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Dynamic Evaluation of Left Ventricular Echocardiogram Parameters in Rabbits Model of Hemorrhagic Shock: Comparative Effects of Ringer's Lactate and Gelatin Therapy

Waode Santa Monica [1], Ida Tjahajati [2,*], Siti Isrina Oktavia Salasia [3], Aris Haryanto [4] and Muhammad Zulfadillah Sinusi [5]

[1]Veterinary Internal Medicine Doctoral Student, Faculty of Veterinary Medicine, Gadjah Mada University, Yogyakarta Indonesia. Department of Veterinary Internal Medicine, Study Program Of Veterinary Medicine, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia
[2]Department of Veterinary Internal Medicine, Faculty of Veterinary Medicine, Gadjah Mada University, Yogyakarta Indonesia
[3]Departement of Veterinary Clinical Pathology, Faculty of Veterinary Medicine, Gadjah Mada University, Yogyakarta Indonesia
[4]Department of Veterinary Biochemistry, Faculty of Veterinary Medicine, Gadjah Mada University, Yogyakarta Indonesia
[5]Department of Veterinary Surgery and Radiology, Study Program Of Veterinary Medicine, Faculty of Medicine, Hasanuddin University, Makassar, Indonesia
***Corresponding author:** ida_tjahajati@ugm.ac.id

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ABSTRACT

Early detection of hemorrhage and evaluation of fluid resuscitation are critical in managing hemorrhagic shock, but traditional clinical parameters are often insensitive for dynamic assessment. Echocardiography has emerged as a superior, non-invasive tool to evaluate fluid responsiveness and cardiac function in real time. This study aimed to evaluate the dynamic changes in left ventricular echocardiographic parameters, providing a comprehensive view of structural and functional responses to fluid therapy in a hemorrhagic shock model. Hemorrhagic shock was induced in New Zealand White rabbits by bleeding 35% of their total blood volume. Echocardiography using 2D and M-mode with a 6 MHz probe was performed at pre-hemorrhagic, hemorrhagic, and post-hemorrhagic phases. After fluid resuscitation, both groups showed a significant increase ($P<0.05$) in left ventricular dimensions and volumes. At 110 minutes post-resuscitation (T110), Group KP2 showed a greater increase in LVIDd (1.30±0.07cm) and LVIDs (0.87±0.05 cm) compared to Group KP1 (1.15±0.09 cm; 0.75±0.07 cm). This was associated with significant improvements in SV (1.74±0.22mL; 2.67±1.35mL), CO (312.95±76.95mL; 437.46±219.08mL), EF (71.32±6.71%; 76.89±7.88%), and FS (36.99±5.71%; 42.28±7.93%). The KP2 group showed more distinct recovery of contractility and pump function. The combination of Ringer's lactate and gelatin resulted in faster and more significant improvements in left ventricular function. These results emphasize the importance of non-invasive echocardiography for real-time fluid responsiveness assessment and guiding individualized resuscitation strategies.

Key words: Hemorrhagic Shock, Fluid Resuscitation, Echocardiography, Rabbits, Gelatin.

INTRODUCTION

Hemorrhagic shock can result from trauma or surgical procedures. This condition leads to disruption of the circulatory system, thereby reducing oxygen transport to tissues (Fülöp et al. 2013) due to a sharp decline in effective circulation (Sun et al. 2017) . Consequently, it induces soft tissue damage and an acute immune response (Saraçoğlu et al. 2023), as well as coagulopathy that causes ischemia in multiple internal organs. In severe decompensated states, ischemia can occur in both the brain and heart (Andrianova et al. 2025). Hemorrhagic shock is also characterized by hemodynamic instability, cellular hypoxia, organ damage, and mortality (Sun et al. 2014). Immediate intervention for hemorrhagic shock is crucial. One of the standard treatments is blood transfusion (Seo et al. 2020).

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However, in some developing countries such as Indonesia, blood transfusion remains challenging due to factors including the unavailability of blood banks and complex procedures for finding suitable donors. Therefore, alternative treatments such as fluid therapy are necessary.

Fluid resuscitation therapy is the initial step in managing hemorrhagic shock (Almac et al. 2012). Early fluid resuscitation is crucial in management, aiming to prevent ischemia and necrosis (Costea et al. 2025). The key to successful resuscitation lies in the rapid administration of fluids to eliminate shock as quickly as possible and restore adequate perfusion (Sun et al. 2017). Rapid volume expansion through intravenous fluid administration is expected to optimize tissue perfusion (Teixeira-Neto and Valverde 2021). Fluid therapy also increases cardiac output and improves oxygen delivery via the Frank–Starling mechanism (Vincent et al. 2020). Both crystalloid and colloid fluids are commonly used for resuscitation. Currently, the ideal choice of fluid therapy remains a subject of debate. Frequently used fluids include Ringer's lactate as the primary resuscitation fluid, while alternatives such as albumin and gelatin are employed as protein colloids (Ramesh et al. 2019).

The ideal fluid choice in terms of efficacy and safety remains uncertain. Compared with crystalloids, colloid solutions may result in a less positive fluid balance (Smart et al. 2021). Crystalloids are the most commonly used resuscitation fluids, while high–molecular weight hydroxyethyl starch as a colloid has been associated with an increased risk of mortality and acute kidney injury (Song et al. 2025). Similarly, the use of intravenous gelatin solutions may contribute to acute kidney injury (Smart et al. 2021). However, available data on gelatin use remains limited. This study therefore focuses on evaluating the effects of fluid therapy, particularly gelatin, in hemorrhagic shock.

In addition to therapy, diagnostic techniques that support monitoring the condition of animals post-resuscitation are also important. Hemorrhage is associated with left ventricular dysfunction (D'Annunzio et al. 2012). Various strategies exist to assess circulatory status, including hemodynamic monitoring and tissue perfusion measurement (Hussmann et al. 2014). Available hemodynamic reports are still limited to mean arterial pressure (MAP), stroke volume (SV), and cardiac output (CO) (Lima et al. 2019). Echocardiography is a non-invasive ultrasound technique for in vivo cardiac imaging (Gugjoo et al. 2014; Piccione et al. 2025). It provides extensive information regarding cardiac morphology and function related to heart size, shape, pumping capacity, and the location and extent of tissue damage, enabling early detection of abnormalities such as regurgitant blood flow (Singh et al. 2014), as well as a monitor that can help clinicians in monitoring hemodynamic changes (Zerbib et al. 2019).

Reported methods for evaluating fluid responsiveness include measuring the aortic flow velocity time integral using echocardiography (Teixeira-Neto and Valverde 2021) and assessing the accuracy of echocardiographic variables in predicting fluid responsiveness in dogs with impaired hemodynamics and tissue hypoperfusion (Donati et al. 2023). The evaluation of the internal jugular vein, left ventricular stroke volume variability, pulmonary hypertension, and right ventricular dysfunction using echocardiographic markers has become the gold standard for non-invasive hemodynamic assessment in ICU patients (Piccione et al. 2025). The use of echocardiography in rabbit models can provide a comprehensive depiction of cardiovascular responses (Giraldo et al. 2019). Furthermore, Exploring the use of echocardiography in assessing left ventricular function after fluid therapy for hemorrhagic shock intervention is interesting to investigate to obtain a comprehensive picture of structural and functional profile of the rabbit left ventricle across pre-hemorrhagic, hemorrhagic, and post-hemorrhagic phases, with and without fluid therapy.

MATERIALS AND METHODS

Object of research

This study was conducted in accordance with the animal testing protocol and the integrated laboratory principles of Hasanuddin University. Animal welfare considerations were applied by minimizing pain and strictly adhering to the 3Rs principles, particularly by reducing the number of animals used. The experimental subjects were male New Zealand White rabbits, weighing 2.0–2.8kg and aged 5–8 months. The rabbits were housed individually in cages measuring 60×42×50cm, with ad libitum access to food and water.

Protocol of research

The experimental animals were divided into four groups: (1) negative control group (KN), without hemorrhage induction; (2) hemorrhage-only group (KP), subjected to hemorrhage without resuscitation; (3) treatment group 1 (KP1), subjected to hemorrhage followed by resuscitation with Ringer's lactate; and (4) treatment group 2 (KP2), subjected to hemorrhage followed by resuscitation with a combination of Ringer's lactate and gelatin. Rabbits were fasted overnight with free access to water. Anesthesia was induced via intramuscular injection of acepromazine (0.75mg/kg), xylazine (3mg/kg), and ketamine (70mg/kg) (Plumb 2018). Anesthesia was maintained with intravenous ketamine at one-third of the initial dose. A 26-gauge intra-auricular catheter was inserted into the auricular artery (a. auricularis) for blood withdrawal, while catheters were also placed in the saphenous and cephalic veins for fluid infusion.

The study was divided into three phases (Fig. 1). Phase 1, the pre-hemorrhagic period, lasted 15 minutes (T15). Phase 2, the hemorrhagic period, lasted 65 minutes and consisted of an initial 15-minute bleeding phase (T30) followed by a 50-minute maintenance period to sustain hemorrhagic shock (T80). Phase 3, the post-hemorrhagic period, lasted 150 minutes and included 30 minutes of fluid therapy administration (T110) followed by 120 minutes of post-resuscitation monitoring (T230), giving a total experimental duration of 230 minutes. Hemorrhage was induced over 15 minutes until 35% of the total blood volume was withdrawn, calculated as 6% of body weight, to establish hemorrhagic shock. At the end of the study, animals were humanely euthanized by intravenous administration of an overdose of ketamine.

Fluid therapy

The fluid therapies used in this experiment were

Ringer's lactate (RL) and synthetic colloids, specifically 4% succinylated gelatin solution (Gel) ®Gelofusal. The fluid dosage calculations were based on the following formula: maintenance volume = (30 × body weight (kg)) + 70 ml; deficit replacement volume = percentage of dehydration × body weight (kg) × 1000 ml × 80%; and fluid loss volume = 2 × estimated volume lost (Wingfield and Raffe 2002) For combination fluid therapy involving crystalloids (RL) and colloids (hydroxyethyl starch), a 2:1 ratio was applied (Zhang et al. 2013).

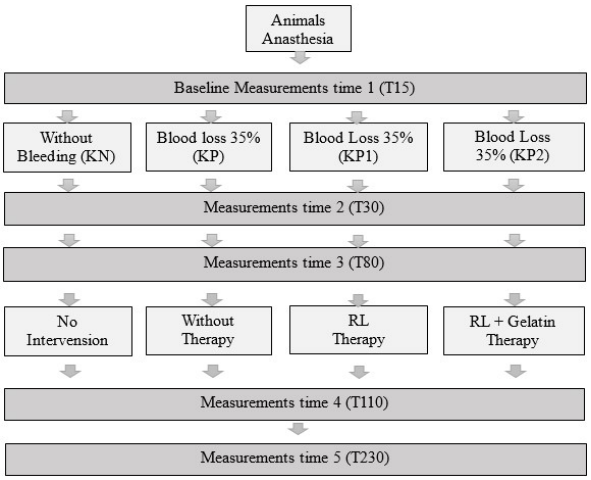


Fig. 1: Summary of the study design and echocardiographic measurement timeline during one treatment cycle of 230 minutes, including the pre-hemorrhagic phase (T15), hemorrhagic phase (T30), hemorrhage maintenance phase (T80), post-hemorrhagic/post-therapy phase (T110) and resuscitation maintenance phase (T230).

Examination of echocardiographic

Measurement of echocardiographic

Echocardiographic data were collected using the BMV® PT50C Veterinary Ultrasound system. Measurements were performed at five time points (T15, T30, T80, T110 and T230) while the rabbits were under anesthesia. Animals were positioned in right lateral recumbency, and the probe was placed on the right parasternal area between the 3rd and 6th intercostal spaces, near the sternum–costochondral junction, in a short-axis view (Thomas et al. 1993). Two-dimensional (2D) guided M-mode tracing was obtained at the level of the papillary muscles (Turner Giannico et al. 2015).

Parameters assessed included left ventricular internal dimension at end-diastole (LVIDd) and end-systole (LVIDs), posterior wall thickness at end-diastole (LVPWd) and end-systole (LVPWs), and interventricular septal thickness at end-diastole (IVSd) and end-systole (IVSs). Functional indices included stroke volume (SV), cardiac output (CO), ejection fraction (EF), fractional shortening (FS) and heart rate (HR). Heart rate was calculated from the interval between two consecutive R waves on the electrocardiogram displayed on the monitor. Wall thickness and chamber dimensions were measured at both end-diastole and end-systole (Bodh et al. 2019;Singh et al. 2014). All echocardiographic procedures were carried out under the supervision of practitioners and faculty members specializing in ultrasound and cardiology.

Echocardiographic formulas

Left ventricular volumes (end-diastolic volume and end-systolic volume) were calculated using the Teichholz Formula (Teichholz et al. 1976) as follows: 1) *End-diastolic volume* (EDV) (ml) = 7 $(LVIDd)^3$/2.4+LVIDd), *End-systolic volume* (ESV) (ml) = 7 $(LVIDs)^3$ /2.4+LVIDs), *Stroke volume* (SV) (ml/beat) = (EDV-ESV), CO (L/min) = (*Heart rate* (HR) × SV), *Fractional shortening* (FS) (%) = (LVIDd-LVIDs/LVIDd)×100), *Ejection fraction* (EF) (%) = (EDV-ESV/ EDV)×100 (Gugjoo et al. 2014).

Histopathology

Cardiac tissue samples were collected and fixed in 10% neutral buffered formalin, and subsequently embedded in paraffin. Sections of 4–5µm thickness were prepared using a microtome and stained with hematoxylin and eosin (H&E). The slides were examined under a light microscope at 400× magnification to evaluate cardiac injury. Cardiac damage was assessed using a modified histopathological scoring system based on four categories: edema, inflammatory cell infiltration, cellular necrosis, and alterations in cardiac muscle fiber structure. Each parameter was graded as absent, mild, moderate, moderately severe, or severe, and scored according to the percentage of damage as 0 (absent), 1 (<25%), 2 (26–50%), 3 (51–75%), or 4 (76–100%).

Statistical analysis

Data were analyzed using IBM SPSS Statistics version 27 (IBM Corp., Armonk, NY, USA) and Microsoft Excel. Sources of variation included treatment group and time. Differences were analyzed using two-way repeated measures analysis of variance (ANOVA) with Tukey's post hoc test. The Shapiro–Wilk test was applied to assess the normality of data distribution. A $P<0.05$ was considered statistically significant. Histopathological scores of cardiac tissue were analyzed using the Kruskal–Wallis chi-square test with Bonferroni correction for multiple comparisons.

RESULTS

Hemorrhage was induced through the auricular artery (a. auricularis), resulting in a 35% reduction of total blood volume, equivalent to approximately 6% of body weight (60mL/kg). Left ventricular function was evaluated by echocardiographic measurements of the interventricular septum (IVS), left ventricular internal dimension (LVID), and left ventricular posterior wall (LVPW), as shown in Fig. 2 and Table 1–3. Echocardiographic measurements of IVSd and IVSs showed no significant differences ($P>0.05$) among groups or across time points, although slight non-significant variations were observed. In contrast, significant thickening of the left ventricular myocardial wall was detected in the hemorrhage-only group (KP), with increased LVPWd and LVPWs values compared to the KN, KP1, and KP2 groups ($P<0.05$). The KP group demonstrated progressive myocardial wall thickening from T30 to T230. Both KP1 and KP2 groups exhibited a reduction in LVPWd and LVPWs after fluid therapy, although these changes were not statistically significant. Increased blood volume following therapy expanded the ventricular lumen, which in turn reduced myocardial wall thickness and improved wall compliance.

Table 1: Comparison of changes in Left Ventricular Internal Dimension at End-Diastole and End-Systole across pre-hemorrhagic, hemorrhagic, and post-hemorrhagic/post-therapy phases at different time points

	Left Ventricular Internal Dimension at End-Diastole (cm)					Left Ventricular Internal Dimension at End-Systole (cm)				
Group	T15 (n=6)	T30 (n=6)	T80 (n=6)	T110 (n=6)	T230 (n=6)	T15 (n=6)	T30 (n=6)	T80 (n=6)	T110 (n=6)	T230 (n=6)
KN	1.14±0.04	1.14±0.05	1.16±0.07	1.15±0.03	1.07±0.03*	0.81±0.04	0.82±0.05	0.85±0.03	0.84±0.04	0.79±0.06
KP	1.16±0.18	0.91±0.08*	0.86±0.12*	0.83±0.10*	0.87±0.13*	0.86±0.18	0.59±0.02*	0.60±0.05*	0.58±0.04*	0.61±0.04*
KP1	1.10±0.14	0.98±0.05	0.89±0.08*	1.15±0.09#	1.06±0.03#	0.79±0.11	0.67±0.09	0.60±0.08*	0.75±0.07	0.67±0.06
KP2	1.24±0.08	0.98±0.22*	0.94±0.07*	1.30±0.07#	1.18±0.20	0.83±0.06	0.67±0.14*	0.64±0.03*	0.87±0.05#	0.67±0.06*
P-Value	0.280	0.022	<0.001	<0.001	0.002	0.771	0.002	<0.001	< 0.001	< 0.001

Time points in the table rows indicate significant differences (P<0.05) compared to baseline at T15 are marked with an asterisk (*), and those showing significant differences compared to the hemorrhagic shock period at T80 are marked with a hash (#)

Table 2: Comparison of changes in interventricular septal dimensions during diastole and systole across pre-hemorrhagic, hemorrhagic, and post-hemorrhagic/post-therapy phases at different time points

	Interventricular Septum at End-Diastole (cm)					Interventricular Septum at End-Systole (cm)				
Group	T15 (n=6)	T30 (n=6)	T80 (n=6)	T110 (n=6)	T230 (n=6)	T15 (n=6)	T30 (n=6)	T80 (n=6)	T110 (n=6)	T230 (n=6)
KN	0.20±0.02	0.19±0.01	0.20±0.01	0.19±0.01	0.19±0.01	0.24±0.02	0.23±0.02	0.23±0.01	0.23±0.02	0.23±0.02
KP	0.20±0.02	0.22±0.01	0.22±0.03	0.21±0.04	0.21±0.04	0.22±0.02	0.25±0.02	0.24±0.05	0.25±0.06	0.23±0.05
KP1	0.20±0.04	0.23±0.09	0.25±0.09	0.21±0.06	0.20±0.04	0.23±0.06	0.27±0.10	0.32±0.09	0.28±0.07	0.25±0.02
KP2	0.19±0.05	0.24±0.05	0.25±0.03	0.22±0.04	0.22±0.04	0.25±0.06	0.28±0.04	0.32±0.02	0.28±0.04	0.31±0.04
p-Value	0.987	0.480	0.191	0.695	0.601	0.760	0.386	0.010	0.315	0.004

Time points in the table rows indicate significant differences (P<0.05) compared to baseline at T15 are marked with an asterisk (*), and those showing significant differences compared to the hemorrhagic shock period at T80 are marked with a hash (#)

Table 3: Comparison of changes in left ventricular wall thickness during diastole and systole across pre-hemorrhagic, hemorrhagic, and post-hemorrhagic/post-therapy phases at different time points

	Left Ventricular Posterior Wall at End-Diastole (cm)					Left Ventricular Posterior Wall at End-Systole (cm)				
Group	T15 (n=6)	T30 (n=6)	T80 (n=6)	T110 (n=6)	T230 (n=6)	T15 (n=6)	T30 (n=6)	T80 (n=6)	T110 (n=6)	T230 (n=6)
KN	0.23±0.01	0.23±0.01	0.23±0.01	0.23±0.01	0.23±0.01	0.28±0.02	0.27±0.02	0.26±0.02	0.27±0.02	0.32±0.14
KP	0.24±0.03	0.28±0.05	0.28±0.03	0.30±0.02*	0.30±0.03*	0.29±0.01	0.33±0.03*	0.34±0.03*	0.35±0.02*	0.37±0.03*
KP1	0.24±0.07	0.26±0.07	0.29±0.07	0.24± 0.05	0.25±0.05	0.29±0.06	0.33±0.09	0.35±0.10	0.33±0.08	0.33±0.09
KP2	0.24±0.06	0.27±0.06	0.29±0.04	0.27±0.06	0.27±0.06	0.30±0.06	0.35±0.08	0.37±0.07	0.33±0.05	0.34±0.03
p-Value	0.985	0.464	0.056	0.041	0.540	0.953	0.159	0.040	0.054	0.019

Time points in the table rows indicate significant differences (P<0.05) compared to baseline at T15 are marked with an asterisk (*), and those showing significant differences compared to the hemorrhagic shock period at T80 are marked with a hash (#)

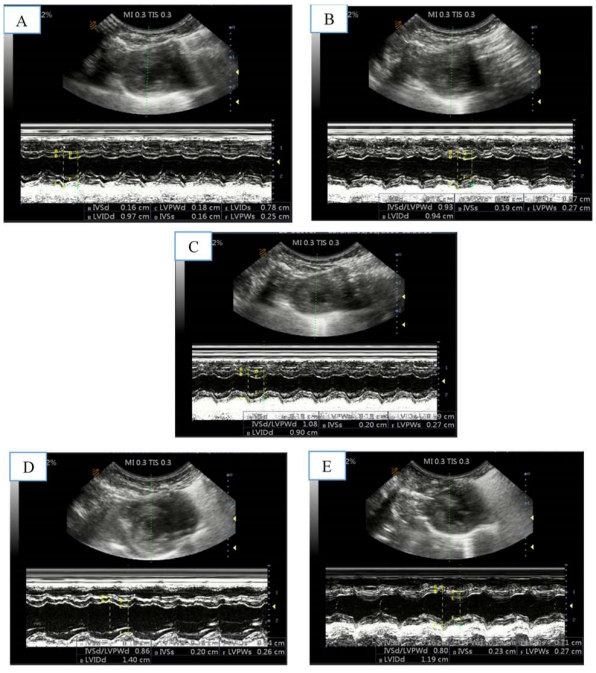
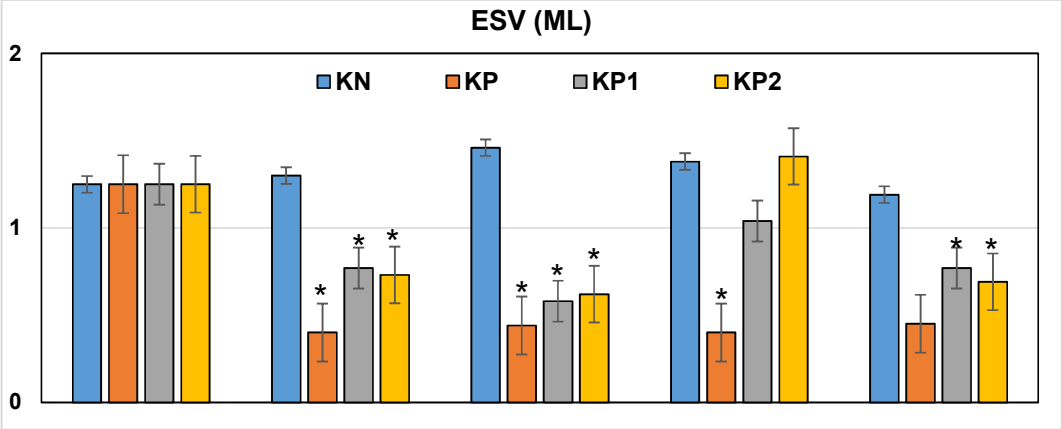


Fig. 2: Echocardiographic measurements in rabbits: (A) T15, pre-hemorrhagic phase; (B) T30, hemorrhagic phase after 15 minutes; (C) T80, hemorrhagic phase maintenance after 50 minutes (total intra-hemorrhagic phase of 65 minutes); (D) T110, post-hemorrhagic phase, 30 minutes after fluid therapy administration; (E) T230, post-hemorrhagic phase, 120 minutes of continued fluid therapy (total therapy phase of 150 minutes).

VIDd and LVIDs significantly decreased (P<0.05) during hemorrhagic shock at T80 (0.94±0.07cm; 0.64±0.03cm) compared to baseline at T15 (1.24±0.08cm; 0.83±0.06cm), reflecting a narrowing of the left ventricular cavity. Following resuscitation, ventricular dimensions significantly increased at T110 (1.30±0.07cm; 0.87±0.05cm), and subsequently showed a non-significant decline at T230 compared to T80 and T15. In all hemorrhaged groups (KP, KP1, and KP2), LVIDd and LVIDs at T80 were significantly reduced compared to T15, while no change was observed in the KN group. After fluid therapy, both KP1 and KP2 demonstrated increases in LVIDd and LVIDs. These findings indicate that hemorrhage reduced left ventricular lumen size due to decreased circulating volume, whereas fluid resuscitation improved cardiac filling and partially restored ventricular dimensions.

Hemodynamic circulation parameters in rabbits are presented in Fig. 3. Heart rate (HR) showed no significant differences (P>0.05) among the KN, KP, KP1 and KP2 groups throughout the study period. During the early phase of hemorrhage, HR tended to increase, but as bleeding progressed, responses varied among individuals. Following resuscitation, HR demonstrated a gradual upward trend, which was evident on echocardiographic monitoring, although the changes were not statistically significant. In contrast, parameters reflecting cardiac pumping performance, including end-diastolic volume (EDV), end-systolic volume (ESV), stroke volume (SV), and cardiac output (CO), showed significant reductions (P<0.05)


ESV (ML)
KN
KP
KP1
KP2
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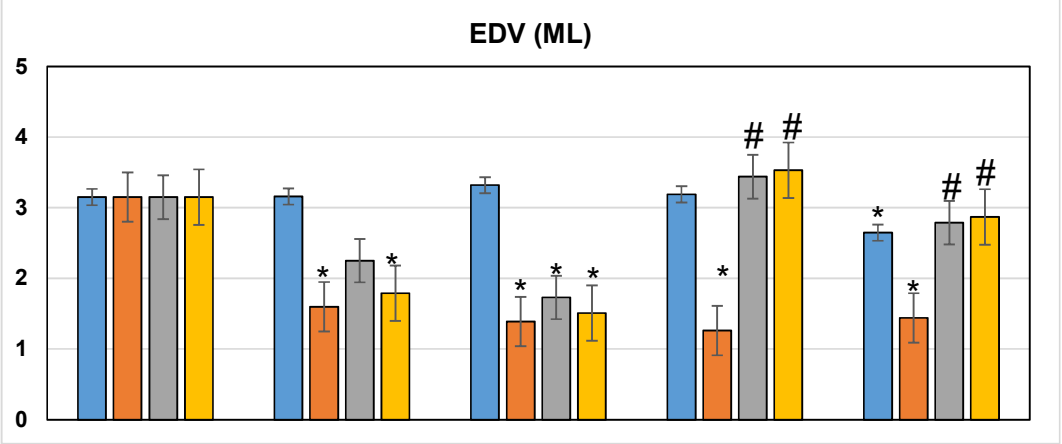
EDV (ML)
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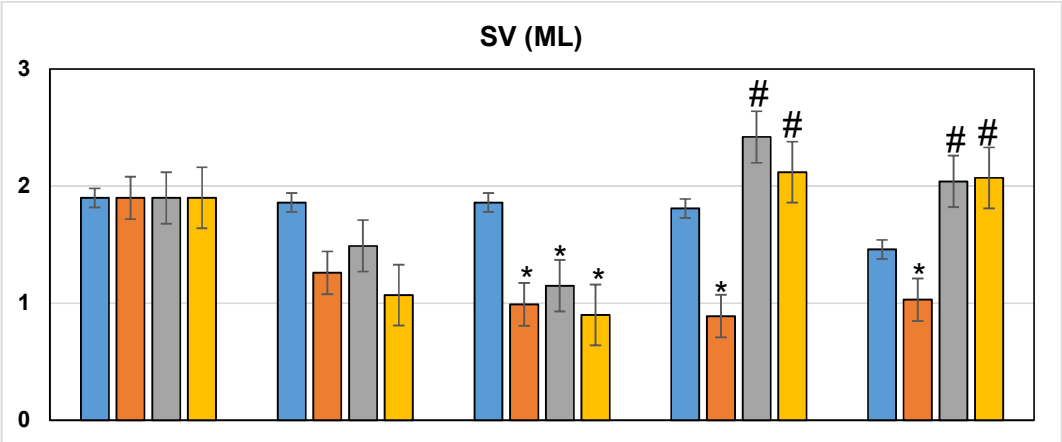
SV (ML)
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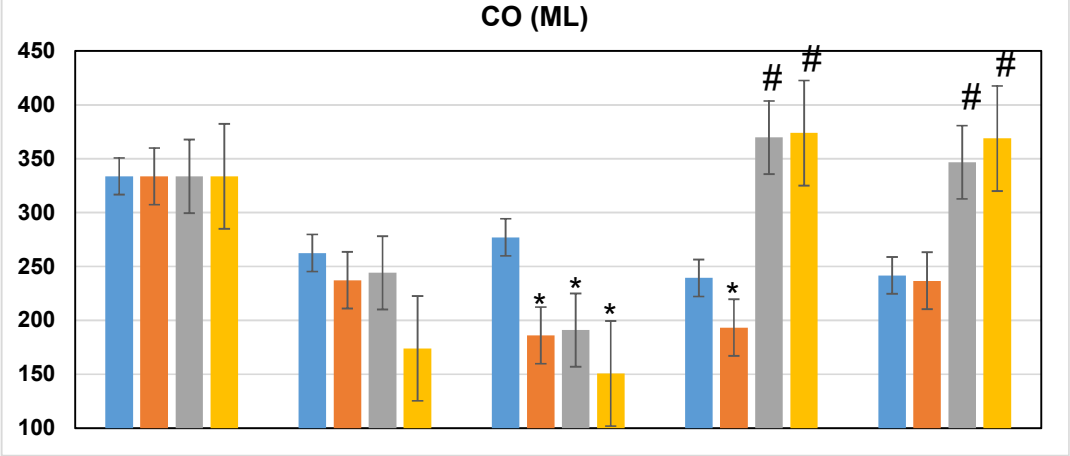
CO (ML)
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150
100

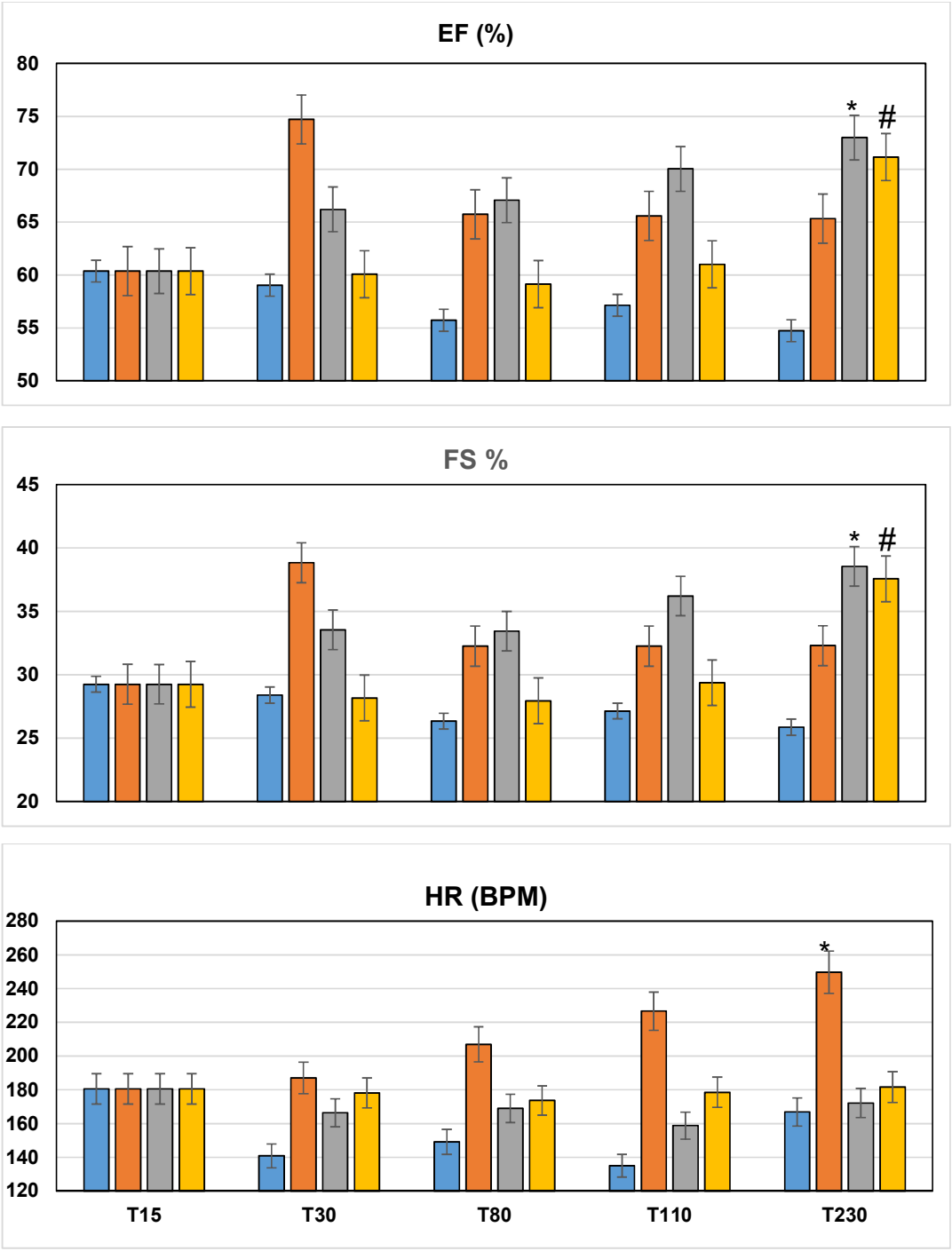

Fig. 3: The graph indicated the differences between groups and across time points in the parameters HR, EDV, ESV, SV, CO, FS, and EF (y-axis) against the duration of time (x-axis) during the pre-hemorrhagic phase (T15), hemorrhagic phase (T30), hemorrhage maintenance phase (T80), post-hemorrhagic/post-therapy phase (T110), and resuscitation maintenance phase (T230). Time points with significant differences ($P<0.05$) compared to baseline at T15 are marked with an asterisk (*), and those with significant differences ($P<0.05$) compared to the hemorrhage maintenance phase at T80 are marked with a hash (#).

during the hemorrhagic shock phase (T80) compared to baseline (T15) in the KP, KP1, and KP2 groups. After resuscitation, both KP1 and KP2 exhibited significant increases ($P<0.05$) in these parameters at T110, indicating improved ventricular filling and output. From T110 to T230, slight declines were observed in both groups, but the changes were not statistically significant ($P>0.05$).

In the KN group, EDV, ESV, SV, and CO showed non-significant fluctuations across phases, likely influenced by the anesthetic condition of the rabbits. In contrast, the KP group demonstrated a gradual decline in ventricular volumes over time, accompanied by a non-significant increase in HR from T30 to T230. All hemorrhaged groups (KP, KP1, and KP2) exhibited significant reductions ($P<0.05$) in EDV, ESV, SV, and CO during the hemorrhagic phase (T80) compared to baseline (T15).

Following resuscitation, both KP1 and KP2 groups showed significant increases (P<0.05) in these parameters at T110. At T230, volumes again decreased, although the changes were not statistically significant. The KP2 group consistently demonstrated a larger EDV and smaller ESV at most time points compared to the KP1 group, which directly contributed to greater stroke volume (SV) and cardiac output (CO).

In the KN group, EF and FS showed no significant changes (P>0.05) with minimal variation from T15 to T230. In the KP group, both parameters increased transiently at T30 during early hemorrhage, followed by progressive declines at T80, T110, and T230. The KP1 and KP2 groups demonstrated similar decreases during the hemorrhagic phase; however, after resuscitation, EF and FS increased significantly at T110 (P<0.05) and continued to rise at T230. Compared to KP1, the KP2 group exhibited greater and earlier recovery, achieving significantly higher EF and FS values at T230, which were close to baseline levels.

In the KN group, cardiac muscle fibers were regularly arranged, intercalated discs were distinct, and nuclei appeared normal, with no histopathological alterations (damage score = 0). In contrast, the KP group exhibited loosely arranged and irregular myocardial fibers, with occasional ruptures. Widespread nuclear necrosis, scattered inflammatory cell infiltration, and interstitial edema were also observed, resulting in a high damage score of 4 (76–100% tissue damage).

In the treatment groups (KP1 and KP2), cardiac muscle fibers appeared relatively better organized with less damage compared to the KP group (Fig. 4). The KP1 group had a mean damage score of 3, corresponding to 51–75% tissue damage. In contrast, the KP2 group showed a markedly lower score (mean 1.3), indicating only mild to moderate injury (<50% damage) (Fig. 5). The histopathological score for KP2 was significantly lower than that of KP (P<0.05) but not significantly different (P>0.05) from the KN group, suggesting that cardiomyocyte integrity in KP2 closely resembled the normal untreated control.

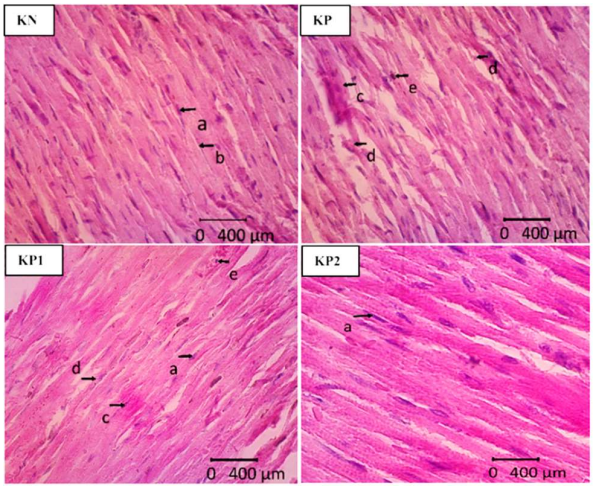

Fig. 4: Histopathology of rabbit heart tissue (H&E staining, 400× magnification): (KN) Normal cell nuclei (a) and intercalated discs (b); (KP) necrosis (d), edema (c), and inflammatory cells (e); (KP1) necrosis (d), edema (c), and cell nuclei (a); (KP2) cell nuclei (a).

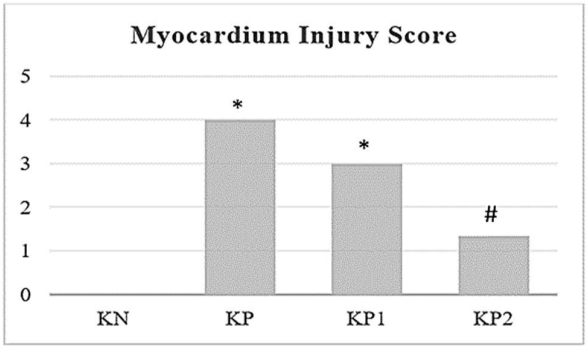

Fig. 5: Histopathological injury scores of the cardiac tissue (y-axis) against treatment groups (x-axis). KN: non-hemorrhaged control group; KP: hemorrhaged group without fluid therapy; KP1: hemorrhaged group treated with Ringer's lactate (RL); KP2: hemorrhaged group treated with RL + Gelatin (Gel). Groups showing significant differences (P<0.05) compared to KN are marked with an asterisk (*), and those showing significant differences (P<0.05) compared to KP are marked with a hash (#).

DISCUSSION

These results provide a compelling explanation for the inconsistencies reported in previous studies regarding the comparative efficacy of crystalloids and colloids. Unlike earlier research that focused primarily on traditional hemodynamic parameters such as blood pressure and heart rate, our findings demonstrate a direct beneficial effect on left ventricular function. This suggests that the hemodynamic improvements observed with colloids are not merely due to passive volume expansion but reflect enhanced cardiac performance. These data offer a deeper physiological perspective on how the heart responds to different fluid therapies. Although both fluids (KP1 and KP2) were effective in restoring hemodynamic parameters following hemorrhagic shock, detailed echocardiographic analysis revealed significant differences in the cardiac response to the two fluid types.

The average heart rate (HR) of rabbits at baseline (T15) under anesthesia was 180.00±40.40bpm, which is higher than the average HR previously reported in anesthetized rabbits 155±29bpm (Fontes-Sousa et al. 2006) but lower than another report of 262±37bpm (Fontes-Sousa et al. 2009). During hemorrhagic shock, HR typically rises during the compensatory phase and falls during the decompensatory phase, marking a critical stage of shock progression. Similar HR elevations during hemorrhage have been reported in previous studies (Salomão et al. 2015; Treml et al. 2023). Tachycardia increases myocardial workload and energy consumption (Mann et al. 2015), while significant blood loss further disrupts hemodynamics (Treml et al. 2023). In this study, HR initially increased during resuscitation and then decreased two hours post-resuscitation. HR, together with stroke volume (SV), serves as an important indicator of fluid therapy effectiveness. Previous studies have shown that HR elevation is characteristic of shock, and its normalization following fluid administration correlates with improved tissue perfusion and cardiac function (Liu et al. 2004)

At T15, representing the pre-hemorrhage condition, LVIDd and LVIDs values averaged 1.16±0.12cm and 0.82±0.11cm, respectively, with ranges of 0.89–1.43cm. A

previous study reported mean values of 1.32±0.19cm and 0.83±0.14cm, with ranges of 0.95–1.70cm and 0.54–1.12cm, respectively (Turner Giannico et al. 2015). During hemorrhagic shock, both LVIDd and LVIDs values decreased, reflecting narrowing of the left ventricular lumen due to reduced blood volume being pumped. Hemorrhage is closely associated with left ventricular dysfunction, characterized by impaired early isovolumic relaxation and increased myocardial stiffness observed 120 minutes after hemorrhage (D'Annunzio et al. 2012).

The resuscitation phase showed a significant increase in left ventricular lumen diameter, indicating lumen expansion, which was followed by a decrease in diameter two hours after resuscitation. Similar findings have been reported, with increases in LVIDs observed after fluid administration (Buba Lucina et al. 2022). The primary aim of fluid resuscitation is to restore circulating blood volume (Ramesh et al. 2019; Munoz et al. 2020) and the additional volume directly influences the internal diameter of the left ventricle (Table 1). At T230, rabbits treated with fluids showed significant increases ($P<0.05$) in ejection fraction (EF) and fractional shortening (FS), reflecting an increased stroke volume in response to enhanced preload (Chaves et al. 2018; Buba Lucina et al. 2022).

During the hemorrhagic period, circulating blood volume decreases, resulting in reductions in stroke volume (SV) and cardiac output (CO). Similar findings have been reported, with significantly impaired cardiac function observed two hours post-trauma, characterized by decreased SV and CO (Yang et al. 2004). A 65% blood loss has also been shown to reduce cardiac output (Treml et al. 2023). Moreover, acute hemorrhage alters not only systolic but also diastolic ventricular function in anesthetized rabbits (D'Annunzio et al. 2012). In this study, post-resuscitation fluid therapy increased circulating blood volume, as evidenced by elevated EDV, ESV, SV, and CO. The primary goal of fluid resuscitation is to restore cardiac output (Messina et al. 2022). Colloid administration causes expansion of blood volume and cardiac output. This is essential for supporting cardiac function. This efficiency allows for more rapid achievement of hemodynamic stability (Shahbazi et al. 2011).

This study introduces a novel dynamic, non-invasive echocardiographic approach for evaluating fluid resuscitation, which overcomes the limitations of static assessments based solely on blood pressure and heart rate (Saraçoğlu et al. 2023). This method provides a more comprehensive understanding of the impact of fluid therapy on cardiac performance and may serve as the foundation for a new paradigm in hemorrhagic shock management. These findings suggest that, in the future, fluid selection and titration could be guided by real-time cardiac performance metrics rather than relying exclusively on vital signs (Donati et al. 2023), thereby enabling the optimization of resuscitation strategies in clinical practice.

Resuscitation induces hemodilution, which increases cardiac output and activates vasoconstriction through baroreceptor reflexes. The resulting reduction in shear stress on the vessel walls decreases nitric oxide (NO) production, thereby promoting vasoconstriction and increasing peripheral vascular resistance (Martini et al. 2005). Early administration of gelatin-polysuccinate or hydroxyethyl starch (HES) has also been shown to produce greater cardiac output and more pronounced hemodilution (Ziebart et al. 2021).

The success of fluid resuscitation depends on the ability of the administered fluid to remain within the intravascular space (Myburgh and Mythen 2013). Combined Ringer's lactate (RL) and gelatin therapy produced superior outcomes compared to RL alone, likely due to the colloid's higher oncotic pressure and greater intravascular volume expansion (Heming et al. 2017). Gelatin remains intravascular longer, thereby improving circulatory hemodynamics and achieving resuscitation targets with lower fluid volumes compared to crystalloids (Heming et al. 2017). Experimental studies have also demonstrated that gelatin colloids exert stronger effects on macrocirculation than crystalloids, both in rabbits and in pig models (Ziebart et al. 2018). Furthermore, concentrated colloid solutions have been shown to restore capillary flow distribution and promote more homogeneous tissue oxygenation in hemorrhagic shock models (He et al. 2018).

Inflammatory cell infiltration was observed in the KP, KP1, and KP2 groups, with the most severe inflammation noted in the KP group compared to KP1 and KP2. Inflammation is a natural response to injury and serves as a prerequisite for tissue remodeling, regeneration, and scar formation. In the context of cardiac injury, the inflammatory response involves the infiltration of immune cells that modulate inflammation and temporally regulate angiogenesis during the process of cell death and tissue repair (Broughton et al. 2018).

Histopathological examination of rabbit hearts in the KP2 group receiving combined RL and gelatin resuscitation showed improvement, with reduced inflammation and decreased nuclear necrosis compared to KP1 and KP groups. These findings indicate that clinically, combined RL and gelatin fluid resuscitation better reduces cardiac injury in animals experiencing hemorrhagic shock. This aligns with Coppola et al. (2014), who stated that fluid resuscitation aims to reduce organ failure due to peripheral tissue hypoperfusion. The same results showed that improvements in heart cells using 7.5% hypertonic saline reduced the cardiac injury score compared to 4.5% hypertonic saline after uncontrolled hemorrhagic shock in rabbits (Xu et al. 2019).

It should be noted that administering large volumes of crystalloids may lead to edema due to their small molecular structure (Vardar et al. 2022), which facilitates the movement of intravascular fluid into the interstitial space through vessel walls (Sun et al. 2017). Furthermore, fluid administration exceeding 2L at infusion rates greater than 0.2L/min has been associated with the risk of rebleeding (Hirshberg et al. 2006). Therefore, careful consideration and close monitoring of dosing and infusion rates are essential during resuscitation.

The main limitation of this study is the use of a rabbit model, as the findings cannot be directly generalized to other species due to differences in physiological responses. Future research should validate these results through clinical trials in species such as dogs or horses, which are also prone to hemorrhagic shock. Such studies will help determine whether the benefits observed in rabbits can be translated into improved clinical outcomes in these animals, thereby strengthening veterinary clinical practice.

The application of echocardiography in these trials will be particularly valuable for optimizing resuscitation strategies in real-world veterinary settings.

Conclusion

This study provides a novel dynamic and non-invasive evaluation of left ventricular function in a rabbit model of hemorrhagic shock. Compared to Ringer's lactate, gelatin colloid produced faster and more significant improvements in key cardiac performance parameters, including left ventricular internal diameter (LVID), ejection fraction (EF), and cardiac output (CO). These findings bridge the gap between traditional hemodynamic assessments and more detailed evaluations of myocardial function, underscoring the value of dynamic echocardiography as a promising tool for optimizing fluid resuscitation strategies in hemorrhagic shock.

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Author's Contribution: Waode Santa Monica[1]: Conceptualization, Methodology, Writing Original Draft. Ida Tjahajati[2]: Investigation, Methodology, Research Process. Siti Isrina Oktavia Salasia[3]: Statistical Analysis, Review & Editing, Conceptualization. Aris Haryanto[4]: Data Analysis, Visualization . Muhammad Zulfadillah Sinusi, DVM, M.Sc: Surgery, Radiology, and Technical Support.

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