals and autopsy data from human cases of COVID-19, principally with regard to the time course of the disease. For example, at the time of death, human patients vary in the presence of comorbidities, ventilator injury, and severity of lung injury. Animals used in research typically lack preexisting comorbidities and have a similar background of genetic and environmental conditions. In addition, animals are euthanized at a predetermined experimental endpoint, thus standardizing the time course of the disease across the cohort, or potentially are euthanized sooner, depending on the clinical course and whether a humane endpoint becomes necessary. Although long-term effects of COVID-19 have been documented in human patients, the constraints of animal models make long-term sequelae difficult to evaluate. These differences between humans and animal models are important potential confounders of direct comparisons between species.

Acknowledgments

We acknowledge training support from the National Institutes of Health (T32 RR07002) for IAJ and SM.

References

1. **Ackermann MR**. 2017. Inflammation and healing, p 73–131. In: Zachary JF, editors. Pathologic basis of veterinary disease, 6th edition. St. Louis (MO): Mosby Elsevier.
2. **Aid M, Busman-Sahay K, Vidal SJ, Maliga Z, Bondoc S, Starke C, Terry M, Jacobson CA, Wrijil L, Ducat S, Brook OR, Miller AD, Porto M, Pellegrini KL, Pino M, Hoang TN, Chandrashekar A, Patel S, Stephenson K, Bosinger SE, Andersen H, Lewis MG, Hecht JL, Sorger PK, Martinot AJ, Estes JD, Barouch DH**. 2020. Vascular disease and thrombosis in SARS-CoV-2–infected rhesus macaques. Cell **183**:1354–1366. https://doi.org/10.1016/j.cell.2020.10.005.
3. **Allnoch L, Beythien G, Leitzen E, Becker K, Kaup FJ, Stanelle-Bertram S, Schaumburg B, Mounogou Kouassi N, Beck S, Zickler M, Herder V, Gabriel G, Baumgärtner W**. 2021. Vascular inflammation is associated with loss of aquaporin 1 expression on endothelial cells and increased fluid leakage in SARS-CoV-2 infected golden Syrian hamsters. Viruses **13**:639. https://doi.org/10.3390/v13040639.
4. **Arentz M, Yim E, Klaff L, Lokhandwala S, Riedo FX, Chong M, Lee M**. 2020. Characteristics and outcomes of 21 critically ill patients with COVID-19 in Washington state. JAMA **323**:1612–1614. https://doi.org/10.1001/jama.2020.4326.
5. **Bao L, Deng W, Huang B, Gao H, Liu J, Ren L, Wei Q, Yu P, Xu Y, Qi F, Qu Y, Li F, Lv Q, Wang W, Xue J, Gong S, Liu M, Wang G, Wang S, Song Z, Zhao L, Liu P, Zhao L, Ye F, Wang H, Zhou W, Zhu N, Zhen W, Yu H, Zhang X, Guo L, Chen L, Wang C, Wang Y, Wang X, Xiao Y, Sun Q, Liu H, Zhu F, Ma C, Yan L, Yang M, Han J, Xu W, Tan W, Peng X, Jin Q, Wu G, Qin C**. 2020. The pathogenicity of SARS-CoV-2 in hACE2 transgenic mice. Nature **583**:830–833. https://doi.org/10.1038/s41586-020-2312-y.
6. **Bao L, Song Z, Xue J, Gao H, Liu J, Wang J, Guo Q, Zhao B, Qu Y, Qi F, Gong S, Liu M, Lv Q, Li D, Han Y, Zhao W, Deng S, Liu Y, Xiang Z, Yang B, Deng W, Yu H, Cong Z, Wei Q, Xu J, Gao GF, Qin C**. 2021. Susceptibility and attenuated transmissibility of SARS-CoV-2 in domestic cats. J Infect Dis **223**:1313–1321. https://doi.org/10.1093/infdis/jiab104.
7. **Barthold SW**. 2004. Genetically altered mice: phenotypes, no phenotypes, and Faux phenotypes. Genetica **122**:75–88. https://doi.org/10.1007/s10709-004-1439-3.
8. **Barthold SW, Borowsky AD, Brayton C, Bronson R, Cardiff RD, Griffey SM, Ince TA, Nikitin AY, Sundberg J, Valli VE, Ward JM**. 2007. From whence will they come? — A perspective on the acute shortage of pathologists in biomedical research. J Vet Diagn Invest **19**:455–456. https://doi.org/10.1177/104063870701900425.
9. **Basso C, Aguilera B, Banner J, Cohle S, d'Amati G, de Gouveia RH, di Gioia C, Fabre A, Gallagher PJ, Leone O, Lucena J, Mitrofanova L, Molina P, Parsons S, Rizzo S, Sheppard MN, Mier MPS, Kim Suvarna S, Thiene G, van der Wal A, Vink A, Michaud K**, Association for European Cardiovascular Pathology. 2017. Guidelines for autopsy investigation of sudden cardiac death: 2017 update from the Association for European Cardiovascular Pathology. Virchows Arch **471**:691–705. https://doi.org/10.1007/s00428-017-2221-0.
10. **Basso C, Leone O, Rizzo S, De Gaspari M, van der Wal AC, Aubry MC, Bois MC, Lin PT, Maleszewski JJ, Stone JR**. 2020. Pathological features of COVID-19–associated myocardial injury: A multicentre cardiovascular pathology study. Eur Heart J **41**:3827–3835. https://doi.org/10.1093/eurheartj/ehaa664.
11. **Bau-Gaudreault L, Arndt T, Provencher A, Brayton CF**. 2021. Research-relevant clinical pathology resources: Emphasis on mice, rats, rabbits, dogs, minipigs, and non-human primates. ILAR J **62**:203–222. https://doi.org/10.1093/ilar/ilab028.
12. **Becker K, Beythien G, de Buhr N, Stanelle-Bertram S, Tuku B, Kouassi NM, Beck S, Zickler M, Allnoch L, Gabriel G, von Köckritz-Blickwede M, Baumgärtner W**. 2021. Vasculitis and neutrophil extracellular traps in lungs of golden Syrian hamsters with SARS-CoV-2. Front Immunol **12**:640842. https://doi.org/10.3389/fimmu.2021.640842.
13. **Becker RC**. 2020. COVID-19 update: Covid-19-associated coagulopathy. J Thromb Thrombolysis **50**:54–67. https://doi.org/10.1007/s11239-020-02134-3.
14. **Beyerstedt S, Casaro EB, Rangel EB**. 2021. COVID-19: Angiotensin-converting enzyme 2 (ACE2) expression and tissue susceptibility to SARS-CoV-2 infection. Eur J Clin Microbiol Infect Dis **40**:905–919. https://doi.org/10.1007/s10096-020-04138-6.
15. **Blair RV, Vaccari M, Doyle-Meyers LA, Roy CJ, Russell-Lodrigue K, Fahlberg M, Monjure CJ, Beddingfield B, Plante KS, Plante**

JA, Weaver SC, Qin X, Midkiff CC, Lehmicke G, Golden N, Threeton B, Penney T, Allers C, Barnes MB, Pattison M, Datta PK, Maness NJ, Birnbaum A, Fischer T, Bohm RP, Rappaport J. 2021. acute respiratory distress in aged, SARS-CoV-2-infected African green monkeys but not rhesus macaques. Am J Pathol **191**:274–282. https://doi.org/10.1016/j.ajpath.2020.10.016.

16. **Boehmer TK, Kompaniyets L, Lavery AM, Hsu J, Ko JY, Yusuf H, Romano SD, Gundlapalli AV, Oster ME, Harris AM**. 2021. Association between COVID-19 and myocarditis using hospital-based administrative data - United States, March 2020-January 2021. MMWR Morb Mortal Wkly Rep **70**:1228–1232. https://doi.org/10.15585/mmwr.mm7035e5.
17. **Bolon B, Brayton C, Cantor GH, Kusewitt DF, Loy JK, Sartin EA, Schoeb TR, Sellers RS, Schuh JC, Ward JM**. 2008. Editorial: Best pathology practices in research using genetically engineered mice. Vet Pathol **45**:939–940. https://doi.org/10.1354/vp.45-6-939.
18. **Bosco-Lauth AM, Hartwig AE, Porter SM, Gordy PW, Nehring M, Byas AD, VandeWoude S, Ragan IK, Maison RM, Bowen RA**. 2020. Experimental infection of domestic dogs and cats with SARS-CoV-2: Pathogenesis, transmission, and response to reexposure in cats. Proc Natl Acad Sci USA **117**:26382–26388. https://doi.org/10.1073/pnas.2013102117.
19. **Böszörményi KP, Stammes MA, Fagrouch ZC, Kiemenyi-Kayere G, Niphuis H, Mortier D, van Driel N, Nieuwenhuis I, Vervenne RAW, Haaksma T, Ouwerling B, Adema D, Acar RF, Zuiderwijk-Sick E, Meijer L, Mooij P, Remarque EJ, Oostermeijer H, Koopman G, Hoste ACR, Sastre P, Haagmans BL, Bontrop RE, Langermans JAM, Bogers WM, Kondova I, Verschoor EJ, Verstrepen BE**. 2021. The post-acute phase of SARS-CoV-2 infection in two macaque species is associated with signs of ongoing virus replication and pathology in pulmonary and extrapulmonary tissues. Viruses **13**:1673. https://doi.org/10.3390/v13081673.
20. **Bradley AE, Wancket LM, Rinke M, Gruebbel MM, Saladino BH, Schafer K, Katsuta O, Garcia B, Chanut F, Hughes K, Nelson K, Himmel L, McInnes E, Schucker A, Uchida K**. 2021. International Harmonization of Nomenclature and Diagnostic Criteria (INHAND): Nonproliferative and proliferative lesions of the rabbit. J Toxicol Pathol **34**:183S–292S. https://doi.org/10.1293/tox.34.183S.
21. **Bullock HA, Goldsmith CS, Zaki SR, Martines RB, Miller SE**. 2021. Difficulties in differentiating coronaviruses from subcellular structures in human tissues by electron microscopy. Emerg Infect Dis **27**:1023–1031. https://doi.org/10.3201/eid2704.204337.
22. **Cardiff RD**. 2007. Pathologists needed to cope with mutant mice. Nature **447**:528. https://doi.org/10.1038/447528c.
23. **Cardiff RD, Ward JM, Barthold SW**. 2008. 'One medicine—one pathology': Are veterinary and human pathology prepared? Lab Invest **88**:18–26. https://doi.org/10.1038/labinvest.3700695.
24. **Castiello T, Georgiopoulos G, Finocchiaro G, Claudia M, Gianatti A, Delialis D, Aimo A, Prasad S**. 2022. COVID-19 and myocarditis: A systematic review and overview of current challenges. Heart Fail Rev **27**:251–261. https://doi.org/10.1007/s10741-021-10087-9.
25. **Chamanza R, Parry NM, Rogerson P, Nicol JR, Bradley AE**. 2006. Spontaneous lesions of the cardiovascular system in purpose-bred laboratory nonhuman primates. Toxicol Pathol **34**:357–363. https://doi.org/10.1080/01926230600809737.
26. **Chan JF, Zhang AJ, Yuan S, Poon VK, Chan CC, Lee AC, Chan WM, Fan Z, Tsoi HW, Wen L, Liang R, Cao J, Chen Y, Tang K, Luo C, Cai JP, Kok KH, Chu H, Chan KH, Sridhar S, Chen Z, Chen H, To KK, Yuen KY**. 2020. Simulation of the clinical and pathological manifestations of coronavirus disease 2019 (COVID-19) in a golden Syrian hamster model: Implications for disease pathogenesis and transmissibility. Clin Infect Dis **71**:2428–2446. https://doi.org/10.1093/cid/ciaa644.
27. **Chandrashekar A, Liu J, Martinot AJ, McMahan K, Mercado NB, Peter L, Tostanoski LH, Yu J, Maliga Z, Nekorchuk M, Busman-Sahay K, Terry M, Wrijil LM, Ducat S, Martinez DR, Atyeo C, Fischinger S, Burke JS, Slein MD, Pessaint L, Van Ry A, Greenhouse J, Taylor T, Blade K, Cook A, Finneyfrock B, Brown R, Teow E, Velasco J, Zahn R, Wegmann F, Abbink P, Bondzie EA, Dagotto G, Gebre MS, He X, Jacob-Dolan C, Kordana N, Li Z, Lifton MA, Mahrokhian SH, Maxfield LF, Nityanandam R, Nkolola JP, Schmidt AG, Miller AD, Baric RS, Alter G, Sorger PK, Estes JD, Andersen H, Lewis MG, Barouch DH**. 2020. SARS-CoV-2 infection protects against rechallenge in rhesus macaques. Science **369**:812–817. https://doi.org/10.1126/science.abc4776.
28. **Chen L, Han X, Li Y, Zhang C, Xing X**. 2021. Complications of cardiovascular events in patients hospitalized with influenza-related pneumonia. Infect Drug Resist **14**:1363–1373. https://doi.org/10.2147/IDR.S305509.
29. **Chetboul V, Foulex P, Kartout K, Klein AM, Sailleau C, Dumarest M, Delaplace M, Gouilh MA, Mortier J, Le Poder S**. 2021. Myocarditis and subclinical-like infection associated with SARS-CoV-2 in two cats living in the same household in France: A case report with literature review. Front Vet Sci **8**:748869. https://doi.org/10.3389/fvets.2021.748869.
30. **Chu H, Chan JFW, Yuen KY**. 2022. Animal models in SARS-CoV-2 research. Nat Methods **19**:392–394. https://doi.org/10.1038/s41592-022-01447-w.
31. **Çinar T, Hayiroğlu MI, Çiçek V, Uzun M, Orhan AL**. 2020. COVID-19 and acute myocarditis: Current literature review and diagnostic challenges. Rev Assoc Med Bras **66**:48–54. https://doi.org/10.1590/1806-9282.66.s2.48.
32. **Clancy CS, Shaia C, Munster V, de Wit E, Hawman D, Okumura A, Feldmann H, Saturday G, Scott D**. 2022. Histologic pulmonary lesions of SARS-CoV-2 in 4 nonhuman primate species: An institutional comparative review. Vet Pathol **59**:673–680. https://doi.org/10.1177/03009858211067468.
33. **Colman K, Andrews RN, Atkins H, Boulineau T, Bradley A, Braendli-Baiocco A, Capobianco R, Caudell D, Cline M, Doi T, Ernst R, van Esch E, Everitt J, Fant P, Gruebbel MM, Mecklenburg L, Miller AD, Nikula KJ, Satake S, Schwartz J, Sharma A, Shimoi A, Sobry C, Taylor I, Vemireddi V, Vidal J, Wood C, Vahle JL**. 2021. International Harmonization of Nomenclature and Diagnostic Criteria (INHAND): Non-proliferative and proliferative lesions of the non-human primate (*M. fascicularis*). J Toxicol Pathol **34**:1S–182S. https://doi.org/10.1293/tox.34.1S.
34. **Cool K, Gaudreault NN, Morozov I, Trujillo JD, Meekins DA, McDowell C, Carossino M, Bold D, Kwon T, Balaraman V, Madden DW, Artiaga BL, Pogranichniy RM, Sosa GR, Henningson J, Wilson WC, Balasuriya UBR, Garcia-Sastre A, Richt JA**. 2022. Infection and transmission of ancestral SARS-CoV-2 and its alpha variant in pregnant white-tailed deer. Emerge Microbes Infect:95–112. https://doi.org/10.1080/22221751.2021.2012528
35. **Cooper TK, Meyerholz DK, Beck AP, Delaney MA, Piersigilli A, Southard TL, Brayton CF**. 2021. Research-relevant conditions and pathology of laboratory mice, rats, gerbils, guinea pigs, hamsters, naked mole rats, and rabbits. ILAR J **62**:77–132. https://doi.org/10.1093/ilar/ilab022.
36. COVID-19 Excess Mortality Collaborators. 2022. Estimating excess mortality due to the COVID-19 pandemic: A systematic analysis of COVID-19-related mortality, 2020-21. Lancet **399**:1513–1536. https://doi.org/10.1016/S0140-6736(21)02796-3.
37. **Cross RW, Agans KN, Prasad AN, Borisevich V, Woolsey C, Deer DJ, Dobias NS, Geisbert JB, Fenton KA, Geisbert TW**. 2020. Intranasal exposure of African green monkeys to SARS-CoV-2 results in acute phase pneumonia with shedding and lung injury still present in the early convalescence phase. Virol J **17**:125. https://doi.org/10.1186/s12985-020-01396-w.
38. **Cunningham AA, Daszak P, Wood JLN**. 2017. One Health, emerging infectious diseases and wildlife: Two decades of progress? Philos Trans R Soc Lond B Biol Sci **372**:20160167. https://doi.org/10.1098/rstb.2016.0167.
39. **Deng W, Bao L, Gao H, Xiang Z, Qu Y, Song Z, Gong S, Liu J, Liu J, Yu P, Qi F, Xu Y, Li F, Xiao C, Lv Q, Xue J, Wei Q, Liu M, Wang G, Wang S, Yu H, Chen T, Liu X, Zhao W, Han Y, Qin C**. 2020. Ocular conjunctival inoculation of SARS-CoV-2 can cause mild COVID-19 in rhesus macaques. Nat Commun **11**:4400. https://doi.org/10.1038/s41467-020-18149-6.

40. **Dinnon KH 3rd, Leist SR, Schafer A, Edwards CE, Martinez DR, Montgomery SA, West A, Yount BL Jr, Hou YJ, Adams LE, Gully KL, Brown AJ, Huang E, Bryant MD, Choong IC, Glenn JS, Gralinski LE, Sheahan TP, Baric RS**. 2020. A mouse-adapted model of SARS-CoV-2 to test COVID-19 countermeasures. Nature **586**:560–566. https://doi.org/10.1038/s41586-020-2708-8.
41. **Driouich JS, Cochin M, Lingas G, Moureau G, Touret F, Petit PR, Piorkowski G, Barthélémy K, Laprie C, Coutard B, Guedj J, de Lamballerie X, Solas C, Nougairède A**. 2021. Favipiravir antiviral efficacy against SARS-CoV-2 in a hamster model. Nat Commun **12**:1735. https://doi.org/10.1038/s41467-021-21992-w.
42. **Edler C, Schröder AS, Aepfelbacher M, Fitzek A, Heinemann A, Heinrich F, Klein A, Langenwalder F, Lütgehetmann M, Meißner K, Püschel K, Schädler J, Steurer S, Mushumba H, Sperhake JP**. 2020. Dying with SARS-CoV-2 infection—An autopsy study of the first consecutive 80 cases in Hamburg, Germany. Int J Legal Med **134**:1275–1284. https://doi.org/10.1007/s00414-020-02317-w.
43. **Enserink M**. 2020. Coronavirus rips through Dutch mink farms, triggering culls. Science **368**:1169. https://doi.org/10.1126/science.368.6496.1169.
44. **Everitt JI, Treuting PM, Scudamore C, Sellers R, Turner PV, Ward JM, Zeiss CJ**. 2018. Pathology study design, conduct, and reporting to achieve rigor and reproducibility in translational research using animal models. ILAR J **59**:4–12. https://doi.org/10.1093/ilar/ily020.
45. **Fathi M, Vakili K, Sayehmiri F, Mohamadkhani A, Hajiesmaeili M, Rezaei-Tavirani M, Eilami O**. 2021. The prognostic value of comorbidity for the severity of COVID-19: A systematic review and meta-analysis study. PLoS One **16**:e0246190. https://doi.org/10.1371/journal.pone.0246190.
46. **Ferasin L, Fritz M, Ferasin H, Becquart P, Corbet S, Ar Gouilh M, Legros V, Leroy EM**. 2021. Infection with SARS-CoV-2 variant B.1.1.7 detected in a group of dogs and cats with suspected myocarditis. Vet Rec **189**:e944. https://doi.org/10.1002/vetr.944.
47. **Festing MF, Altman DG**. 2002. Guidelines for the design and statistical analysis of experiments using laboratory animals. ILAR J **43**:244–258. https://doi.org/10.1093/ilar.43.4.244.
48. **Fischer RJ, van Doremalen N, Adney DR, Yinda CK, Port JR, Holbrook MG, Schulz JE, Williamson BN, Thomas T, Barbian K, Anzick SL, Ricklefs S, Smith BJ, Long D, Martens C, Saturday G, de Wit E, Gilbert SC, Lambe T, Munster VJ**. 2021. ChAdOx1 nCoV-19 (AZD1222) protects Syrian hamsters against SARS-CoV-2 B.1.351 and B.1.1.7. Nat Commun **12**:5868. https://doi.org/10.1038/s41467-021-26178-y.
49. **Fox SE, Heider RSV**. 2021. COVID-19: The heart of the matter—Pathological changes and a proposed mechanism. J Cardiovasc Pharmacol Ther **26**:217–224. https://doi.org/10.1177/1074248421995356.
50. **Francis ME, Goncin U, Kroeker A, Swan C, Ralph R, Lu Y, Etzioni AL, Falzarano D, Gerdts V, Machtaler S, Kindrachuk J, Kelvin AA**. 2021. SARS-CoV-2 infection in the Syrian hamster model causes inflammation as well as type I interferon dysregulation in both respiratory and non-respiratory tissues including the heart and kidney. PLoS Pathog **17**:e1009705. https://doi.org/10.1371/journal.ppat.1009705.
51. **Francis ME, Richardson B, Goncin U, McNeil M, Rioux M, Foley MK, Ge A, Pechous RD, Kindrachuk J, Cameron CM, Richardson C, Lew J, Machtaler S, Cameron MJ, Gerdts V, Falzarano D, Kelvin AA**. 2021. Sex and age bias viral burden and interferon responses during SARS-CoV-2 infection in ferrets. Sci Rep **11**:14536. https://doi.org/10.1038/s41598-021-93855-9.
52. **Frangogiannis NG**. 2020. The significance of COVID-19-associated myocardial injury: How overinterpretation of scientific findings can fuel media sensationalism and spread misinformation. Eur Heart J **41**:3836–3838. https://doi.org/10.1093/eurheartj/ehaa727.
53. **Fu L, Liu X, Su Y, Ma J, Hong K**. 2021. Prevalence and impact of cardiac injury on COVID-19: A systematic review and meta-analysis. Clin Cardiol **44**:276–283. https://doi.org/10.1002/clc.23540.
54. **Gabrielson K, Behera A, Sysa-Shah P, Creamer T, Cooper T**. 2022. Cardiovascular system, p 284–306. In: Sundberg JP, Vogel P, Ward JM, eds. Pathology of genetically engineered and other mutant mice. Hoboken (NJ): John Wiley & Sons. https://doi.org/10.1002/9781119624608.ch14
55. **Gaudreault NN, Trujillo JD, Carossino M, Meekins DA, Morozov I, Madden DW, Indran SV, Bold D, Balaraman V, Kwon T, Artiaga BL, Cool K, Garcia-Sastre A, Ma W, Wilson WC, Henningson J, Balasuriya UBR, Richt JA**. 2020. SARS-CoV-2 infection, disease and transmission in domestic cats. Emerg Microbes Infect **9**:2322–2332. https://doi.org/10.1080/22221751.2020.1833687.
56. **Ghallab MA, Barsoum CH, Polak S, El Hassoun O, Ghallab AM**. 2021. Electron microscope images of human coronaviruses - Reality versus illusion. Bratisl Lek Listy **122**:900–911. https://doi.org/10.4149/BLL_2021_146.
57. **Giannico GA, Miller SE**. 2021. Electron microscopy identification of SARS-COV-2: What is the evidence? Cardiovasc Pathol **52**:107338. https://doi.org/10.1016/j.carpath.2021.107338.
58. **Gruber AD, Firsching TC, Trimpert J, Dietert K**. 2022. Hamster models of COVID-19 pneumonia reviewed: How human can they be? Vet Pathol **59**:528–545. https://doi.org/10.1177/03009858211057197.
59. **Gruber AD, Osterrieder N, Bertzbach LD, Vladimirova D, Greuel S, Ihlow J, Horst D, Trimpert J, Dietert K**. 2020. Standardization of reporting criteria for lung pathology in SARS-CoV-2-infected hamsters: What matters? Am J Respir Cell Mol Biol **63**:856–859. https://doi.org/10.1165/rcmb.2020-0280LE.
60. **Guo H, Sheng Y, Li W, Li F, Xie Z, Li J, Zhu Y, Geng J, Liu G, Wang L, Li J, Wang F**. 2020. Coagulopathy as a Prodrome of Cytokine Storm in COVID-19-Infected Patients. Front Med (Lausanne) **7**:572989. https://doi.org/10.3389/fmed.2020.572989.
61. **Guo YR, Cao QD, Hong ZS, Tan YY, Chen SD, Jin HJ, Tan KS, Wang DY, Yan Y**. 2020. The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak - An update on the status. Mil Med Res **7**:11. https://doi.org/10.1186/s40779-020-00240-0.
62. **Hale VL, Dennis PM, McBride DS, Nolting JM, Madden C, Huey D, Ehrlich M, Grieser J, Winston J, Lombardi D, Gibson S, Saif L, Killian ML, Lantz K, Tell RM, Torchetti M, Robbe-Austerman S, Nelson MI, Faith SA, Bowman AS**. 2022. SARS-CoV-2 infection in free-ranging white-tailed deer. Nature **602**:481–486. https://doi.org/10.1038/s41586-021-04353-x.
63. **Halushka MK, Vander Heide RS**. 2021. Myocarditis is rare in COVID-19 autopsies: cardiovascular findings across 277 postmortem examinations. Cardiovasc Pathol **50**:107300. https://doi.org/10.1016/j.carpath.2020.107300.
64. **Hammer AS, Quaade ML, Rasmussen TB, Fonager J, Rasmussen M, Mundbjerg K, Lohse L, Strandbygaard B, Jorgensen CS, Alfaro-Nunez A, Rosenstierne MW, Boklund A, Halasa T, Fomsgaard A, Belsham GJ, Botner A**. 2021. SARS-CoV-2 transmission between mink (*Neovison vison*) and humans, Denmark. Emerg Infect Dis **27**:547–551. https://doi.org/10.3201/eid2702.203794.
65. **Hancock TJ, Hickman P, Kazerooni N, Kennedy M, Kania SA, Dennis M, Szafranski N, Gerhold R, Su C, Masi T, Smith S, Sparer TE**. 2022. Possible cross-reactivity of feline and white-tailed deer antibodies against the SARS-CoV-2 receptor binding domain. J Virol **96**:e0025022. https://doi.org/10.1128/jvi.00250-22.
66. **Hanson PJ, Liu-Fei F, Ng C, Minato TA, Lai C, Hossain AR, Chan R, Grewal B, Singhera G, Rai H, Hirota J, Anderson DR, Radio SJ, McManus BM**. 2022. Characterization of COVID-19–associated cardiac injury: Evidence for a multifactorial disease in an autopsy cohort. Lab Invest **102**:814–825. https://doi.org/10.1038/s41374-022-00783-x.
67. **Helke KL, Meyerholz DK, Beck AP, Burrough ER, Derscheid RJ, Lohr C, McInnes EF, Scudamore CL, Brayton CF**. 2021. Research relevant background lesions and conditions: Ferrets, dogs, swine, sheep, and goats. ILAR J **62**:133–168. https://doi.org/10.1093/ilar/ilab005.
68. **Hickman DL, Johnson J, Vemulapalli TH, Crisler JR, Shepherd R**. 2017. Commonly used animal models, p 117–175. In: Suckow MA, Stewart KL, editors. Principles of animal research for graduate and undergraduate students. San Diego (CA): Academic Press. https://doi.org/10.1016/B978-0-12-802151-4.00007-4.

69. **Hobbs EC, Reid TJ**. 2021. Animals and SARS-CoV-2: Species susceptibility and viral transmission in experimental and natural conditions, and the potential implications for community transmission. Transbound Emerg Dis **68**:1850–1867. https://doi.org/10.1111/tbed.13885.
70. **Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B**. 2020. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet **395**:497–506. https://doi.org/10.1016/s0140-6736(20)30183-5.
71. **Hughes CF**. 1986. Mediastinal carcinoid tumour: Pre-operative arterial embolisation. Aust N Z J Med **16**:808–810. https://doi.org/10.1111/j.1445-5994.1986.tb00045.x.
72. **Imai M, Iwatsuki-Horimoto K, Hatta M, Loeber S, Halfmann PJ, Nakajima N, Watanabe T, Ujie M, Takahashi K, Ito M, Yamada S, Fan S, Chiba S, Kuroda M, Guan L, Takada K, Armbrust T, Balogh A, Furusawa Y, Okuda M, Ueki H, Yasuhara A, Sakai-Tagawa Y, Lopes TJS, Kiso M, Yamayoshi S, Kinoshita N, Ohmagari N, Hattori SI, Takeda M, Mitsuya H, Krammer F, Suzuki T, Kawaoka Y**. 2020. Syrian hamsters as a small animal model for SARS-CoV-2 infection and countermeasure development. Proc Natl Acad Sci USA **117**:16587–16595. https://doi.org/10.1073/pnas.2009799117.
73. **Ince TA, Ward JM, Valli VE, Sgroi D, Nikitin AY, Loda M, Griffey SM, Crum CP, Crawford JM, Bronson RT, Cardiff RD**. 2008. Do-it-yourself (DIY) pathology. Nat Biotechnol **26**:978–979, discussion 979. https://doi.org/10.1038/nbt0908-978.
74. **Jamal M, Bangash HI, Habiba M, Lei Y, Xie T, Sun J, Wei Z, Hong Z, Shao L, Zhang Q**. 2021. Immune dysregulation and system pathology in COVID-19. Virulence **12**:918–936. https://doi.org/10.1080/21505594.2021.1898790.
75. **Jennette JC, Falk RJ, Bacon PA, Basu N, Cid MC, Ferrario F, Flores-Suarez LF, Gross WL, Guillevin L, Hagen EC, Hoffman GS, Jayne DR, Kallenberg CG, Lamprecht P, Langford CA, Luqmani RA, Mahr AD, Matteson EL, Merkel PA, Ozen S, Pusey CD, Rasmussen N, Rees AJ, Scott DG, Specks U, Stone JH, Takahashi K, Watts RA**. 2013. 2012 Revised International Chapel Hill Consensus Conference nomenclature of vasculitides. Arthritis Rheum **65**:1–11. https://doi.org/10.1002/art.37715.
76. **Johnston SC, Ricks KM, Jay A, Raymond JL, Rossi F, Zeng X, Scruggs J, Dyer D, Frick O, Koehler JW, Kuehnert PA, Clements TL, Shoemaker CJ, Coyne SR, Delp KL, Moore J, Berrier K, Esham H, Shamblin J, Sifford W, Fiallos J, Klosterman L, Stevens S, White L, Bowling P, Garcia T, Jensen C, Ghering J, Nyakiti D, Bellanca S, Kearney B, Giles W, Alli N, Paz F, Akers K, Danner D, Barth J, Johnson JA, Durant M, Kim R, Hooper JW, Smith JM, Kugelman JR, Beitzel BF, Gibson KM, Pitt MLM, Minogue TD, Nalca A**. 2021. Development of a coronavirus disease 2019 nonhuman primate model using airborne exposure. PLoS One **16**:e0246366. https://doi.org/10.1371/journal.pone.0246366.
77. **Karlstad Ø, Hovi P, Husby A, Härkänen T, Selmer RM, Pihlström N, Hansen JV, Nohynek H, Gunnes N, Sundström A, Wohlfahrt J, Nieminen TA, Grünewald M, Gulseth HL, Hviid A, Ljung R**. 2022. SARS-CoV-2 vaccination and myocarditis in a Nordic cohort study of 23 million residents. JAMA Cardiol **7**:600–612. https://doi.org/10.1001/jamacardio.2022.0583.
78. **Karmouty-Quintana H, Thandavarayan RA, Keller SP, Sahay S, Pandit LM, Akkanti B**. 2020. Emerging mechanisms of pulmonary vasoconstriction in SARS-CoV-2-induced acute respiratory distress syndrome (ARDS) and potential therapeutic targets. Int J Mol Sci **21**:8081. https://doi.org/10.3390/ijms21218081.
79. **Kastenhuber ER, Mercadante M, Nilsson-Payant B, Johnson JL, Jaimes JA, Muecksch F, Weisblum Y, Bram Y, Chandar V, Whittaker GR, tenOever BR, Schwartz RE, Cantley L**. 2022. Coagulation factors directly cleave SARS-CoV-2 spike and enhance viral entry. eLife **11**:e77444. https://doi.org/10.7554/eLife.77444.
80. **Kawakami R, Sakamoto A, Kawai K, Gianatti A, Pellegrini D, Nasr A, Kutys B, Guo L, Cornelissen A, Mori M, Sato Y, Pescetelli I, Brivio M, Romero M, Guagliumi G, Virmani R, Finn AV**. 2021. Pathological evidence for SARS-CoV-2 as a cause of myocarditis: JACC review topic of the week. J Am Coll Cardiol **77**:314–325. https://doi.org/10.1016/j.jacc.2020.11.031.
81. **Kennedy AR, Desrosiers A, Terzaghi M, Little JB**. 1978. Morphometric and histological analysis of the lungs of Syrian golden hamsters. J Anat **125**:527–553.
82. **Kim YI, Kim SG, Kim SM, Kim EH, Park SJ, Yu KM, Chang JH, Kim EJ, Lee S, Casel MAB, Um J, Song MS, Jeong HW, Lai VD, Kim Y, Chin BS, Park JS, Chung KH, Foo SS, Poo H, Mo IP, Lee OJ, Webby RJ, Jung JU, Choi YK**. 2020. Infection and rapid transmission of SARS-CoV-2 in ferrets. Cell Host Microbe **27**:704–709. https://doi.org/10.1016/j.chom.2020.03.023.
83. **Kim YI, Yu KM, Koh JY, Kim EH, Kim SM, Kim EJ, Casel MAB, Rollon R, Jang SG, Song MS, Park SJ, Jeong HW, Kim EG, Lee OJ, Kim YD, Choi Y, Lee SA, Choi YJ, Park SH, Jung JU, Choi YK**. 2022. Age-dependent pathogenic characteristics of SARS-CoV-2 infection in ferrets. Nat Commun **13**:21. https://doi.org/10.1038/s41467-021-27717-3.
84. **Koo BS, Oh H, Kim G, Hwang EH, Jung H, Lee Y, Kang P, Park JH, Ryu CM, Hong JJ**. 2020. Transient lymphopenia and interstitial pneumonia with endotheliitis in SARS-CoV-2-infected macaques. J Infect Dis **222**:1596–1600. https://doi.org/10.1093/infdis/jiaa486.
85. **Kreft IC, Winiarczyk RRA, Tanis FJ, van der Zwaan C, Schmitz KS, Hoogendijk AJ, de Swart RL, Moscona A, Porotto M, Salvatori DCF, de Vries RD, de Maat MPM, van den Biggelaar M, van Vlijmen BJM**. 2022. Absence of COVID-19-associated changes in plasma coagulation proteins and pulmonary thrombosis in the ferret model. Thromb Res **210**:6–11. https://doi.org/10.1016/j.thromres.2021.12.015.
86. **Kreye J, Reincke SM, Kornau HC, Sanchez-Sendin E, Corman VM, Liu H, Yuan M, Wu NC, Zhu X, Lee CD, Trimpert J, Holtje M, Dietert K, Stoffler L, von Wardenburg N, van Hoof S, Homeyer MA, Hoffmann J, Abdelgawad A, Gruber AD, Bertzbach LD, Vladimirova D, Li LY, Barthel PC, Skriner K, Hocke AC, Hippenstiel S, Witzenrath M, Suttorp N, Kurth F, Franke C, Endres M, Schmitz D, Jeworowski LM, Richter A, Schmidt ML, Schwarz T, Muller MA, Drosten C, Wendisch D, Sander LE, Osterrieder N, Wilson IA, Pruss H**. 2020. A therapeutic non-self-reactive SARS-CoV-2 antibody protects from lung pathology in a COVID-19 hamster model. Cell **183**:1058–1069. https://doi.org/10.1016/j.cell.2020.09.049.
87. **Kytö V, Saukko P, Lignitz E, Schwesinger G, Henn V, Saraste A, Voipio-Pulkki LM**. 2005. Diagnosis and presentation of fatal myocarditis. Hum Pathol **36**:1003–1007. https://doi.org/10.1016/j.humpath.2005.07.009.
88. **Lee AC, Zhang AJ, Chan JF, Li C, Fan Z, Liu F, Chen Y, Liang R, Sridhar S, Cai JP, Poon VK, Chan CC, To KK, Yuan S, Zhou J, Chu H, Yuen KY**. 2020. Oral SARS-CoV-2 inoculation establishes subclinical respiratory infection with virus shedding in golden Syrian hamsters. Cell Rep Med **1**:100121. https://doi.org/10.1016/j.xcrm.2020.100121.
89. **Lee H, Lee TY, Jeon P, Kim N, Kim JW, Yang JS, Kim KC, Lee JY**. 2022. J2N-k hamster model simulates severe infection caused by severe acute respiratory syndrome coronavirus 2 in patients with cardiovascular diseases. J Virol Methods **299**:114306. https://doi.org/10.1016/j.jviromet.2021.114306.
90. **Leentjens J, van Haaps TF, Wessels PF, Schutgens REG, Middeldorp S**. 2021. COVID-19-associated coagulopathy and antithrombotic agents-lessons after 1 year. Lancet Haematol **8**:e524–e533. https://doi.org/10.1016/S2352-3026(21)00105-8.
91. **Lindner D, Fitzek A, Brauninger H, Aleshcheva G, Edler C, Meissner K, Scherschel K, Kirchhof P, Escher F, Schultheiss HP, Blankenberg S, Puschel K, Westermann D**. 2020. Association of cardiac infection with SARS-CoV-2 in confirmed COVID-19 autopsy cases. JAMA Cardiol **5**:1281–1285. https://doi.org/10.1001/jamacardio.2020.3551.
92. **Lu S, Zhao Y, Yu W, Yang Y, Gao J, Wang J, Kuang D, Yang M, Yang J, Ma C, Xu J, Qian X, Li H, Zhao S, Li J, Wang H, Long H, Zhou J, Luo F, Ding K, Wu D, Zhang Y, Dong Y, Liu Y, Zheng Y, Lin X, Jiao L, Zheng H, Dai Q, Sun Q, Hu Y, Ke C, Liu H, Peng X**. 2020. Comparison of nonhuman primates identified the suitable model for COVID-19. Signal Transduct Target Ther **5**:157. https://doi.org/10.1038/s41392-020-00269-6.

93. **Maiese A, Frati P, Del Duca F, Santoro P, Manetti AC, La Russa R, Di Paolo M, Turillazzi E, Fineschi V**. 2021. Myocardial pathology in COVID-19-associated cardiac injury: A systematic review. Diagnostics (Basel) **11**:1647. https://doi.org/10.3390/diagnostics11091647.
94. **Martins M, Boggiatto PM, Buckley A, Cassmann ED, Falkenberg S, Caserta LC, Fernandes MHV, Kanipe C, Lager K, Palmer MV, Diel DG**. 2022. From deer-to-deer: SARS-CoV-2 is efficiently transmitted and presents broad tissue tropism and replication sites in white-tailed deer. PLoS Pathog **18**:e1010197. https://doi.org/10.1371/journal.ppat.1010197.
95. **Mazzoni A, Salvati L, Maggi L, Annunziato F, Cosmi L**. 2021. Hallmarks of immune response in COVID-19: Exploring dysregulation and exhaustion. Semin Immunol **55**:101508. https://doi.org/10.1016/j.smim.2021.101508.
96. **McAuliffe J, Vogel L, Roberts A, Fahle G, Fischer S, Shieh WJ, Butler E, Zaki S, St Claire M, Murphy B, Subbarao K**. 2004. Replication of SARS coronavirus administered into the respiratory tract of African green, rhesus, and cynomolgus monkeys. Virology **330**:8–15. https://doi.org/10.1016/j.virol.2004.09.030.
97. **McInnes EF**. 2011. Chapter 5 - Hamsters and guinea pigs, p 73–79. In: McInnes EF, Mann P, editors. Background lesions in laboratory animals. Saint Louis (MO): W.B. Saunders.
98. **McInnes EF, Ernst H, Germann PG**. 2015. Spontaneous non-neoplastic lesions in control Syrian hamsters in three 24-month long-term carcinogenicity studies. Toxicol Pathol **43**:272–281. https://doi.org/10.1177/0192623314532569.
99. **Melton A, Doyle-Meyers LA, Blair RV, Midkiff C, Melton HJ, Russell-Lodrigue K, Aye PP, Schiro F, Fahlberg M, Szeltner D, Spencer S, Beddingfield BJ, Goff K, Golden N, Penney T, Picou B, Hensley K, Chandler KE, Plante JA, Plante KS, Weaver SC, Roy CJ, Hoxie JA, Gao H, Montefiori DC, Mankowski JL, Bohm RP, Rappaport J, Maness NJ**. 2021. The pigtail macaque (*Macaca nemestrina*) model of COVID-19 reproduces diverse clinical outcomes and reveals new and complex signatures of disease. PLoS Pathog **17**:e1010162. https://doi.org/10.1371/journal.ppat.1010162.
100. **Meyerholz DK, Beck AP**. 2018. Principles and approaches for reproducible scoring of tissue stains in research. Lab Invest **98**:844–855. https://doi.org/10.1038/s41374-018-0057-0.
101. **Mitrani RD, Dabas N, Goldberger JJ**. 2020. COVID-19 cardiac injury: Implications for long-term surveillance and outcomes in survivors. Heart Rhythm **17**:1984–1990. https://doi.org/10.1016/j.hrthm.2020.06.026.
102. **Moore JB, June CH**. 2020. Cytokine release syndrome in severe COVID-19. Science **368**:473–474. https://doi.org/10.1126/science.abb8925.
103. **Mulka KR, Beck SE, Solis CV, Johanson AL, Queen SE, McCarron ME, Richardson MR, Zhou R, Marinho P, Jedlicka A, Guerrero-Martin S, Shirk EN, Braxton AM, Brockhurst J, Creisher PS, Dhakal S, Brayton CF, Veenhuis RT, Metcalf Pate KA, Karakousis PC, Zahnow CA, Klein SL, Jain SK, Tarwater PM, Pekosz AS, Villano JS, Mankowski JL, Johns Hopkins C-HSG**. 2022. Progression and resolution of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in golden Syrian hamsters. Am J Pathol **192**:195–207. https://doi.org/10.1016/j.ajpath.2021.10.009.
104. **Munster VJ, Feldmann F, Williamson BN, van Doremalen N, Pérez-Pérez L, Schulz J, Meade-White K, Okumura A, Callison J, Brumbaugh B, Avanzato VA, Rosenke R, Hanley PW, Saturday G, Scott D, Fischer ER, de Wit E**. 2020. Respiratory disease in rhesus macaques inoculated with SARS-CoV-2. Nature **585**:268–272. https://doi.org/10.1038/s41586-020-2324-7.
105. **Munster VJ, Flagg M, Singh M, Yinda CK, Williamson BN, Feldmann F, Pérez-Pérez L, Schulz J, Brumbaugh B, Holbrook MG, Adney DR, Okumura A, Hanley PW, Smith BJ, Lovaglio J, Anzick SL, Martens C, van Doremalen N, Saturday G, de Wit E**. 2021. Subtle differences in the pathogenicity of SARS-CoV-2 variants of concern B.1.1.7 and B.1.351 in rhesus macaques. Sci Adv **7**:eabj3627. https://doi.org/10.1126/sciadv.abj3627.
106. **Nouailles G, Wyler E, Pennitz P, Postmus D, Vladimirova D, Kazmierski J, Pott F, Dietert K, Muelleder M, Farztdinov V, Obermayer B, Wienhold SM, Andreotti S, Hoefler T, Sawitzki B, Drosten C, Sander LE, Suttorp N, Ralser M, Beule D, Gruber AD, Goffinet C, Landthaler M, Trimpert J, Witzenrath M**. 2021. Temporal omics analysis in Syrian hamsters unravel cellular effector responses to moderate COVID-19. Nat Commun **12**:4869. https://doi.org/10.1038/s41467-021-25030-7.
107. **Ohno M, Sasaki M, Orba Y, Sekiya T, Masum MA, Ichii O, Sawamura T, Kakino A, Suzuki Y, Kida H, Sawa H, Shingai M**. 2021. Abnormal blood coagulation and kidney damage in aged hamsters infected with severe acute respiratory syndrome coronavirus 2. Viruses **13**:2137. https://doi.org/10.3390/v13112137.
108. **Osterrieder N, Bertzbach LD, Dietert K, Abdelgawad A, Vladimirova D, Kunec D, Hoffmann D, Beer M, Gruber AD, Trimpert J**. 2020. Age-dependent progression of SARS-CoV-2 infection in Syrian hamsters. Viruses **12**:779. https://doi.org/10.3390/v12070779.
109. **Ozieranski K, Tyminska A, Jonik S, Marcolongo R, Baritussio A, Grabowski M, Filipiak KJ, Opolski G, Caforio ALP**. 2021. Clinically suspected myocarditis in the course of severe acute respiratory syndrome novel coronavirus-2 infection: Fact or fiction? J Card Fail **27**:92–96. https://doi.org/10.1016/j.cardfail.2020.11.002.
110. **Palmer MV, Martins M, Falkenberg S, Buckley A, Caserta LC, Mitchell PK, Cassmann ED, Rollins A, Zylich NC, Renshaw RW, Guarino C, Wagner B, Lager K, Diel DG**. 2021. Susceptibility of white-tailed deer (*Odocoileus virginianus*) to SARS-CoV-2. J Virol **95**:e00083-21. https://doi.org/10.1128/jvi.00083-21.
111. **Patania OM, Chiba S, Halfmann PJ, Hatta M, Maemura T, Bernard KA, Kawaoka Y, Crawford LK**. 2022. Pulmonary lesions induced by SARS-CoV-2 infection in domestic cats. Vet Pathol **59**:696–706. https://doi.org/10.1177/03009858211066840.
112. **Percie du Sert N, Ahluwalia A, Alam S, Avey MT, Baker M, Browne WJ, Clark A, Cuthill IC, Dirnagl U, Emerson M, Garner P, Holgate ST, Howells DW, Hurst V, Karp NA, Lazic SE, Lidster K, MacCallum CJ, Macleod M, Pearl EJ, Petersen OH, Rawle F, Reynolds P, Rooney K, Sena ES, Silberberg SD, Steckler T, Wurbel H**. 2020. Reporting animal research: Explanation and elaboration for the ARRIVE guidelines 2.0. PLoS Biol **18**:e3000411. https://doi.org/10.1371/journal.pbio.3000411.
113. **Percie du Sert N, Hurst V, Ahluwalia A, Alam S, Avey MT, Baker M, Browne WJ, Clark A, Cuthill IC, Dirnagl U, Emerson M, Garner P, Holgate ST, Howells DW, Karp NA, Lazic SE, Lidster K, MacCallum CJ, Macleod M, Pearl EJ, Petersen OH, Rawle F, Reynolds P, Rooney K, Sena ES, Silberberg SD, Steckler T, Wurbel H**. 2020. The ARRIVE guidelines 2.0: Updated guidelines for reporting animal research. BMJ Open Sci **4**:e100115. https://doi.org/10.1136/bmjos-2020-100115.
114. **Port JR, Yinda CK, Owusu IO, Holbrook M, Fischer R, Bushmaker T, Avanzato VA, Schulz JE, Martens C, van Doremalen N, Clancy CS, Munster VJ**. 2021. SARS-CoV-2 disease severity and transmission efficiency is increased for airborne compared to fomite exposure in Syrian hamsters. Nat Commun **12**:4985. https://doi.org/10.1038/s41467-021-25156-8.
115. **Puntmann VO, Carerj ML, Wieters I, Fahim M, Arendt C, Hoffmann J, Shchendrygina A, Escher F, Vasa-Nicotera M, Zeiher AM, Vehreschild M, Nagel E**. 2020. Outcomes of cardiovascular magnetic resonance imaging in patients recently recovered from coronavirus disease 2019 (COVID-19). JAMA Cardiol **5**:1265–1273. https://doi.org/10.1001/jamacardio.2020.3557.
116. **Raman B, Bluemke DA, Lüscher TF, Neubauer S**. 2022. Long COVID: Post-acute sequelae of COVID-19 with a cardiovascular focus. Eur Heart J **42**:1157–1172. https://doi.org/10.1093/eurheartj/ehac031.
117. **Rizvi ZA, Dalal R, Sadhu S, Binayke A, Dandotiya J, Kumar Y, Shrivastava T, Gupta SK, Aggarwal S, Tripathy MR, Rathore DK, Yadav AK, Medigeshi GR, Pandey AK, Samal S, Asthana S, Awasthi A**. 2022. Golden Syrian hamster as a model to study cardiovascular complications associated with SARS-CoV-2 infection. eLife **11**:e73522. https://doi.org/10.7554/elife.73522.
118. **Rockx B, Kuiken T, Herfst S, Bestebroer T, Lamers MM, Oude Munnink BB, de Meulder D, van Amerongen G, van den Brand J, Okba NMA, Schipper D, van Run P, Leijten L, Sikkema R, Verschoor E, Verstrepen B, Bogers W, Langermans J, Drosten C,**

Fentener van Vlissingen M, Fouchier R, de Swart R, Koopmans M, Haagmans BL. 2020. Comparative pathogenesis of COVID-19, MERS, and SARS in a nonhuman primate model. Science **368**:1012–1015. https://doi.org/10.1126/science.abb7314.

119. **Rosenke K, Meade-White K, Letko M, Clancy C, Hansen F, Liu Y, Okumura A, Tang-Huau TL, Li R, Saturday G, Feldmann F, Scott D, Wang Z, Munster V, Jarvis MA, Feldmann H**. 2020. Defining the Syrian hamster as a highly susceptible preclinical model for SARS-CoV-2 infection. Emerg Microbes Infect **9**:2673–2684. https://doi.org/10.1080/22221751.2020.1858177.
120. **Roshdy A, Zaher S, Fayed H, Coghlan JG**. 2020. COVID-19 and the heart: A systematic review of cardiac autopsies. Front Cardiovasc Med **7**:626975. https://doi.org/10.3389/fcvm.2020.626975.
121. **Ruan Q, Yang K, Wang W, Jiang L, Song J**. 2020. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med **46**:846–848. https://doi.org/10.1007/s00134-020-05991-x.
122. **Ryan KA, Bewley KR, Fotheringham SA, Slack GS, Brown P, Hall Y, Wand NI, Marriott AC, Cavell BE, Tree JA, Allen L, Aram MJ, Bean TJ, Brunt E, Buttigieg KR, Carter DP, Cobb R, Coombes NS, Findlay-Wilson SJ, Godwin KJ, Gooch KE, Gouriet J, Halkerston R, Harris DJ, Hender TH, Humphries HE, Hunter L, Ho CMK, Kennard CL, Leung S, Longet S, Ngabo D, Osman KL, Paterson J, Penn EJ, Pullan ST, Rayner E, Skinner O, Steeds K, Taylor I, Tipton T, Thomas S, Turner C, Watson RJ, Wiblin NR, Charlton S, Hallis B, Hiscox JA, Funnell S, Dennis MJ, Whittaker CJ, Catton MG, Druce J, Salguero FJ, Carroll MW**. 2021. Dose-dependent response to infection with SARS-CoV-2 in the ferret model and evidence of protective immunity. Nat Commun **12**:81. https://doi.org/10.1038/s41467-020-20439-y.
123. **Salguero FJ, White AD, Slack GS, Fotheringham SA, Bewley KR, Gooch KE, Longet S, Humphries HE, Watson RJ, Hunter L, Ryan KA, Hall Y, Sibley L, Sarfas C, Allen L, Aram M, Brunt E, Brown P, Buttigieg KR, Cavell BE, Cobb R, Coombes NS, Darby A, Daykin-Pont O, Elmore MJ, Garcia-Dorival I, Gkolfinos K, Godwin KJ, Gouriet J, Halkerston R, Harris DJ, Hender T, Ho CMK, Kennard CL, Knott D, Leung S, Lucas V, Mabbutt A, Morrison AL, Nelson C, Ngabo D, Paterson J, Penn EJ, Pullan S, Taylor I, Tipton T, Thomas S, Tree JA, Turner C, Vamos E, Wand N, Wiblin NR, Charlton S, Dong X, Hallis B, Pearson G, Rayner EL, Nicholson AG, Funnell SG, Hiscox JA, Dennis MJ, Gleeson FV, Sharpe S, Carroll MW**. 2021. Comparison of rhesus and cynomolgus macaques as an infection model for COVID-19. Nat Commun **12**:1260. https://doi.org/10.1038/s41467-021-21389-9.
124. **Saravanan C, Flandre T, Hodo CL, Lewis AD, Mecklenburg L, Romeike A, Turner OC, Yen HY**. 2020. Research relevant conditions and pathology in nonhuman primates. ILAR J **61**:139–166. https://doi.org/10.1093/ilar/ilab017.
125. **Selvaraj P, Lien CZ, Liu S, Stauft CB, Nunez IA, Hernandez M, Nimako E, Ortega MA, Starost MF, Dennis JU, Wang TT**. 2021. SARS-CoV-2 infection induces protective immunity and limits transmission in Syrian hamsters. Life Sci Alliance **4**:e202000886. https://doi.org/10.26508/lsa.202000886.
126. **Shan C, Yao YF, Yang XL, Zhou YW, Gao G, Peng Y, Yang L, Hu X, Xiong J, Jiang RD, Zhang HJ, Gao XX, Peng C, Min J, Chen Y, Si HR, Wu J, Zhou P, Wang YY, Wei HP, Pang W, Hu ZF, Lv LB, Zheng YT, Shi ZL, Yuan ZM**. 2020. Infection with novel coronavirus (SARS-CoV-2) causes pneumonia in Rhesus macaques. Cell Res **30**:670–677. https://doi.org/10.1038/s41422-020-0364-z.
127. **Sharun K, Dhama K, Pawde AM, Gortazar C, Tiwari R, Bonilla-Aldana DK, Rodriguez-Morales AJ, de la Fuente J, Michalak I, Attia YA**. 2021. SARS-CoV-2 in animals: Potential for unknown reservoir hosts and public health implications. Vet Q **41**:181–201. https://doi.org/10.1080/01652176.2021.1921311.
128. **Shi J, Wen Z, Zhong G, Yang H, Wang C, Huang B, Liu R, He X, Shuai L, Sun Z, Zhao Y, Liu P, Liang L, Cui P, Wang J, Zhang X, Guan Y, Tan W, Wu G, Chen H, Bu Z**. 2020. Susceptibility of ferrets, cats, dogs, and other domesticated animals to SARS-coronavirus 2. Science **368**:1016–1020. https://doi.org/10.1126/science.abb7015.
129. **Shi S, Qin M, Shen B, Cai Y, Liu T, Yang F, Gong W, Liu X, Liang J, Zhao Q, Huang H, Yang B, Huang C**. 2020. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. JAMA Cardiol **5**:802–810. https://doi.org/10.1001/jamacardio.2020.0950.
130. **Shou S, Liu M, Yang Y, Kang N, Song Y, Tan D, Liu N, Wang F, Liu J, Xie Y**. 2021. Animal models for COVID-19: Hamsters, mouse, ferret, mink, tree shrew, and non-human primates. Front Microbiol **12**:626553. https://doi.org/10.3389/fmicb.2021.626553.
131. **Sia SF, Yan LM, Chin AWH, Fung K, Choy KT, Wong AYL, Kaewpreedee P, Perera R, Poon LLM, Nicholls JM, Peiris M, Yen HL**. 2020. Pathogenesis and transmission of SARS-CoV-2 in golden hamsters. Nature **583**:834–838. https://doi.org/10.1038/s41586-020-2342-5.
132. **Singh MK, Mobeen A, Chandra A, Joshi S, Ramachandran S**. 2021. A meta-analysis of comorbidities in COVID-19: Which diseases increase the susceptibility of SARS-CoV-2 infection? Comput Biol Med **130**:104219. https://doi.org/10.1016/j.compbiomed.2021.104219.
133. **Sit THC, Brackman CJ, Ip SM, Tam KWS, Law PYT, To EMW, Yu VYT, Sims LD, Tsang DNC, Chu DKW, Perera R, Poon LLM, Peiris M**. 2020. Infection of dogs with SARS-CoV-2. Nature **586**:776–778. https://doi.org/10.1038/s41586-020-2334-5.
134. **Skydsgaard M**. 2016. International Harmonization of Nomenclature and Diagnostic Criteria (INHAND) for lesions in the minipig. Toxicol Pathol **44**:480–481. https://doi.org/10.1177/0192623315614119.
135. **Song Z, Bao L, Yu P, Qi F, Gong S, Wang J, Zhao B, Liu M, Han Y, Deng W, Liu J, Wei Q, Xue J, Zhao W, Qin C**. 2021. SARS-CoV-2 causes a systemically multiple organs damages and dissemination in hamsters. Front Microbiol **11**:618891. https://doi.org/10.3389/fmicb.2020.618891.
136. **Sørensen LL, Bedja D, Sysa-Shah P, Liu H, Maxwell A, Yi X, Pozios I, Olsen NT, Abraham TP, Abraham R, Gabrielson K**. 2016. Echocardiographic characterization of a murine model of hypertrophic obstructive cardiomyopathy induced by cardiac-specific overexpression of epidermal growth factor receptor 2. Comp Med **66**:268–277.
137. **Speranza E, Williamson BN, Feldmann F, Sturdevant GL, Pérez-Pérez L, Meade-White K, Smith BJ, Lovaglio J, Martens C, Munster VJ, Okumura A, Shaia C, Feldmann H, Best SM, de Wit E**. 2021. Single-cell RNA sequencing reveals SARS-CoV-2 infection dynamics in lungs of African green monkeys. Sci Transl Med **13**:eabe8146. https://doi.org/10.1126/scitranslmed.abe8146.
138. **Storey J, Gobbetti T, Olzinski A, Berridge BR**. 2021. a structured approach to optimizing animal model selection for human translation: The animal model quality assessment. ILAR J **62**:66–76. https://doi.org/10.1093/ilar/ilac004.
139. **Tan CCS, Lam SD, Richard D, Owen CJ, Berchtold D, Orengo C, Nair MS, Kuchipudi SV, Kapur V, van Dorp L, Balloux F**. 2022. Transmission of SARS-CoV-2 from humans to animals and potential host adaptation. Nat Commun **13**:2988. https://doi.org/10.1038/s41467-022-30698-6.
140. **Tanriver-Ayder E, Faes C, van de Casteele T, McCann SK, Macleod MR**. 2021. Comparison of commonly used methods in random effects meta-analysis: application to preclinical data in drug discovery research. BMJ Open Sci **5**:e100074. https://doi.org/10.1136/bmjos-2020-100074.
141. **Tay MZ, Poh CM, Renia L, MacAry PA, Ng LFP**. 2020. The trinity of COVID-19: Immunity, inflammation and intervention. Nat Rev Immunol **20**:363–374. https://doi.org/10.1038/s41577-020-0311-8.
142. **Thomas T, Stefanoni D, Dzieciatkowska M, Issaian A, Nemkov T, Hill RC, Francis RO, Hudson KE, Buehler PW, Zimring JC, Hod EA, Hansen KC, Spitalnik SL, D'Alessandro A**. 2020. Evidence of structural protein damage and membrane lipid remodeling in red blood cells from COVID-19 patients. J Proteome Res **19**:4455–4469. https://doi.org/10.1021/acs.jproteome.0c00606.
143. **Tiwari R, Dhama K, Sharun K, Iqbal Yatoo M, Malik YS, Singh R, Michalak I, Sah R, Bonilla-Aldana DK, Rodriguez-Morales AJ**. 2020. COVID-19: Animals, veterinary and zoonotic links. Vet Q **40**:169–182. https://doi.org/10.1080/01652176.2020.1766725.

144. **Tostanoski LH, Wegmann F, Martinot AJ, Loos C, McMahan K, Mercado NB, Yu J, Chan CN, Bondoc S, Starke CE, Nekorchuk M, Busman-Sahay K, Piedra-Mora C, Wrijil LM, Ducat S, Custers J, Atyeo C, Fischinger S, Burke JS, Feldman J, Hauser BM, Caradonna TM, Bondzie EA, Dagotto G, Gebre MS, Jacob-Dolan C, Lin Z, Mahrokhian SH, Nampanya F, Nityanandam R, Pessaint L, Porto M, Ali V, Benetiene D, Tevi K, Andersen H, Lewis MG, Schmidt AG, Lauffenburger DA, Alter G, Estes JD, Schuitemaker H, Zahn R, Barouch DH**. 2020. Ad26 vaccine protects against SARS-CoV-2 severe clinical disease in hamsters. Nat Med **26**:1694–1700. https://doi.org/10.1038/s41591-020-1070-6.
145. **Treuting PM, Snyder JM, Ikeno Y, Schofield PN, Ward JM, Sundberg JP**. 2016. The vital role of pathology in improving reproducibility and translational relevance of aging studies in rodents. Vet Pathol **53**:244–249. https://doi.org/10.1177/0300985815620629.
146. **Trimpert J, Vladimirova D, Dietert K, Abdelgawad A, Kunec D, Dökel S, Voss A, Gruber AD, Bertzbach LD, Osterrieder N**. 2020. The Roborovski dwarf hamster is a highly susceptible model for a rapid and fatal course of SARS-CoV-2 infection. Cell Rep **33**:108488. https://doi.org/10.1016/j.celrep.2020.108488.
147. **Urano E, Okamura T, Ono C, Ueno S, Nagata S, Kamada H, Higuchi M, Furukawa M, Kamitani W, Matsuura Y, Kawaoka Y, Yasutomi Y**. 2021. COVID-19 cynomolgus macaque model reflecting human COVID-19 pathological conditions. Proc Natl Acad Sci USA **118**:e2104847118. https://doi.org/10.1073/pnas.2104847118.
148. **van de Ven K, van Dijken H, Wijsman L, Gomersbach A, Schouten T, Kool J, Lenz S, Roholl P, Meijer A, van Kasteren PB, de Jonge J**. 2021. Pathology and immunity after SARS-CoV-2 infection in male ferrets is affected by age and inoculation route. Front Immunol **12**:750229. https://doi.org/10.3389/fimmu.2021.750229.
149. **van Doremalen N, Lambe T, Spencer A, Belij-Rammerstorfer S, Purushotham JN, Port JR, Avanzato VA, Bushmaker T, Flaxman A, Ulaszewska M, Feldmann F, Allen ER, Sharpe H, Schulz J, Holbrook M, Okumura A, Meade-White K, Pérez-Pérez L, Edwards NJ, Wright D, Bissett C, Gilbride C, Williamson BN, Rosenke R, Long D, Ishwarbhai A, Kailath R, Rose L, Morris S, Powers C, Lovaglio J, Hanley PW, Scott D, Saturday G, de Wit E, Gilbert SC, Munster VJ**. 2020. ChAdOx1 nCoV-19 vaccine prevents SARS-CoV-2 pneumonia in rhesus macaques. Nature **586**:578–582. https://doi.org/10.1038/s41586-020-2608-y.
150. **van Doremalen N, Purushotham JN, Schulz JE, Holbrook MG, Bushmaker T, Carmody A, Port JR, Yinda CK, Okumura A, Saturday G, Amanat F, Krammer F, Hanley PW, Smith BJ, Lovaglio J, Anzick SL, Barbian K, Martens C, Gilbert SC, Lambe T, Munster VJ**. 2021. Intranasal ChAdOx1 nCoV-19/AZD1222 vaccination reduces viral shedding after SARS-CoV-2 D614G challenge in preclinical models. Sci Transl Med **13**:eabh0755. https://doi.org/10.1126/scitranslmed.abh0755.
151. **Ward JM, Schofield PN, Sundberg JP**. 2017. Reproducibility of histopathological findings in experimental pathology of the mouse: A sorry tail. Lab Anim (NY) **46**:146–151. https://doi.org/10.1038/laban.1214.
152. **Williamson BN, Feldmann F, Schwarz B, Meade-White K, Porter DP, Schulz J, van Doremalen N, Leighton I, Yinda CK, Pérez-Pérez L, Okumura A, Lovaglio J, Hanley PW, Saturday G, Bosio CM, Anzick S, Barbian K, Cihlar T, Martens C, Scott DP, Munster VJ, de Wit E**. 2020. Clinical benefit of remdesivir in rhesus macaques infected with SARS-CoV-2. Nature **585**:273–276. https://doi.org/10.1038/s41586-020-2423-5.
153. **Woicke J, Al-Haddawi MM, Bienvenu JG, Caverly Rae JM, Chanut FJ, Colman K, Cullen JM, Davis W, Fukuda R, Huisinga M, Walker UJ, Kai K, Kovi RC, Macri NP, Marxfeld HA, Nikula KJ, Pardo ID, Rosol TJ, Sharma AK, Singh BP, Tamura K, Thibodeau MS, Vezzali E, Vidal JD, Meseck EK**. 2021. International Harmonization of Nomenclature and Diagnostic Criteria (INHAND): Nonproliferative and proliferative lesions of the dog. Toxicol Pathol **49**:5–109. https://doi.org/10.1177/0192623320968181.
154. **Wong K, Farooq Alam Shah MU, Khurshid M, Ullah I, Tahir MJ, Yousaf Z**. 2022. COVID-19 associated vasculitis: A systematic review of case reports and case series. Ann Med Surg (Lond) **74**:103249. https://doi.org/10.1016/j.amsu.2022.103249.
155. **Woolsey C, Borisevich V, Prasad AN, Agans KN, Deer DJ, Dobias NS, Heymann JC, Foster SL, Levine CB, Medina L, Melody K, Geisbert JB, Fenton KA, Geisbert TW, Cross RW**. 2021. Establishment of an African green monkey model for COVID-19 and protection against re-infection. Nat Immunol **22**:86–98. https://doi.org/10.1038/s41590-020-00835-8.
156. **Yang MS, Oh BK, Yang D, Oh EY, Kim Y, Kang KW, Lim CW, Koh GY, Lee SM, Kim B**. 2021. Ultra- and micro-structural changes of respiratory tracts in SARS-CoV-2 infected Syrian hamsters. Vet Res **52**:121. https://doi.org/10.1186/s13567-021-00988-w.
157. **Yin FC, Spurgeon HA, Rakusan K, Weisfeldt ML, Lakatta EG**. 1982. Use of tibial length to quantify cardiac hypertrophy: Application in the aging rat. Am J Physiol **243**:H941–H947. https://doi.org/10.1152/ajpheart.1982.243.6.H941.
158. **Yu P, Qi F, Xu Y, Li F, Liu P, Liu J, Bao L, Deng W, Gao H, Xiang Z, Xiao C, Lv Q, Gong S, Liu J, Song Z, Qu Y, Xue J, Wei Q, Liu M, Wang G, Wang S, Yu H, Liu X, Huang B, Wang W, Zhao L, Wang H, Ye F, Zhou W, Zhen W, Han J, Wu G, Jin Q, Wang J, Tan W, Qin C**. 2020. Age-related rhesus macaque models of COVID-19. Animal Model Exp Med **3**:93–97. https://doi.org/10.1002/ame2.12108.
159. **Yu WL, Toh HS, Liao CT, Chang WT**. 2021. Cardiovascular complications of COVID-19 and associated concerns: A review. Acta Cardiol Sin **37**:9–17.
160. **Zaeck LM, Scheibner D, Sehl J, Müller M, Hoffmann D, Beer M, Abdelwhab EM, Mettenleiter TC, Breithaupt A, Finke S**. 2021. Light sheet microscopy-assisted 3D analysis of SARS-CoV-2 infection in the respiratory tract of the ferret model. Viruses **13**:529. https://doi.org/10.3390/v13030529.
161. **Zeiss CJ, Compton S, Veenhuis RT**. 2021. Animal models of COVID-19. I. comparative virology and disease pathogenesis. ILAR J **62**:35–47. https://doi.org/10.1093/ilar/ilab007.
162. **Zhai C, Wang M, Chung HJ, Hassan M, Lee S, Kim HJ, Hong ST**. 2021. Roborovski hamster *(Phodopus roborovskii)* strain SH101 as a systemic infection model of SARS-CoV-2. Virulence **12**:2430–2442. https://doi.org/10.1080/21505594.2021.1972201.
163. **Zhao X, Chen D, Szabla R, Zheng M, Li G, Du P, Zheng S, Li X, Song C, Li R, Guo JT, Junop M, Zeng H, Lin H**. 2020. Broad and differential animal angiotensin-converting enzyme 2 receptor usage by SARS-CoV-2. J Virol **94**:e00940-20. https://doi.org/10.1128/JVI.00940-20.
164. **Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, Guan L, Wei Y, Li H, Wu X, Xu J, Tu S, Zhang Y, Chen H, Cao B**. 2020. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: A retrospective cohort study. Lancet **395**:1054–1062. https://doi.org/10.1016/s0140-6736(20)30566-3.
165. Zoo Atlanta. 2021. [Internet]. Update on Zoo Atlanta gorilla population. [Cited 20 Jan 2023]. Available at: https://zooatlanta.org/update-on-zoo-atlanta-gorilla-population/.