



**UNIVERSITI PUTRA MALAYSIA**

**RETROSPECTIVE STUDY ON PREOPERATIVE LEUKOCYTOSIS AND  
ITS RELATIONSHIP WITH POSTOPERATIVE WOUND COMPLICATIONS  
IN CATS AND DOGS PRESENTED FOR MASTECTOMY AT UNIVERSITY  
VETERINARY HOSPITAL, UNIVERSITI PUTRA MALAYSIA FROM 2017  
TO 2021**

**SARWESHWARY SUBRAMANIAM**

**Ip  
FPV 2022 55**

**RETROSPECTIVE STUDY ON PREOPERATIVE LEUKOCYTOSIS AND ITS  
RELATIONSHIP WITH POSTOPERATIVE WOUND COMPLICATIONS IN CATS  
AND DOGS PRESENTED FOR MASTECTOMY AT UNIVERSITY VETERINARY  
HOSPITAL, UNIVERSITI PUTRA MALAYSIA FROM 2017 TO 2021**

**SARWESHWARY SUBRAMANIAM**

A project paper submitted to the  
Faculty of Veterinary Medicine, Universiti Putra Malaysia  
In partial fulfillment of the requirement for the  
**DEGREE OF DOCTOR OF VETERINARY MEDICINE**  
Universiti Putra Malaysia  
Serdang, Selangor Darul Ehsan

2022/2023

## CERTIFICATION

It is hereby certified that we have read this project paper entitled "Retrospective study of Preoperative Leukocytosis and its relationship with Postoperative Wound Complications in cats and dogs presented for Mastectomy in University Veterinary Hospital from 2017 to 2019" by Sarweshwary Subramaniam and in our opinion, it is satisfactory in terms of scope, quality and presentation as partial fulfillment of the requirement for the course VPD 4999 – Final Year Project.

---

**DR. ROZANALIZA RADZI**

**DVM (UPM), Ph.D. (Yamaguchi University, Japan )**

Senior Lecturer,

Faculty of Veterinary Medicine,

Universiti Putra Malaysia.

(Supervisor)

---

**DR. AZALEA HANI OTHMAN**

**DVM (UPM), Ph.D. (UPM),**

Senior Lecturer,

Faculty of Veterinary Medicine,

Universiti Putra Malaysia.

(Co-Supervisor)

## ACKNOWLEDGMENTS

As this project marks the end of my Veterinary Medicine degree, I am grateful to everyone who has helped me with this project and throughout my five years of vet school.

I am grateful to God for giving me the strength and patience to pursue my dream and endure all the challenges that came my way.

I would like to express my sincere gratitude to my supervisor, Dr. Rozanaliza Radzi and co-supervisor, Dr. Azalea Hani Othman for accepting me as a final year project student and supporting me in conducting this project. Despite their busy schedule, they were constantly available to give inputs and suggestions till the end. Also, they objectively pointed out mistakes for corrections and guided me until the completion of this project.

I am immensely grateful to my family and friends who have been a huge support in this tough yet a fruitful journey.

Last but not least, I will forever be grateful to every single person who has been part of this important journey of mine be it directly or indirectly.

## TABLE OF CONTENTS

|   |      |
|---|------|
| <b>TITLE</b> .....                          | i    |
| <b>CERTIFICATION</b> .....                  | ii   |
| <b>ACKNOWLEDGMENTS</b> .....                | iii  |
| <b>TABLE OF CONTENTS</b> .....              | iv   |
| <b>LIST OF FIGURES</b> .....                | vi   |
| <b>LIST OF TABLES</b> .....                 | vii  |
| <b>ABSTRAK</b> .....                        | viii |
| <b>ABSTRACT</b> .....                       | x    |
| <b>1.0 INTRODUCTION</b> .....               | 1    |
| <b>1.1 Objective</b> .....                  | 2    |
| <b>1.2 Justification</b> .....              | 2    |
| <b>2.0 LITERATURE REVIEW</b> .....          | 2    |
| <b>2.1 Leukocytosis</b> .....               | 2    |
| <b>2.2 Mastectomy</b> .....                 | 5    |
| <b>2.3 Canine Mammary Gland Tumor</b> ..... | 6    |
| <b>2.4 Feline Mammary Gland Tumor</b> ..... | 6    |
| <b>2.5 Postoperative Morbidity</b> .....    | 7    |
| <b>3.0 MATERIALS AND METHODS</b> .....      | 8    |

|  |    |
|--|----|
| <b>3.1 Experimental Design</b> .....   | 8  |
| <b>3.2 Data Analysis</b> .....   | 8  |
| <b>4.0 RESULTS</b> .....   | 9  |
| <b>4.1 Neutrophilic Leukocytosis</b> .....   | 11 |
| <b>4.2 Postoperative Wound Complications</b> .....   | 12 |
| <b>4.3 Statistical Analysis</b> .....  | 15 |
| <b>5.0 DISCUSSION</b> .....  | 15 |
| <b>5.1 Neutrophilic Leukocytosis</b> .....   | 15 |
| <b>5.1 Association between Neutrophilic Leukocytosis and Postoperative Wound<br/>Complications</b> ..... | 16 |
| <b>6.0 CONCLUSION</b> .....  | 18 |

**LIST OF FIGURES**

|                  |   |    |
|------------------|---|----|
| <b>Figure 1:</b> | Eligibility criteria                                      | 10 |
| <b>Figure 2:</b> | Distribution of postoperative wound complications in dogs | 13 |
| <b>Figure 3:</b> | Distribution of postoperative wound complications in cats | 14 |



**LIST OF TABLES**

|                 |   |    |
|-----------------|---|----|
| <b>Table 1:</b> | Patient eligibility criteria  | 9  |
| <b>Table 2:</b> | Frequency of preoperative leukocytosis in the study population of 36 dogs and 26 cats that underwent mastectomy | 11 |
| <b>Table 3:</b> | Postoperative wound complications dogs with and without preoperative leukocytosis                               | 12 |
| <b>Table 4:</b> | Postoperative wound complications cats with and without preoperative leukocytosis                               | 13 |

**ABSTRAK**

Abstrak daripada kertas projek yang dikemukakan kepada Fakulti Perubatan Veterinar untuk memenuhi sebahagian daripada keperluan kursus VPD 4999 -Projek Ilmiah Tahun Akhir.

**KAJIAN RETROSPEKTIF TERHADAP *PREOPERATIVE LEUKOCYTOSIS* DAN  
HUBUNGANYA DENGAN KOMPLIKASI LUKA SELEPAS SURGERI DALAM  
ANJING DAN KUCING YANG MENJALANI *MASTECTOMY* DI HOSPITAL  
VETERINAR UNIVERSITI, UNIVERSITI PUTRA MALAYSIA ANTARA TAHUN 2017  
HINGGA 2021**

oleh

**Sarweshwary Subramaniam**

**2022**

**Penyelia: Dr Rozanaliza Radzi**

**Penyelia Bersama: Dr Azalea Hani Othman**

Beberapa bukti dalam kajian manusia telah mencadangkan perkaitan antara *preoperative leukocytosis* dan komplikasi selepas operasi merentasi pelbagai prosedur operasi. Leukositosis selalunya merupakan penemuan sampingan semasa pemeriksaan darah pra-operasi tetapi kaitannya dengan morbiditi selepas operasi tidak ditangani dengan secukupnya dalam bidang veterinar. Leukositosis dicirikan oleh peningkatan dalam kiraan sel darah putih melebihi nilai julat atas  $19.5 \times 10^9/L$  pada kucing dan  $14.1 \times 10^9/L$  pada anjing. Tumor *mammary gland* adalah salah satu tumor yang paling biasa pada anjing dan kucing, di mana mastektomi adalah rawatan utama yang ditunjukkan.

Insiden tumor *mammary gland* adalah 52% pada anjing dan 17% pada kucing daripada semua tumor pada haiwan betina. Kira-kira 45% tumor *mammary gland* adalah malignan pada anjing dan 90% malignan pada kucing. Anjing dan kucing yang menjalani mastektomi sering mengalami komplikasi luka di tapak pembedahan seperti pembentukan seroma, jangkitan luka, *dehiscence* luka, pendarahan dan keradangan. Kajian ini bertujuan untuk mengenal pasti perkaitan antara leukositosis praoperasi dan komplikasi luka selepas surgery pada anjing dan kucing yang menjalani mastektomi. Kajian retrospektif ini melibatkan 62 pesakit: 36 adalah anjing dan 26 adalah kucing yang menjalani mastektomi untuk tumor *mammary gland* antara tahun 2017 hingga 2021 di Hospital Veterinar Universiti, Universiti Putra Malaysia. Hasil yang diukur termasuk komplikasi luka yang merupakan keradangan, pembentukan seroma, pendarahan dan kerosakan jahitan sepanjang tempoh kemasukan di hospital. Kekekapan leukositosis pra surgery pada kucing dan anjing yang telah menjalani mastektomi adalah 62% dan 47% masing-masing. Didapati terdapat perkaitan antara leukositosis pra surgery dan komplikasi luka mastektomi ( $p \leq 0.05$ ). Pesakit dengan leukositosis pra surgery lebih berkemungkinan mengalami komplikasi luka selepas pembedahan berbanding mereka yang tidak mempunyai leukositosis pra surgery. Kajian lanjut ditunjukkan untuk mengesahkan dan menjelaskan penemuan ini.

**Kata Kunci:** Mastektomi; komplikasi luka; leukositosis pra surgery

**ABSTRACT**

An abstract of the project paper presented to the Faculty of Veterinary Medicine in partial fulfillment of the course VPD 4999-Final Year Project.

**RETROSPECTIVE STUDY ON PREOPERATIVE LEUKOCYTOSIS AND ITS  
RELATIONSHIP WITH POSTOPERATIVE WOUND COMPLICATIONS IN CATS  
AND DOGS PRESENTED FOR MASTECTOMY AT UNIVERSITY VETERINARY  
HOSPITAL, UNIVERSITY PUTRA MALAYSIA FROM THE YEAR 2017 TO 2021**

by

**Sarweshwary Subramaniam**

**2022**

**Supervisor: Dr. Rozanaliza Radzi**

**Co-supervisor: Dr. Azalea Hani Othman**

Human studies have suggested an association between preoperative leukocytosis and postoperative complications in various surgical procedures. Leukocytosis is often an incidental finding during pre-surgical blood screening. The association of leukocytosis with postoperative morbidity is inadequately addressed in the veterinary field. Leukocytosis is characterized by the elevation in white blood cell count above the upper range value of  $19.5 \times 10^9/L$  in cats and  $14.1 \times 10^9/L$  in dogs. Mammary gland tumor is one of the most common tumors in small animals, in which mastectomy is the primary treatment indicated. The incidence of mammary gland tumors is 52% in dogs and 17% in cats of all tumors in females. Approximately 45% and 90% of mammary gland tumors are malignant in dogs and cats. Small animals undergoing mastectomy often develop surgical site wound complications such as seroma formation, wound infection, wound dehiscence,

hemorrhage and inflammation. This study aims to identify the association between preoperative leukocytosis and postoperative wound complications in small animals undergoing mastectomy. This retrospective study included 62 patients: 36 were dogs and 26 were cats that underwent mastectomy for mammary gland tumors between the year 2017 to 2021 at University Veterinary Hospital, Universiti Putra Malaysia. Outcomes measured included wound complications such as inflammation, seroma formation, hemorrhage and suture breakdown during hospitalization. The frequency of preoperative leukocytosis in cats and dogs subjected to mastectomy was 62% and 47%, respectively. This study found an association between preoperative leukocytosis and postoperative wound complications ( $p \leq 0.05$ ). Patients with preoperative leukocytosis are more likely to develop postoperative wound complications than those without preoperative leukocytosis. Further studies are indicated to validate and explain these findings.

**Keywords:** Mastectomy; postoperative wound complications; preoperative leukocytosis

## 1.0 INTRODUCTION

Preoperative leukocytosis is a factor that affects the morbidity of human surgical patients (Patel et al., 2021), and multiple focused studies have demonstrated the significance of preoperative leukocytosis as a marker of specific outcomes such as morbidity and mortality following a wide variety of surgeries (Tang *et al.*, 2022). Leukocytosis is a non-specific marker for a systemic inflammatory state. While systemic inflammation is a biological protective response, it is associated with humoral and cellular components resulting in vascular injury and postoperative complications. Surgical trauma-induced non-specific inflammation is possibly the "second hit" in patients with pre-existing systemic inflammatory state plausibly associated with adverse outcomes (Mahmood et al., 2017). Leukocytosis in patients is determined via leukogram, a part of the complete blood count (CBC). A CBC is done as a pre-surgical screening before surgical procedures. The effect of preoperative leukocytosis in small animals on postoperative morbidity and mortality is unclear.

Patients with mammary gland tumors are primarily indicated for a mastectomy due to its malignancy characteristic, and it is one of the most common tumors in cats and dogs (Horta et al., 2015). Patients undergoing mastectomy often develop postoperative wound complications at the surgical site, which include wound dehiscence, inflammation, seroma formation and hemorrhage (Papazoglou *et al.*, 2014). This study aimed to determine the pre-existing leukocytosis before surgery increases the chances of developing postoperative wound complications in patients that underwent a mastectomy and to identify if preoperative leukocytosis is a risk factor in animals undergoing mastectomy.

## **1.1 Objective**

This retrospective study determines the association between preoperative leukocytosis and postoperative wound complications in cats and dogs undergoing mastectomy.

## **1.2 Justification**

Leukocytosis is often an incidental finding in pre-surgical blood screening (Shin and Kim, 2018). However, the association between preoperative leukocytosis and the postoperative outcome is unclear in the veterinary field. Hence, analyzing the relationship between preoperative leukocytosis with postoperative outcomes in small animal surgical patients offers identification and validation of postoperative morbidity, mortality and complications to facilitate optimal therapeutic regimens (Beetz et al., 2020).

## **2.0 LITERATURE REVIEW**

### **2.1 Leukocytosis**

Leukocytes are referred to as white blood cells. Leukocytosis is characterized by an elevation in white blood cell count above the upper range value of  $19.5 \times 10^9/L$  in cats and  $14.1 \times 10^9/L$  in dogs which is often a common laboratory finding (Richards and George, 2014). According to (Tvedten and Raskin, 2012), leukocyte response in a patient is evaluated via a leukogram which comprises neutrophils, basophils, eosinophils that are granulocytes, as well as lymphocytes and monocytes, which are agranulocytes. (Tvedten and Raskin, 2012) also stated that leukocytes are inflammatory cells, and changes in the leukogram are mainly used to detect inflammation or infection and determine the severity and type. Besides, leukocytosis is one of the hallmarks of infection. The leukocyte differential may show neutrophilia in the case of bacterial infection, eosinophilia in

parasitic or allergic conditions and lymphocytosis in viral infections (Tvedten and Harold, 2012). Similar to erythrocytes, leukocytes are constitutively produced from hematopoietic stem cells in the red bone marrow. They are released into the circulation when needed and removed from the blood by the liver and spleen (Chmielewski and Strzelec, 2017).

(Thrall et al., 2006) stated that leukocytosis can result from neutrophilia, eosinophilia, basophilia, lymphocytosis, or monocytosis. Neutrophils compose the majority of leukocytes in the blood; thus, leukocytosis is usually caused by neutrophilia. The three most common causes of neutrophilic leukocytosis are inflammation, corticosteroid-induced and physiological (Tvedten and Raskin, 2012). During inflammation, neutrophils are released from the bone marrow at an increased rate. As the release rate increases, band neutrophils also are increased, creating a left shift. The degree of left shift is proportional to the inflammatory stimulus (Kociba, 2014). Increased tissue demand for neutrophils frequently results from viral and non-infectious inflammatory disorders. The condition of an increase in circulating neutrophils without a corresponding increase in the need for neutrophils in the tissue, is physiological neutrophilic leukocytosis (Thrall et al., 2006). Any stressful situation, including anxiety, excitement, physical activity, severe illness, trauma, or shock, can cause physiological leukocytosis.

As soon as stress sets in, the pituitary-adrenal axis is activated to cause the adrenal gland to release corticosteroids. Corticosteroids make marginated cells circulate, prevent neutrophils from randomly migrating from the circulation to tissue, and degrade neutrophil functionality. Lysosomal membrane stabilization leads to functional impairment. Therefore, corticosteroids produce a neutrophilic leukocytosis for the total and differential

leukocyte count (Chmielewski and Strzelec, 2017). Cats are more likely than dogs to experience physiological leukocytosis. Physical leukocytosis, however, is less likely to happen in a sick cat. It is thought that illness alone can change the cat's perception of unfamiliar surroundings, lowering the excitement and stress that lead to the physiological leukocytosis (Rebar and Metzger, 2014).

The increase in circulating lymphocytes is known as lymphocytosis, which can also result in leukocytosis. The thymus, lymph nodes, spleen, and sporadic lymphocytic foci are the primary lymphoid tissues from which the lymphocyte is derived. In both cats and dogs, they are the second most common type of leukocyte. The ability of lymphocytes to produce antibodies explains why their cytoplasm is so abundant in gamma globulin. Lymphocytes live much longer than neutrophils do because they move between the lymph, blood, and tissue instead of perishing in the tissue like neutrophils. The quantity of lymphocytes in the blood is a good indicator of the quantity in the tissue as well as the general activity and health of the lymphoid tissue. (Herder and Prasse, 2011)

Physiologic causes, chronic inflammation, hypoadrenocorticism and neoplasia can cause lymphocytosis. Young animals typically exhibit physiological responses from excitement or fear, which releases adrenaline. This adrenaline release increases blood flow, which flushes lymphocytes out of the endothelium wall and into the bloodstream, resulting in temporary lymphocytosis (Burton and Jandrey, 2015). The next condition is chronic inflammation, which frequently results in inflammatory lymphocytosis from lymphoid hyperplasia and prolonged antigenic stimulation (Rebar and Metzger, 2010). Chronic

antigenic stimulation causes lymphoid hyperplasia in lymphoid tissue secondary to infectious disease, non-infectious inflammatory disease, immune-mediated disease or even recent vaccination. The absence of cortisol in hypoadrenocorticism animals often results in a mild to moderate lymphocytosis. Neoplastic lymphocytosis is caused by lymphoid neoplasms such as lymphoma and lymphoid leukemia, leading to over-neoplastic cell proliferation (Richards and George, 2014).

## **2.2 Mastectomy**

Mastectomy is the primary treatment indicated for mammary gland tumors in cats and dogs (Papazoglou *et al.*, 2014). Surgical resection is the current gold standard therapy for mammary gland tumors in cats and dogs. It is considered the single most effective method to attain local tumor control except for inflammatory carcinoma or distant metastases (Papazoglou *et al.*, 2014). Based on the size of the primary tumor, its location, adherence and fixation to the underlying tissues, its potential extension through the lymphatic routes to regional lymph nodes, the total number of lesions, and the likelihood of achieving local tumor control, the extent of surgical excision and the type of surgery are better determined individually for each patient (Cassali *et al.*, 2019). Surgical options may include regional mastectomy, unilateral or bilateral, and radical mastectomy. Regional mastectomy is the removal of the affected gland only, modified radical mastectomy is the removal of the affected gland and those that share lymphatic drainage and associated lymph nodes, and radical mastectomy is the removal of the entire mammary chain and associated lymph nodes. (Cassali *et al.*, 2019).

### **2.3 Canine Mammary Gland Tumor**

Mammary tumors are the most common neoplasm in the female dog. The incidence of mammary gland tumors is 52% of all tumors in female dogs, where approximately 45% of mammary gland tumors are malignant (Fesseha, 2020). The development of mammary gland tumors in dogs is hormone-dependent, and the incidence increases with age (Evans *et al.*, 2015). The risk of developing mammary neoplasia can be reduced by ovariectomy before the first estrus. The risk can be minimized up to 0.5% in intact bitches, whereas ovariectomy after one estrus reduces the risk to 8% in intact bitches. Bitches neutered after maturity are generally considered to have the same risk as intact bitches (Fesseha, 2020).

### **2.4 Feline Mammary Gland Tumor**

Feline mammary gland tumor has been recorded as the most frequent disease after hematopoietic and skin tumors. In cats, mammary gland tumors are more aggressive than in dogs, as at least 80% of feline mammary tumors are malignant (Cassali *et al.*, 2019). Many of these, mainly large and invasive tumors, adhere to the skin and are ulcerated. In addition, invasion of lymphatic vessels and lymph nodes is common. Regional or distant metastasis can be found in more than 80% of cats with mammary cancer, mainly in the lungs (Antunes, 2014). Like dogs, hormonal fluctuations associated with repeated oestrus cycles influence the development of mammary tumors in cats (Morris, 2014).

## 2.5 Postoperative Morbidity

Postoperative morbidity, on the other hand, refers to adverse events and complications following surgery (Khuri et al., 1999). Surgical adverse events contribute significantly to postoperative morbidity, yet the measurement and monitoring of these events are often imprecise and of uncertain validity (Bruce *et al.*, 2001). Postmastectomy-related complications may include seroma formation, wound infection, dehiscence of the incision, hemorrhage and inflammation at the surgical site (Papazoglou *et al.*, 2014). Seroma is a collection of serous fluid in the dead space of post-mastectomy (Sampathraju and Rodrigues, 2010). The pathogenesis of seroma has not been fully elucidated, but acute inflammatory exudates form the seroma in response to surgical trauma and the acute phase of wound healing. Seroma formation after mastectomy surgery appears to be a persistent problem despite advances in surgical techniques and hemostasis (Lotfy *et al.*, 2022).

Postmastectomy seroma is likely a proinflammatory process, and the incidence was significantly reduced after reducing the inflammatory mediators in a study (Talhan *et al.*, 2015). Inflammation at the surgical site is often observed post-surgery. It is one of the phases in wound healing, but persistence in this inflammation causes delays in wound healing, eventually resulting in postoperative complications. A prolonged inflammatory phase of wound healing often results in increased matrix metalloproteinases (MMPs), elastase and leukocytes, compromising wound healing (Lux, 2022).

### 3.0 MATERIALS AND METHODS

#### 3.1 Experimental Design

Medical records of the Small Animal Unit of the University Veterinary Hospital, Universiti Putra Malaysia, were reviewed to identify cats and dogs that underwent mastectomies from January 2017 to December 2021. Small animal surgery patient case logbooks were used to retrieve records from the archives.

Data collected were: the patient signalment (age, species, breed, sex, neutering status), patient's clinical presentation, history of underlying diseases, pre-surgical blood results, medications that the patient was on, intraoperative complications if there were and postoperative wound complications during the hospitalization period. The inclusion and exclusion criterias are listed in Table 1.

#### 3.2 Data Analysis

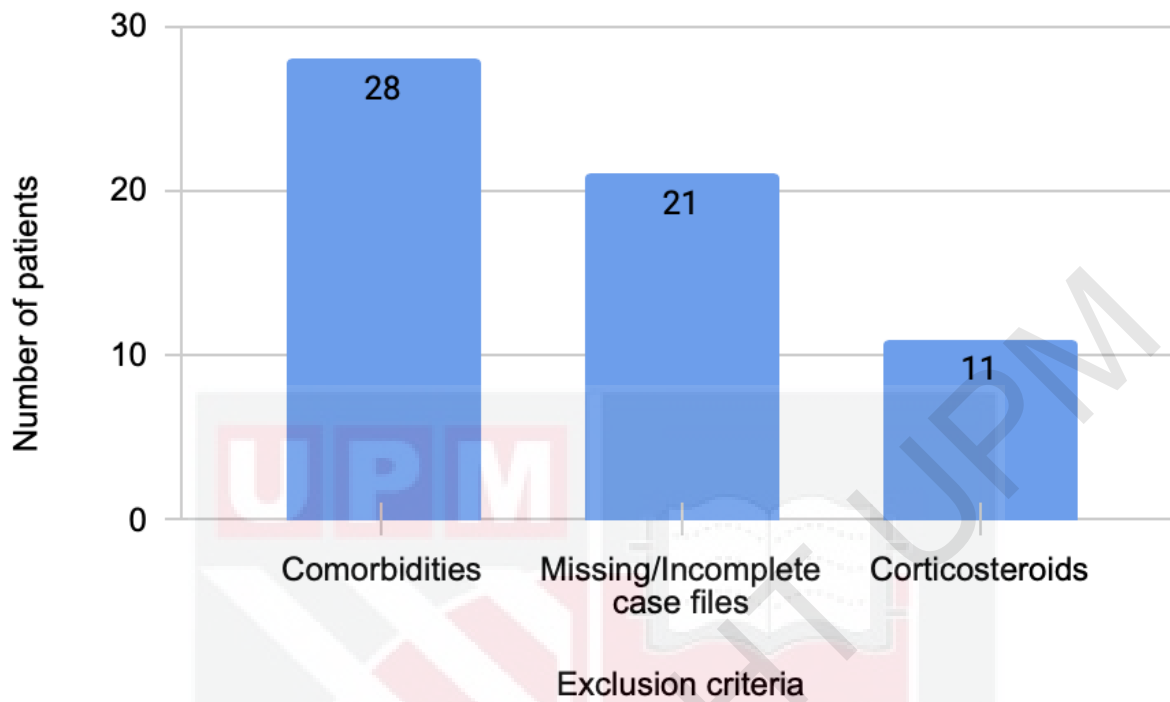
Microsoft Excel software was used for data tabulation. Descriptive analysis for qualitative data was done to present the data on the frequency of preoperative leukocytosis in cats and dogs before mastectomy. A chi-square test was used for statistical analysis, and a *p-value*  $\leq 0.05$  was considered significant, indicating an association between preoperative leukocytosis and postoperative wound complications in cats and dogs undergoing mastectomy.

| Inclusion Criteria                                 | Exclusion Criteria   |
|--|--|
| 1. Cats and dogs underwent mastectomy              | 1. Cats and dogs with comorbidities                                  |
| 2. Cats and dogs with preoperative leukocytosis    | 2. Missing information from patient case files or missing case files |
| 3. Cats and dogs without preoperative leukocytosis | 3. Cats and dogs that were on corticosteroids                        |

**Table 1: Patient eligibility criteria**

#### 4.0 RESULTS

In total, 127 patients underwent mastectomies from the year 2017 to 2021. After adhering to the eligibility criterias, sixty-two patients were recruited, of which thirty-six were dogs and twenty-six were cats. Out of thirty-six dogs included in this study, the frequency of dogs with preoperative leukocytosis was 47.2% (17/36), while the frequency of dogs without preoperative leukocytosis was 52.8% (19/36). Out of the twenty-six cats included in this study, the frequency of cats with preoperative leukocytosis was 61.5% (16/26), while the frequency of cats without preoperative leukocytosis was 38.5% (10/26). Detail characteristics are presented in Figure 1 and Table 2, respectively.



**Figure 1: Eligibility Criteria**

Exclusion criteria are the confounding factors that could potentially affect the outcome and reliability of this study. Figure 1 above shows the number of patients excluded in this study. Twenty-eight patients with comorbidities such as concurrent cardiac disease, renal disease and Ehrlichiosis were excluded. Twenty-one patients with missing and incomplete case data were excluded from this study. Eleven patients that were under corticosteroid prescription were excluded as well.

| Species                          | Dogs (n=36)   | Cats (n=26)   |
|----------------------------------|---------------|---------------|
| <b>Preoperative Leukocytosis</b> |               |               |
| With                             | n= 17 (47.2%) | n= 16 (61.5%) |
| Without                          | n= 19 (52.8%) | n= 10 (38.5%) |

**Table 2: Frequency of preoperative leukocytosis in the study population of 36 dogs and 26 cats that underwent Mastectomy**

#### **4.1 Neutrophilic Leukocytosis**

Seventeen dogs and sixteen cats with preoperative leukocytosis before mastectomy specifically had neutrophilic leukocytosis, which means the elevation in the white blood cells is mainly caused by neutrophils.

#### 4.2 Postoperative Wound Complications

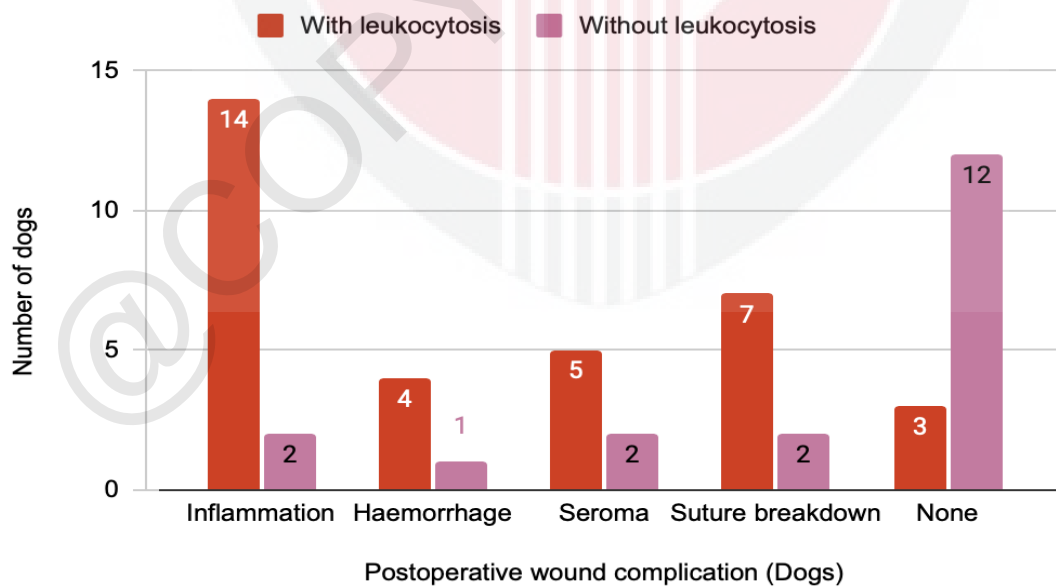
Postoperative wound complications observed in the patients that underwent mastectomy were seroma formation, suture breakdown, inflammation and hemorrhage at the surgical site. Some patients had more than one complication post-mastectomy. These data were further categorized into different groups, as listed in Table 3 and Table 4 below.

| <b>Preoperative Leukocytosis</b>         | <b>With (n=17)</b> | <b>Without (n=19)</b> |
|--|--------------------|-----------------------|
| <b>Postoperative Wound Complications</b> |                    |                       |
| Inflammation                             | n= 14              | n= 2                  |
| Suture breakdown                         | n= 7               | n= 2                  |
| Seroma formation                         | n= 5               | n= 2                  |
| Hemorrhage                               | n= 4               | n= 1                  |
| None                                     | n= 3               | n= 12                 |

**Table 3: Postoperative wound complications dogs with and without preoperative leukocytosis**

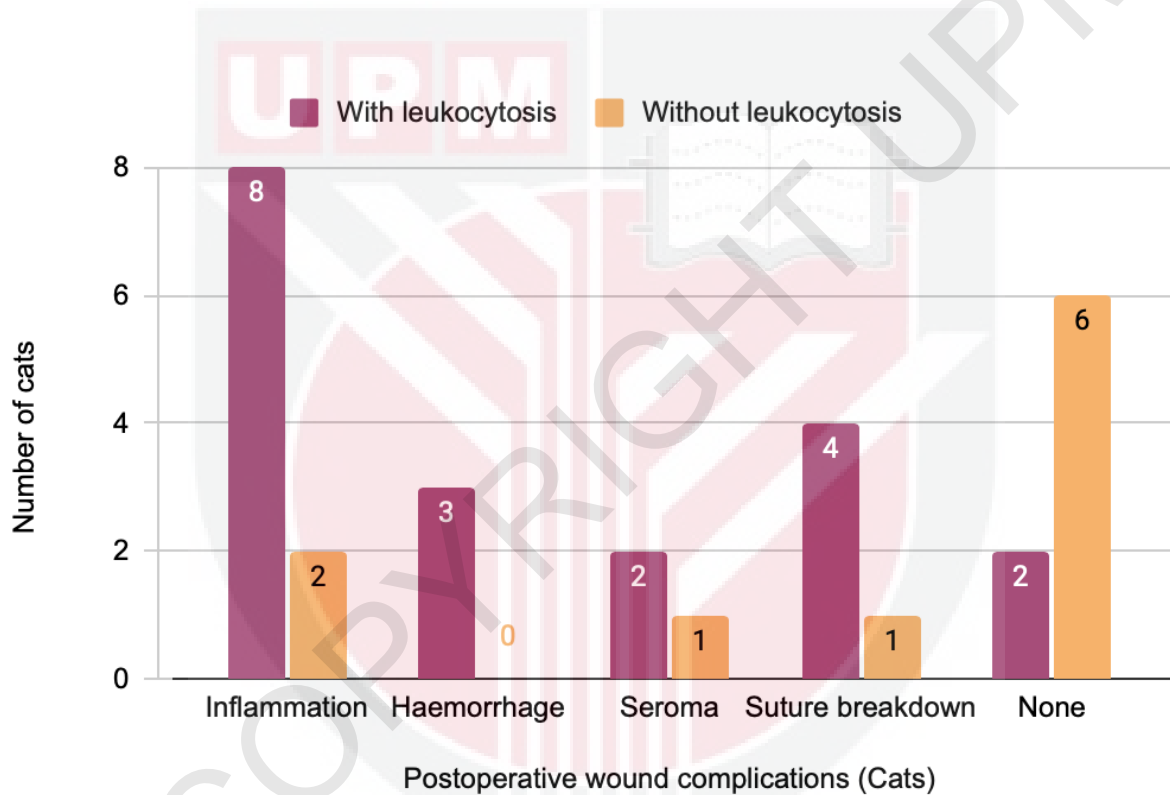
| Preoperative Leukocytosis                | With (n=16) | Without (n= 10) |
|--|-------------|-----------------|
| <b>Postoperative Wound Complications</b> |             |                 |
| Inflammation                             | n= 8        | n= 2            |
| Suture breakdown                         | n= 4        | n= 1            |
| Seroma formation                         | n= 2        | n= 1            |
| Hemorrhage                               | n= 3        | n= 0            |
| None                                     | n= 2        | n= 6            |

**Table 4: Postoperative wound complications cats with and without preoperative leukocytosis**



**Figure 2: Distribution of postoperative wound complications in dogs**

Figure 2 shows postoperative wound complications over the number of dogs with and without preoperative leukocytosis. Postoperative wound complication is significantly higher in dogs with preoperative leukocytosis. The highest wound complication observed in dogs with preoperative leukocytosis is seroma, while the lowest is suture breakdown. And among the nineteen dogs without preoperative leukocytosis, twelve dogs did not develop any postoperative wound complications.



**Figure 3: Distribution of postoperative wound complications in cats**

Figure 3 shows postoperative wound complications over the number of cats with and without preoperative leukocytosis. Similar to dogs, postoperative wound complication is significantly higher in cats with preoperative leukocytosis. The highest wound complication observed in cats with preoperative leukocytosis is seroma, while the lowest is suture breakdown. And among the ten cats without preoperative leukocytosis, six cats did not develop any postoperative wound complications.

### **4.3 Statistical Analysis**

Chi-square was used to test the association between preoperative leukocytosis and postoperative wound complications. The null hypothesis was rejected with the p-value < 0.05. This study found an association between preoperative leukocytosis and postoperative wound complications in cats and dogs that underwent mastectomy.

## **5.0 DISCUSSION**

### **5.1 Neutrophilic Leukocytosis**

Neutrophilic leukocytosis is often correlated with bacterial infection but can also be seen during inflammation. Infection is not a synonym for inflammation, infection often leads to inflammation, but inflammation can be a problem on its own. During inflammation, the inflammatory cytokines stimulate the production of neutrophils and their release from the bone marrow (Tahir and Zahra, 2022). A study by Hristov and Binev, which evaluated hematological parameters in a dog with a mammary gland tumor, found neutrophilic leukocytosis is frequently encountered in dogs with neoplastic growths, and the usual cause is due to inflammation and tissue degradation.

According to (Munn 2017), the tumor itself can initiate inflammation. Tumors can induce inflammatory responses through several mechanisms. Tumors produce granulocyte colony-stimulating factor (G-CSF), which skews the neutrophil retention or release balance in bone marrow, leading to increased blood neutrophils. Besides, the growing tumor can physically damage the normal tissues by releasing DAMP (Damage Associated Molecular Patterns). DAMP activates the receptors on resident granulocytes which initiates inflammatory repair mechanisms (Munn, 2017). The predominance of granulocytes is often presumed to be due to bacterial infections. In this study, animals with ulcerated mammary gland masses with bacterial infections could be confounding factors. This is because true neutrophilic leukocytosis could not be distinguished in this study, either caused by a bacterial infection or tumor-induced leukocytosis.

### **5.1 Association between Neutrophilic Leukocytosis and Postoperative Wound Complications**

The exact pathogenesis on how preoperative neutrophilic leukocytosis could lead to postoperative wound complications is unclear. No research has been done extensively on this, but neutrophilia is associated with wound healing. Activation of neutrophils occurs in response to tissue injury, which recruits the neutrophils at the injury site. Upon reaching the site of damage, activated neutrophils undergo degranulation which releases proteases such as elastase that target the cellular debris for clearance to aid wound healing. However, these proteases could potentially aggravate tissue damage (Wang, 2017).

Neutrophil-derived proteases aid in wound debridement and facilitate cellular migration when present at appropriate levels. Conversely, excessive levels of proteases in the tissue resulting from overly active neutrophils or prolonged neutrophil recruitment can be detrimental by causing additional tissue damage and further inflammation (Wilgus *et al.*, 2013). Neutrophils are not frequently observed in normal skin, but they are recruited in high numbers after tissue injury, whether traumatic or surgery-induced (Wang, 2017). They are the first inflammatory cells to move to the wound site to aid healing. So, neutrophilia is often observed post-surgery.

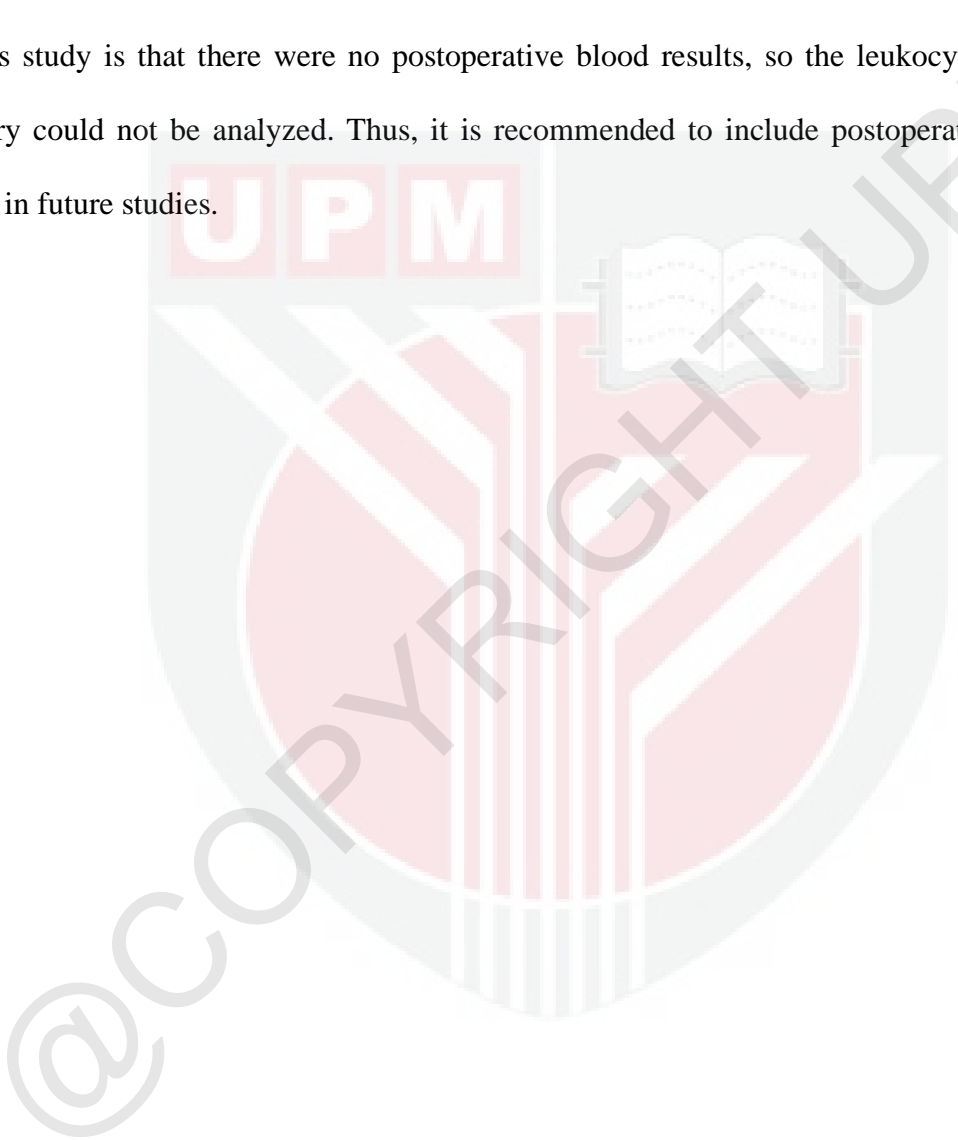
But in this study, postoperative neutrophils were not analyzed as postoperative blood screening is not routinely done in University Veterinary Hospital (UVH) unless indicated. Whether the pre-existing neutrophilia was further accelerated post-surgery, possibly leading to the wound complications observed in this study, could not be determined. Hence, further studies are indicated to validate and explain these findings.

## 6.0 CONCLUSION

Our retrospective study found that there is an association between preoperative leukocytosis and postoperative wound complications in patients undergoing mastectomy in this study. The significance of this study is that it can be used to identify patients at risk of developing postoperative wound complications post-mastectomy. In this study, patients with preoperative neutrophilia developed the most wound complications post-surgery. The pre-surgical neutrophilia could have possibly added up to the neutrophilia that is usually observed post-surgery. This could have resulted in the over-activation of neutrophils, causing increased release of proteases which in turn affects the wound healing resulting in wound complications that were observed in this study.

## 7.0 RECOMMENDATIONS

In future studies, a prospective study is highly recommended to determine the significance of the association and how strong the causality is. Besides, increasing the sample size is recommended to obtain better results with higher accuracy and precision. One of the limitations of this study is that there were no postoperative blood results, so the leukocyte count post-surgery could not be analyzed. Thus, it is recommended to include postoperative leukocyte count in future studies.



## 8.0 REFERENCE

- Beetz, O., Weigle, C. A., Cammann, S., Vondran, F. W., Timrott, K., Kulik, U., ... & Oldhafer, F. (2020). Preoperative leukocytosis and the resection severity index are independent risk factors for survival in patients with intrahepatic cholangiocarcinoma. *Langenbeck's Archives of Surgery*, 405(7), 977-988.
- Berliner, N. (2012). Leukocytosis and leukopenia. *Goldman's Cecil Medicine. 24th ed. Philadelphia, Pa.: Elsevier/Saunders.*
- Blackwood, L. (2016). Disorders of leukocytes. In *BSAVA Manual of canine and feline clinical pathology* (pp. 67-93). BSAVA Library.
- Budd, D. C., Cochran, R. C., Sturtz, D. L., & Fouty Jr, W. J. (2011). Surgical morbidity after mastectomy operations. *The American Journal of Surgery*, 135(2), 218-220.
- Burton, A. G., & Jandrey, K. E. (2018). Leukocytosis and Leukopenia. *Textbook of Small Animal Emergency Medicine*, 405-412.
- Chabot-Richards, D. S., & George, T. I. (2014). Leukocytosis. *International journal of laboratory hematology*, 36(3), 279-288.

- Chmielewski, P. P., & Strzelec, B. J. F. M. (2018). Elevated leukocyte count as a harbinger of systemic inflammation, disease progression, and poor prognosis: a review. *Folia morphologica*, 77(2), 171-178
- Coussens, L. M., & Werb, Z. (2002). Inflammation and cancer. *Nature*, 420(6917), 860-867.
- Den Herder, J., & Prasse, K. W. (2015). Leukocyte response in the dog and cat. *Iowa State University Veterinarian*, 34(2).
- Fesseha, H. (2020). Mammary mastectomy due to mammary gland tumors in intact female dog. *Biomedical Journal of Scientific & Technical Research*, 28(1), 21224-21228.
- Greten, F. R., & Grivennikov, S. I. (2019). Inflammation and cancer: triggers, mechanisms, and consequences. *Immunity*, 51(1), 27-41.
- Hambal, M., Ayuni, R., Vanda, H., & Sabri, M. (2018). Mammary Gland Tumor In Cat And Therapeutic Approach: A Case Report. *The International Journal of Tropical Veterinary and Biomedical Research*, 3(1), 60-63.
- Herrero-Cervera, A., Soehnlein, O., & Kenne, E. (2022). Neutrophils in chronic inflammatory diseases. *Cellular & Molecular Immunology*, 19(2), 177-191.
- Hristov, T., & Binev, R. (2018). Blood count in dogs with mammary gland carcinoma. *Agricultural Science and Technology*, 10(1), 44-47.

- Jark, P. C., Raposo-Ferreira, T. M., Terra, E. M., Sierra Matiz, O. R., Anai, L. A., Fonseca-Alves, C. E., ... & De Nardi, A. B. (2015). Paraneoplastic neutrophilic leukocytosis syndrome in a cat with recurrent mammary carcinoma. *Journal of Feline Medicine and Surgery Open Reports*, 1(2), 2055116915608202.
- Mahmood, E., Knio, Z. O., Mahmood, F., Amir, R., Shahul, S., Mahmood, B., ... & Matyal, R. (2017). Preoperative asymptomatic leukocytosis and postoperative outcome in cardiac surgery patients. *PloS one*, 12(9), e0182118.
- McCarty, S. M., & Percival, S. L. (2013). Proteases and delayed wound healing. *Advances in wound care*, 2(8), 438-447.
- Moghadamyeghaneh, Z., Hanna, M. H., Carmichael, J. C., Mills, S. D., Pigazzi, A., & Stamos, M. J. (2015). Preoperative leukocytosis in colorectal cancer patients. *Journal of the American College of Surgeons*, 221(1), 207-214.
- Munn, L. L. (2017). Cancer and inflammation. *Wiley Interdisciplinary Reviews: Systems Biology and Medicine*, 9(2), e1370.
- Papazoglou, L. G., Basdani, E., Rabidi, S., Patsikas, M. N., & Karayiannopoulou, M. (2014). Current surgical options for mammary tumor removal in dogs. *J Veter Sci Med*, 2(1), 6.

- Riley, L. K., & Rupert, J. (2015). Evaluation of patients with leukocytosis. *American family physician*, 92(11), 1004-1011.
- Spåre, P., Ljungvall, I., Ljungvall, K., & Bergström, A. (2021). Evaluation of post-operative complications after mastectomy performed without perioperative antimicrobial prophylaxis in dogs. *Acta Veterinaria Scandinavica*, 63(1), 1-6.
- Szender, J. B., Grzankowski, K. S., Akers, S. N., Frederick, P. J., Lele, S. B., & Odunsi, K. O. (2016). Investigating the impact of asymptomatic leukocytosis on postoperative outcomes in ovarian cancer. *Gynecologic Oncology*, 141, 166.
- Tahir, N., & Zahra, F. (2022). Neutrophilia. In *StatPearls [Internet]*. StatPearls Publishing.
- Tang, S. P. K., Moy, L. T., Wan, K. H. M., Wong, H. C., Wong, K. K. H., & Wong, K. K. (2022). Preoperative leukocytosis and postoperative outcomes in geriatric hip fracture patients: a retrospective cohort study. *Current Orthopaedic Practice*, 10-1097.
- Tvedten, H., & Raskin, R. E. (2012). Leukocyte disorders. *Small animal clinical diagnosis by laboratory methods*, 63.
- Uribe-Querol, E., & Rosales, C. (2015). Neutrophils in cancer: two sides of the same coin. *Journal of immunology research*, 2015.

Uribe-Querol, E., & Rosales, C. (2015). Neutrophils in cancer: two sides of the same coin. *Journal of immunology research*, 2015.

Villiers, E., & Ristić, J. (2016). *BSAVA manual of canine and feline clinical pathology* (No. Ed. 3). British Small Animal Veterinary Association.

Wilgus, T. A., Roy, S., & McDaniel, J. C. (2013). Neutrophils and wound repair: positive actions and negative reactions. *Advances in wound care*, 2(7), 379-388.

Zainab, S., Akbar, A., Mahboob, S., & Ikram, M. (2020). CORRELATION OF PRE-OPERATIVE LEUKOCYTOSIS WITH POST-OPERATIVE WOUND INFECTION IN CAESAREAN-SECTION. *PAFMJ*, 70(5), 1439-42.

Zhao, H., Wu, L., Yan, G., Chen, Y., Zhou, M., Wu, Y., & Li, Y. (2021). Inflammation and tumor progression: Signaling pathways and targeted intervention. *Signal transduction and targeted therapy*, 6(1), 1-46.