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Immunosuppressive Effects Of Dexamethasone In A BALB/C Mice (Mus Musculus) Cancer Model

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Abstract:
Background*: Based on data from the Global Cancer Observatory (GLOBOCAN) of the International Agency for Research on Cancer (IARC) in 2022, global cancer prevalence is projected to increase by 63%, reaching 6,445,346 cases by 2040. In Indonesia, cancer research frequently relies on animal models; however, limited availability and high costs remain significant constraints. Therefore, the development of affordable and reproducible cancer animal models is essential. BALB/c mice (Mus musculus) are widely used due to their low cost, ease of breeding, and immunological characteristics. Immunosuppression is a critical requirement for cancer model establishment, and dexamethasone is known to suppress T-cell function and induce splenic alterations. This study aimed to evaluate the effects of dexamethasone administration at doses of 10 mg/kg body weight (BW) and 15 mg/kg BW on body weight, total and differential leukocyte counts, tumor development, and splenic histopathology in BALB/c mice.*
Materials and Methods*: This experimental study was conducted over two months and involved dexamethasone intraperitoneal injection, cancer cell inoculation, nodule palpation, hematological assessment, and histological analysis of the spleen. Data were analyzed using IBM SPSS version 25 with One-Way ANOVA or Kruskal–Wallis tests.*
Results*: The results demonstrated significant reductions in body weight, total leukocytes, and lymphocytes in dexamethasone-treated groups, accompanied by a significant increase in neutrophils. Tumor nodules were observed exclusively in the 15 mg/kg BW group after 14 days.*
Conclusion: *These findings indicate that dexamethasone at 15 mg/kg BW effectively induces immunosuppression and supports successful cancer model establishment in BALB/c mice. Immunosuppression intensity, including dosage and duration, is a critical determinant of model success.*
Key Word: *Dexamethasone; Immunosuppression; Cancer animal model; Splenic histopathology*

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I. Introduction

Data from the Global Cancer Observatory (Globocan), developed by the International Agency for Research on Cancer (IARC), reported more than 408,661 new cancer cases in Indonesia in 2022, with cancer-related mortality reaching nearly 242,099 deaths. The prevalence of cancer in Indonesia is projected to increase by approximately 63%, reaching 6,445,346 cases by 2040, and is expected to be accompaniedby a proportional rise in mortality rates. Moreover, cancer ranks as the third leading cause of death in Indonesia, following stroke and cardiovascular disease. This alarming trend highlights the urgent need for comprehensive and strategic efforts in cancer management and control[1].

Cancer management in Indonesia is conducted through multiple approaches, one of which involves the development and evaluation of cancer therapies through scientific research. Such research is essential to improve the efficacy and safety of anticancer treatments. A critical component of cancer research is the use of animal cancer models, which play a fundamental role in elucidating disease mechanisms and evaluating therapeutic candidates prior to clinical application in humans. Ideally, animal cancer models should closely

represent human biological conditions, particularly with respect to interactions between the immune system and cancer cells, thereby ensuring relevance for preclinical drug testing[2]. However, the availability of cancer animal models in Indonesia remains limited and relatively expensive. Consequently, there is a pressing need for research focused on designing cancer animal models that are more affordable, readily available, and applicable to research settings in resource-limited countries. Animal cancer models serve as substitutes for human biological systems due to ethical constraints associated with the direct use of human cells and tissues. Mammalian species with genomic and physiological similarities to humans, such as rats and mice, are therefore widely used in cancer research. Mice offer several advantages, including small body size, ease of handling and maintenance, short reproductive cycles, and high amenability to genetic manipulation[3]. These characteristics make mice highly relevant and practical models for biomedical research.

Among the most commonly used experimental animals in cancer research is the BALB/c strain of mice (*Mus musculus*)[4]. This strain is favored due to its ease of breeding, relatively low maintenance costs[5], and status as an inbred albino strain with high genetic homogeneity. Such genetic uniformity contributes to reduced inter-individual biological variability, thereby enhancing the reproducibility and reliability of experimental data[6]. Furthermore, BALB/c mice possess an intact immune system, making them particularly suitable for studies on immunotherapy and immunomodulation, including investigations involving immunosuppressive agents[7].

In the design of cancer animal models, controlled suppression of the immune system is often required to prevent rejection of inoculated cancer cells. Therefore, agents capable of modulating immune responses in a predictable manner are essential. Immunosuppressive agents are compounds that reduce immune system activity, thereby facilitating the implantation and growth of cancer cells. Several chemical agents exhibit immunosuppressive properties, one of which is dexamethasone. Dexamethasone is a synthetic corticosteroid widely used as an anti-inflammatory and immunosuppressive agent in various clinical conditions[8]. Its mechanism of action involves suppression of excessive immune responses, and the compound is known for its high bioavailability and ability to readily penetrate biological membranes and enter systemic circulation[9].

Previous studies have demonstrated that dexamethasone exerts significant immunosuppressive effects, including suppression of T-cell function and induction of T-cell apoptosis in experimental animals[10]. Other studies have reported that dexamethasone administration alters T-cell ratios and distribution within the immune system[11,12]. In mice, T lymphocytes are abundantly distributed in the spleen, which functions as a secondary lymphoid organ responsible for coordinating immune responses and filtering blood[13]. The immunosuppressive effects of dexamethasone in mice have been investigated across a range of doses. Januarisasi and Igadwi (2015) reported that administration of dexamethasone at both low (0.5 mg/kg body weight) and high doses (10 mg/kg body weight) for seven days resulted in significant alterations in the quantity and functional status of T lymphocytes *in vivo*[14].

Although dexamethasone has long been recognized for its immunosuppressive effects through modulation of both cellular and humoral immune responses[9,10], most previous studies have focused primarily on its molecular mechanisms or clinical implications, rather than evaluating its role as a supportive factor in the design of cancer animal models. To date, limited research has examined the strategic use of dexamethasone to enhance the success of cancer model establishment, particularly in BALB/c mice, with respect to immunosuppressive efficacy, biological feasibility of the animals, and potential applicability in cancer research within resource-limited settings. Therefore, further investigation is warranted to position dexamethasone not merely as a pharmacological agent, but as a methodological tool for optimizing the design of experimental cancer animal models.

II. Material And Methods

Study Location and Duration

This study was conducted at the Immunology Laboratory, University of Mataram, from September to November 2025. Complete blood profile analyses were performed at the Hepatica Laboratory, Mataram, while histological examinations of spleen tissue were conducted at the Denpasar Veterinary Research Center.

Study Design

An experimental laboratory study was conducted using a post-test only control group design, in which observations were performed following treatment and compared with control groups.

Experimental Animals and Housing Conditions

A total of 12 female BALB/c mice (*Mus musculus*), aged six weeks and weighing 20–25 g, were used in this study. Inclusion criteria included healthy appearance, active movement, and absence of physical deformities. Mice that showed lethargy or died during the acclimatization period were excluded.

Animals were housed in cages measuring 45 × 45 × 25 cm (three mice per cage) under standard laboratory conditions at room temperature. Mice were provided RH11S pellet feed and water *ad libitum*.

Bedding material was replaced every three days.

Dexamethasone-Induced Immunosuppression

Mice were divided into four groups:

- Negative control (KN)
- Positive control (KP): inoculated with HeLa cells only
- Treatment group P1: dexamethasone 10 mg/kg body weight
- Treatment group P2: dexamethasone 15 mg/kg body weight

Each group consisted of three animals (n = 3). Dexamethasone (Cortidex®, 5 mg/mL) was administered intraperitoneally once daily for seven consecutive days. Injection volumes were calculated according to body weight:

- 10 mg/kg BW = 0.02 × BW (kg)
- 15 mg/kg BW = 0.03 × BW (kg)

Cancer Cell Inoculation

HeLa cervical cancer cells were used as the tumor model. On day 8, mice in groups KP, P1, and P2 were subcutaneously injected with 3×10^6 HeLa cells in the right flank region using a 1 mL syringe with a 25G needle, following established xenograft protocols[15].

Tumor Palpation and Measurement

Tumor palpation was performed two days after cell inoculation to assess the presence of nodules. Tumor dimensions were measured every two days for 14 days using a digital caliper. Tumor volume was calculated using the formula:

$$V=\frac{(L\times W2)}{2}$$

where *L* represents tumor length and *W* represents tumor width[15].

Probability of Tumor Formation

Tumor formation probability was calculated as follows:

$$\text{Tumor incidence (\%)}=\frac{\text{Number of mice with tumors x 100\%}}{\text{Total mice per group}}$$

Hematological Analysis

Peripheral blood samples were collected on day 0 and day 7 using heparinized tubes. Total leukocyte counts were analyzed using a Sysmex XN-350 hematology analyzer. Differential leukocyte counts were determined using Giemsa-stained blood smears observed under a light microscope at 100× magnification with immersion oil.

Necropsy and Histopathological Examination

Mice were euthanized via cervical dislocation in accordance with ethical animal handling guidelines[16]. Spleen tissues were harvested, fixed in 10% neutral buffered formalin, embedded in paraffin, sectioned at 4–5 µm thickness, and stained using hematoxylin and eosin (H&E).

Histological evaluation focused on the diameter of splenic white pulp, observed at 200× magnification. Measurements were performed using Olympus cellSens 1.17 imaging software.

Ethical Approval

The Ethics Research Commission of the Faculty of Medicine and Health Sciences, University of Mataram, approved all experimental procedures in this study (reference number: 217/UN18.F8/ETIK/2025, September 26, 2025).

Statistical Analysis

Data were analyzed using IBM SPSS Statistics version 25. Normality was assessed using the Shapiro–Wilk test, and homogeneity of variance was evaluated using Levene's test. Parametric data were analyzed using one-way ANOVA followed by Tukey's HSD post hoc test. Non-parametric data were analyzed using Kruskal–Wallis followed by Mann–Whitney tests. Statistical significance was set at $p < 0.05$.

III. Result

This study aimed to explore The effect of dexamethasone administration as an immunosuppressant in BALB/c mice as a cancer model.

Mean Body Weight

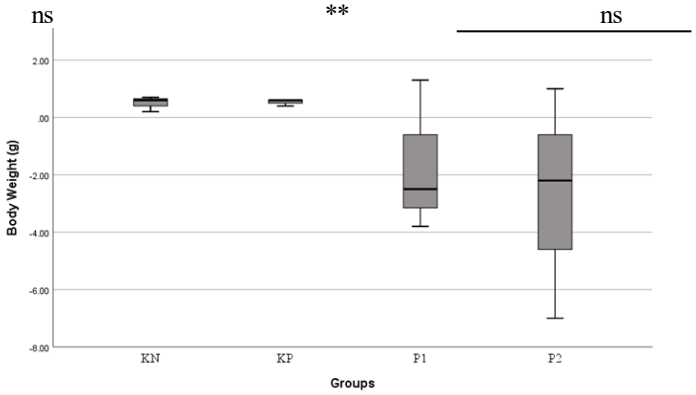

Figure 1. The effect of dexamethasone on the body weight of mice in the control group and the treatment groups (Group KN: negative control; Group KP: positive control; P1: dexamethasone 10 mg/kg BW; P2: dexamethasone 15 mg/kg BW). Values are presented as the mean±SD (n = 3). **p < 0.05.

Figure 1,The effect of dexamethasone on the body weight of mice in the control group and the treatment group. Changes in body weight were observed across all experimental groups in this study. An increase in body weight was noted in the negative control group (3,73 ± 2.16; p = 0.082), although this change was not statistically significant. In contrast, a statistically significant increase in body weight was observed in the positive control group (KP) (2,70 ± 4,10; p = 0.015). Meanwhile, body weight loss was recorded in the treatment groups P1 (−8,68 ± 0,94; p = 0.390) and P2 (−9,26 ± 4,63; p = 0.361); however, these decreases were not statistically significant.

Hematological Parameter
Total White Blood Cell Count

Table no.1, Effect of Dexamethasone on Total White Blood Cell (WBC) Count in BALB/c Mice.

Group	Change in WBC Count (x 10^3/µL)
KN	3,733 ± 2,16[b]
KP	2,704 ± 4,10[b]
P1	-8,677 ± 0,94[a]
P2	-9,264 ± 4,63[a]

Values are mean ± SD (n = 3). Data were analyzed using Kruskal–Wallis
(description: a and b are different superscripts in the same column indicating a significant difference (p>0.05)

As shown in Table no. 1, the treatment groups (P1 and P2) exhibited a reduction in WBC counts, whereas the control groups (KN and KP) demonstrated an increase in WBC counts. The differences in WBC counts among the groups were statistically significant (p = 0.015). Furthermore, post hoc analysis using the Tukey HSD test indicated no significant difference between the P1 and P2 groups. These findings suggest that both treatments exerted relatively comparable effectiveness in modulating leukocyte counts.

Differential Counting

Table no.2, Effect of Dexamethasone on Differential Counting in BALB/c Mice.

Group	Examination Results on the 2nd Day	Mean ± Standard Deviation	
		Lymphocytes	Neutrophils
KN	0	72 ± 1,00	14 ± 2,00
	7	72 ± 4,04	13 ± 4,04
KP	0	62 ± 4,73	15 ± 5,86
	7	57 ± 4,04	20 ± 3,21
P1	0	60 ± 2,52	18 ± 7,00
	7	26 ± 4,16	28 ± 4,04
P2	0	75 ± 2,08	5 ± 1,73
	7	17 ± 2,08	35 ± 9,87

As presented in **Table no. 2**, four leukocyte subtypes exhibited measurable changes during the observation period. Analysis of the effects of dexamethasone administration on lymphocyte counts in BALB/c mice between day 0 and day 7 revealed a consistent decrease in lymphocyte numbers in the treatment groups (P1 and P2), whereas an increase was observed in the control groups (KN and KP). The Kruskal–Wallis test demonstrated a statistically significant difference in lymphocyte count changes among the experimental groups (p = 0.015).

Post hoc analysis using the Mann–Whitney test with Bonferroni correction indicated that pairwise comparisons between groups did not reach statistical significance. Nevertheless, from a biological perspective, the consistent pattern of lymphocyte reduction observed across the P1 and P2 groups suggests a clear immunosuppressive effect of dexamethasone. The lack of statistically significant differences between treatment groups after multiple comparison correction indicates that increasing the dose did not confer a substantially greater effect on lymphocyte depletion.

Tumor Nodule Formation Following Cancer Cell Injection

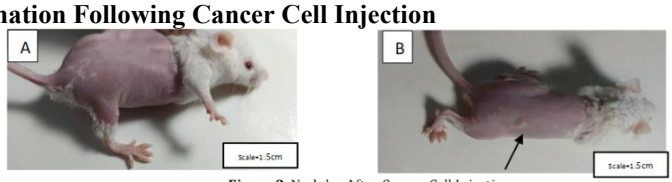

Figure 2. Nodules After Cancer Cell Injection
(a) Mice without nodules in the right hip area; (b) Mice with nodules in the right hip area

As shown in **Figure 2**, showing (a) mice without detectable nodules in the right hip area and (b) mice exhibiting palpable nodules at the injection site. In this study, cancer cell injection was performed on day 8 of the experimental period. Mice in the positive control (KP), P1, and P2 groups were subcutaneously injected with HeLa cells into the right hip region. Each mouse received an inoculum of 3×10^6 HeLa cells. Following a 14-day observation period, tumor nodule formation was detected exclusively in mice from the P2 group. According to Sung et al. (2021)[15], tumor volume was measured using a digital caliper and calculated using the following formula:

$V = (P \times L^2) / 2 = (3{,}9 \text{ mm} \times 2{,}2^2 \text{ mm}^2) / 2 = 7{,}8 \text{ mm}^3$

Based on the measurement obtained in this study (P = 3,9 mm; L = 2,2 mm), the calculated tumor volume was approximately 7.8 mm^3.

Analysis of the Structure of the Mouse Spleen Organ

The data presented in **Figure 3** and **Table 3**, indicate that the smallest mean diameter of the splenic white pulp was observed in the positive control (KP) group (258,97 µm). A reduction in white pulp diameter in this group may reflect the mobilization of lymphocytes from the spleen toward the tumor site, representing a biological indication of an antitumor immune response. This observation is consistent with previous reports demonstrating that effective antitumor immune activation is often accompanied by the egress of activated T and B lymphocytes from the spleen, resulting in decreased lymphoid cell density within the white pulp[31,32]. Several studies have further suggested that morphometric alterations of the splenic white pulp can reflect dynamic changes in systemic immune cell distribution during inflammatory or antitumor responses[33,34]. In contrast, the largest mean white pulp diameter was observed in the P2 group (306,15 µm).

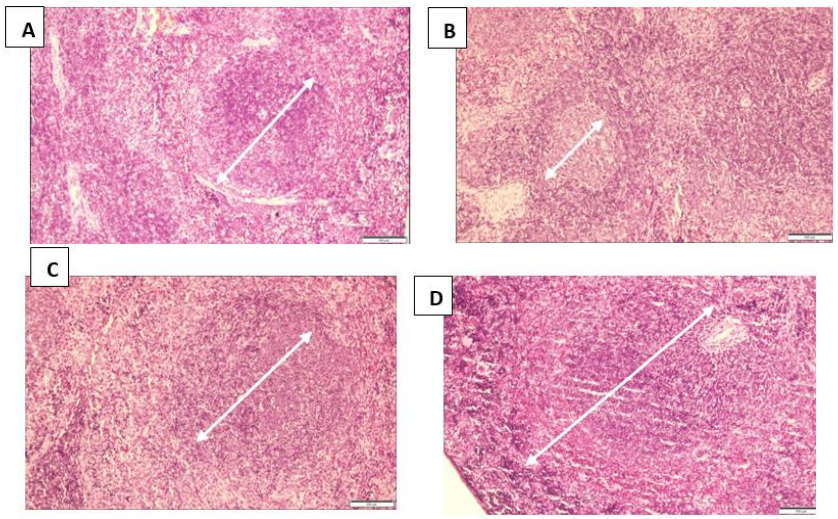

Figure 3. Effect of dexamethasone and cancer cells on spleen histopathology in different experimental groups. Each image represents the mean ± SD (n = 3). Arrows on spleen histopathology photomicrographs (200x magnification) A: negative control; B: positive control: induced HeLa cells on day 8; C: P1: injection of dexamethasone at a dose of 10 mg/kg BW for 7 days and HeLa cells on day 8; D: P2: injection of dexamethasone at a dose of 15 mg/kg BW for 7 days and HeLa cells on day 8.
Diameter of the Pulpa Alba of the Mouse Spleen in µm.

Table 3. Diameter of the Pulpa Alba of the Mouse Spleen in µm

Group	Mean Diameter of Splenic Pulp Alba (µm) ± Standard Deviation
KN	270,81 ± 21,70
KP	258,97 ± 26,22
P1	276,32 ± 37,53
P2	306,15 ± 48,27

IV. Discussion

The reduction in body weight observed in BALB/c mice treated with dexamethasone in the present study is consistent with findings from previous animal model studies. Filippopoulou et al. (2021)[17] reported that dexamethasone administration in mice resulted in significant body weight loss compared to control groups, despite no significant changes in food intake. This finding suggests that weight loss is more closely associated with the metabolic effects of glucocorticoids rather than alterations in caloric consumption.

Similarly, Koorneef et al. (2022)[18] demonstrated that dexamethasone reduced body weight gain and adipose tissue accumulation in mice, in line with mechanisms involving enhanced lipolysis and glucocorticoid-induced metabolic alterations in adipose tissue. Furthermore, dexamethasone exposure has been associated with accelerated body weight reduction, indicating that the systemic metabolic effects of exogenous glucocorticoids play a substantial role in overall body weight changes[19].

As a synthetic glucocorticoid, dexamethasone is known to induce increased protein catabolism, lipid mobilization, and stimulation of gluconeogenesis, which collectively contribute to body weight loss in experimental animals[20,21].

From a biological perspective, this condition may be interpreted to indicate that increasing the dose or variation of treatment in the P2 group did not confer a significant additional effect compared with P1. Experimental studies have demonstrated that repeated administration of dexamethasone in animal models leads to a significant reduction in total white blood cell counts, primarily due to enhanced apoptosis and diminished proliferative capacity of immune cells[22]. Therefore, the decrease in WBC counts observed in the P1 and P2 groups in the present study can be attributed to the direct pharmacological effects of dexamethasone on immune system regulation rather than to responses associated with infection or systemic inflammation. This finding supports the successful establishment of an experimental immunosuppression model[23].

Mechanistically, dexamethasone affects lymphocyte populations through two primary pathways: redistribution of lymphocytes from peripheral circulation to lymphoid tissues and the induction of lymphocyte apoptosis. Lymphocyte redistribution reduces the number of circulating lymphocytes detected in peripheral blood, while apoptosis directly decreases the viable lymphocyte population[24].

Experimental evidence has consistently demonstrated that apoptosis plays a central role in glucocorticoid-induced lymphodepletion. Dexamethasone has been shown to induce apoptosis in lymphocytes both in vivo and in vitro, including T cells and precursor cells within lymphoid tissues, through activation of the glucocorticoid receptor and subsequent engagement of intracellular pro-apoptotic signaling pathways[25]. Furthermore, clinical and experimental studies involving human immune cells have reported that glucocorticoid exposure accelerates apoptosis in specific T-cell subsets, contributing to a marked reduction in circulating lymphocyte numbers[26].

The observed decrease in lymphocyte counts in this study reflects lymphodepletion mediated by both redistribution and apoptosis induced by dexamethasone as a glucocorticoid agent[27,22]. These findings support the use of lymphocyte parameters as a reliable indicator of successful immunosuppression in the development of experimental animal cancer models.

As shown in Table 2, neutrophil counts increased in the treatment groups (P1 and P2), whereas no notable changes were observed in the control groups (KN and KP). Statistical analysis using one-way ANOVA revealed a significant difference in neutrophil count changes among the groups ($p < 0.05$). Post hoc analysis with the Tukey HSD test demonstrated statistically significant differences between the control groups (KN and KP) and the treatment groups (P1 and P2) ($p < 0.05$).

The observed increase in neutrophil counts was not attributed to enhanced neutrophil production in the bone marrow but rather to glucocorticoid-induced demargination of neutrophils from the vascular endothelium into peripheral circulation, along with suppression of neutrophil migration into tissues. These effects represent a direct consequence of glucocorticoid receptor activation in immune cells[28]. In addition to altering neutrophil distribution, dexamethasone has been shown to impair key neutrophil functions, including chemotaxis toward inflammatory signals, phagocytic activity, and the formation of neutrophil extracellular traps.

Experimental studies have demonstrated that although circulating neutrophil numbers may increase following glucocorticoid exposure, their functional capacity is markedly reduced. Consequently, neutrophilia does not translate into enhanced innate immune effectiveness[29]. Thus, the neutrophilia observed in the P1 and P2 groups in the present study reflects functional immunosuppression rather than immune activation.

The appearance of nodules at the injection site following subcutaneous HeLa cell inoculation represents the formation of a spontaneous xenograft tumor. HeLa cells, a human cervical cancer cell line, are

characterized by high proliferative capacity and the ability to survive within the host tissue microenvironment, particularly when inoculated into immunosuppressed laboratory animals. In subcutaneous xenograft models, injected tumor cells proliferate locally and form solid masses that can be palpated and visually observed as tumor nodules within days to weeks after injection[30].

Based on the experimental results, the P2 group exhibited a cancer occurrence probability of 33%. Cancer incidence was calculated as the proportion of tumor-bearing mice relative to the total number of experimental animals and expressed as a percentage.

Administration of dexamethasone as an immunosuppressive agent appears to increase the likelihood of tumor nodule formation in the HeLa cell xenograft model by inducing an immunological environment that is less capable of recognizing and rejecting foreign tumor cells. This synthetic glucocorticoid suppresses lymphocyte activation and proliferation, particularly T cells, thereby attenuating cell-mediated immune responses that are critical for immune surveillance against xenogeneic tumor cells. Moreover, dexamethasone has been shown to reduce the production of key cytokines such as interleukin-2 (IL-2) and interferon-gamma (IFN-γ), which are essential for the activation of T cells and natural killer (NK) cells through glucocorticoid-mediated immunosuppressive mechanisms. Consequently, these conditions facilitate the survival, proliferation, and tumor nodule formation of subcutaneously inoculated HeLa cells at a higher frequency[11].

White pulp enlargement in this group may be interpreted as lymphoid cell accumulation or retention within splenic follicles, potentially reflecting compensatory follicular hyperplasia resulting from local proliferation of B and T lymphocytes. Such changes have been reported under conditions of chronic immune stimulation or altered lymphocyte trafficking, leading to increased cellular density within the white pulp[32,35]. Moreover, white pulp hyperplasia has been associated with enhanced humoral immune activity and germinal center formation as part of an adaptive immune response to immunological stimuli[36].

Normality testing revealed that white pulp diameter data across all experimental groups were normally distributed ($p > 0.05$), and homogeneity of variance testing confirmed equal variances among groups ($p > 0.05$). These findings satisfied the assumptions required for parametric analysis using one-way analysis of variance (ANOVA). However, the one-way ANOVA results indicated no statistically significant differences in white pulp diameter among the experimental groups ($p > 0.05$); therefore, post hoc analyses were not performed.

Nevertheless, the observed variations in white pulp diameter provide histopathological evidence that complements the hematological findings and tumor outcomes, supporting the interpretation that the applied treatments influenced systemic immune response dynamics. Accordingly, alterations in splenic white pulp structure may serve as a histological indicator of immune cell redistribution and antitumor immune activation in this experimental model.

V. Conclusion

Intraperitoneal administration of dexamethasone for seven days successfully induced immunosuppression in BALB/c mice, as evidenced by alterations in body weight, leukocyte profiles, and splenic histology. A dexamethasone dose of 15 mg/kg body weight provided sufficient immunosuppressive intensity to support successful HeLa cell engraftment. These findings demonstrate that controlled immunosuppression is a critical determinant in cancer animal model establishment and position dexamethasone as an effective methodological tool for optimizing experimental tumor models in resource-limited research settings.

However, future studies are recommended to employ larger sample sizes and incorporate functional immunological analyses, such as cytokine measurements and immune cell subpopulation characterization, to further strengthen the validity of the developed cancer model.

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