Feline coronavirus and feline infectious peritonitis (FIP) – Russian roulette for your pet

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Utilising Machine Learning on clinical datasets could help to crack the enigma of feline infectious peritonitis diagnosis

Coronaviruses came to the forefront of public consciousness in 2019 with the outbreak of the SARS-CoV-2 pandemic. However, this family of viruses has long been recognised as important pathogens of animals and man. Feline coronavirus (FCoV) is a ubiquitous pathogen of cats, which can sometimes cause a devastating disease called 'feline infectious peritonitis' (FIP) in both domestic and wild felids. This virus is common among pet cats and in multi-cat households and shelters, where its prevalence can be extremely high. Infection is reasonably innocuous for most cats, who may experience asymptomatic infection or develop a mild gastrointestinal upset. However, similar to COVID-19 in humans, sometimes infection has more severe consequences. In a small fraction of cases, usually between 5 and 10% of FCoV-infected individuals, (1) cats develop a severe aberrant immune response to the virus, resulting in FIP. Different types of FIP occur, affecting different tissues, and until very recently, the disease was invariably fatal.

It is unknown whether or when an FCoV infection will switch from being asymptomatic to being FIP, and for this reason, contracting FCoV can be considered somewhat similar to playing a game of Russian Roulette for a cat. While there are known predisposing factors such as age and environment,
it has also been suggested that an individual's genetics play a role in the development and outcome of infection. (2) Efforts have been ongoing for decades to elucidate the mechanism underlying the development of FIP. However, veterinary medicine is still to discover many of the secrets held by this enigmatic virus.

Feline Infectious Peritonitis: A complex diagnosis

Despite knowing the causative agent of this disease and being able to readily test for its presence, FIP remains an extremely difficult disease to diagnose. The presence of the pathogen is not diagnostic for FIP, as many cats will have an FCoV infection without developing the disease. Definitive diagnosis of FIP requires invasive sample collection and demonstration of the virus within diseased tissues. The clinician's current approach to diagnosis relies on evaluating clinical signs together with multiple biomarkers, all of which are compiled to build a body of evidence. In some instances, more invasive samples are collected and evaluated alongside the initial bloodwork. (3) The crossover in clinical signs and biomarkers with several other feline diseases often confounds a diagnosis.

We hypothesised that we could use Machine Learning to develop a diagnostic model for FIP, using curated retrospective clinical data from our veterinary diagnostic service gathered over the course of more than two decades. [4] Our team's clinical knowledge and expertise in feline infectious disease would be integral to developing such models. FIP testing is a major focus of efforts at the University of Glasgow Veterinary Diagnostic Service. Having researchers with clinical experience of this disease as part of the scientific team would be essential for building, fine-tuning and validating any tool proposed for implementation in a clinical setting. This would allow us to account for nuances in sample quality and differences in test methodology and, importantly, establish the clinical relevance of specific features which may be the building blocks of the models.

We elected to investigate the difficult-to-diagnose, non-effusive form of FIP in the first instance. To begin, we assessed the suitability of the data stored within our clinical laboratory records. We methodically examined each FIP biomarker, and an expert veterinary panel was assembled to determine the optimal biomarkers to be included in the initial modelling based on clinical relevance and technical reasoning. We then removed selected markers, those effectively providing the same type of signal, as these can be detrimental to model performance.

We next explored the types of models to use, selecting a number of different styles of algorithms from which to build our models, ranging from basic statistical types to Machine Learning-based methods. We examined them individually and found that each had unique properties that exploited different nuances in the data. Based on this, we decided to incorporate a number of different types of individual models into larger 'ensemble' models, which exhibited the benefits of all their contributors. Our ensemble models produced excellent results with predictive accuracies comparable to gold-standard testing.

Challenges to the application of Machine Learning for FIP diagnosis

The quality of the results produced by our research effort is certainly encouraging. However, we acknowledge that there may be an overestimation of the predictive capabilities due to having less than one hundred cases and controls with FIP being confirmed on the basis of post-mortem or immunohistopathology, the current gold-standard method. While this modelling appears to work very well for 'classical non-effusive' FIP, it is unknown how well it can detect cases of less common variants of the disease, such as neurological or occular FIP, where pathological changes may be more subtle and focussed on specific tissues.

The greatest challenge to developing a deployable Machine Learning diagnostic tool for FIP is gathering sufficient cases and controls with a definite diagnosis. The intractable nature of the disease and the complexity of diagnosis make it difficult to collect a sizeable number of definitively diagnosed cases. One solution would be to establish a global collaboration to provide the necessary case numbers, though differences in diagnostic testing and inter-laboratory variation provide yet more hurdles to overcome.

Light at the end of the tunnel for Feline Infectious Peritonitis

Despite the limitations described above, our results appear very promising. Indeed, several other research groups in different parts of the world have started to investigate how Machine Learning can be applied to the diagnostic complexity of FIP. Accurately diagnosing a living cat without the need for invasive sampling is a laudable goal since such sampling can harm the patient, with the additional stress potentially exacerbating the disease. FIP has been an untreatable and incurable disease for decades. The COVID-19 pandemic was responsible for the rapid licensing of anti-viral treatments for coronavirus infection. Targeted therapy, however, depends on timely and accurate diagnosis. While we are a step closer to this goal, there remains work to be done to translate Machine Learning into a clinical diagnostic tool for FIP.

References

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