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Laboratory findings of postoperative venous thromboembolism (VTE) in Dr. Sardjito General Hospital, Yogyakarta

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ABSTRACT

Venous thromboembolism (VTE) is a significant risk, especially for older individuals. Indonesian studies found 37.1% VTE incidence in bedridden patients over 40 and 2.1% in major surgeries. Surgery, like hip fractures, raises the risk temporarily. Diagnosis relies on tests like ultrasound with Doppler, Wells score, and neutrophil-to-lymphocyte ratio (NLR). This study aimed to evaluate the laboratory findings of postoperative VTE. A retrospective analysis was conducted in Dr. Sardjito General Hospital, Yogyakarta using medical record data of VTE patients who underwent major surgery. The laboratory data, including complete blood count characteristics for every month for three months after postsurgery and DVT presentation when it occurred on the diagnostic day were collected. In total of 27 patients involved in this study, VTE cases were more common in digestive (41.2%) and obstetric gynecology surgeries (29.4%) for females, and nervous (44.4%) and cardiovascular surgeries (22.2%) for males. Females had a higher prevalence of Well Score ≥3 (82.4% vs 40%; p=0.058) and longer VTE therapy durations (65.50 ± 46.51 vs 39.60 ± 41.04 d; p=0.172). Males had more unilateral VTE occurrences (90.9 vs 56.3%; p=0.070) and a higher proportion of total occlusion cases (60 vs 37.5%; p=0.422). NLR exhibited a significant decrease from the 1st to the 2nd month (10.52 vs 3.64; p=0.009), followed by an insignificant increase in the 3rd month (3.64 vs 3.98; p=0.878). Notably, NLR trended downward in the 2nd month examination. In conclusion, VTE occurs in 0.21% of postoperative patients, with the highest incidence observed in post-gynecological surgery patients. The NLR can serve as a diagnostic tool for VTE in extremities, as an elevated NLR indicates the presence of a more proximal thrombus.

ABSTRAK

Tromboemboli vena (VTE) merupakan risiko nyata, terutama pada orang lanjut usia. Penelitian di Indonesia menemukan 37,1% kejadian VTE pada pasien berusia di atas 40 tahun yang terbaring di tempat tidur dan 2,1% pada pasien operasi besar. Pembedahan, seperti patah tulang pinggul, meningkatkan risiko untuk sementara. Diagnosis bergantung pada tes seperti USG dengan Doppler, skor Wells, dan rasio neutrofil-limfosit (NLR). Penelitian ini bertujuan untuk mengevaluasi temuan laboratorium pasca operasi VTE. Analisis retrospektif dilakukan di RSUP Dr. Sardjito Yogyakarta dengan menggunakan data rekam medis pasien VTE yang menjalani operasi besar. Data laboratorium dikumpulkan, termasuk karakteristik hitung darah lengkap setiap bulan selama tiga bulan setelah pasca operasi dan gambaran DVT yang terjadi pada saat diagnosis. Sebanyak 27 pasien yang terlibat dalam penelitian ini, kasus VTE lebih banyak terjadi pada operasi pencernaan (41,2%) dan obstetri-ginekologi (29,4%) pada wanita serta operasi saraf (44,4%) dan kardiovaskular (22,2%) untuk pria. Perempuan memiliki prevalensi skor Wells ≥3 yang lebih tinggi (82,4% vs 40%; p=0,058) dan durasi terapi VTE yang lebih lama (65,50 ± 46,51 vs 39,60 ± 41,04 hari; p=0,172). Laki-laki memiliki lebih banyak kejadian VTE unilateral (90,9 vs 56,3%; p=0,070) dan proporsi total kasus oklusi yang lebih tinggi (60 vs 37,5%; p=0,422). NLR menunjukkan penurunan nyata pada bulan ke-1 hingga ke-2 (10,52 vs 3,64; p=0,009), diikuti peningkatan tidak nyata pada bulan ke-3 (3,64 vs 3,98; p=0,878). Khususnya, NLR cenderung menurun pada pemeriksaan bulan ke-2. Kesimpulannya, VTE terjadi pada 0,21% pasien pasca operasi, dengan insiden tertinggi terjadi pada pasien pasca operasi ginekologi. NLR dapat berfungsi sebagai alat diagnostik untuk VTE pada ekstremitas, karena peningkatan NLR menunjukkan adanya trombus yang lebih proksimal.

Keywords:
postoperative; venous thromboembolism; neutrophil to lymphocyte ratio; complete blood count; pulmonary embolism

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INTRODUCTION

Venous thromboembolism (VTE) is a disease that includes pulmonary embolism (PE) and deep vein thrombosis (DVT). Every year, about 900,000 people in the United States are estimated to suffer from VTE, and up to 100,000 of them may not survive. The probability of developing VTE increases with age, with 60% of all cases occurring in individuals aged 70 years and above.[1] VTE incidence varies by race, with higher incidence in African Americans and lower incidence in Asians, Asian Americans, and Native Americans. Age is a significant factor in VTE incidence, with both men and women experiencing higher rates of DVT and PE as they age. Men have a higher overall incidence rate of VTE compared to women, but women have slightly higher rates during their childbearing years. Men are also at a higher risk of VTE recurrence than women, due in part to the low recurrence risk in women with hormone-related index thrombosis. Women are at an increased risk of VTE during their fertile years, with additional burden associated with hormonal contraceptives or pregnancy, and in later life due to hormone therapy for menopause. Therefore, gender, age, and exposure to sex-specific triggers all play a role in the incidence of VTE.[2,3] In Indonesia, a prospective observational registry study found that the incidence of DVT was 37.1% in eligible patients and 40.3% in evaluable patients who were over 40 years old and bedridden due to acute medical illnesses.[4] Meanwhile, another cross-sectional study found that the incidence of VTE was 2.1% among patients who underwent major orthopedic or abdominal surgery. In their report, DVT and PE accounted for 1.3% and 0.8% of cases.[5]

Virchow's triad, comprising venous stasis, blood hypercoagulability, and vascular wall injury, is the basis for venous thrombosis. There are some risk factors contribute for DVT, which can be provoked or unprovoked, transient or persistent. Major surgery are transient risk factors for DVT; however, the risk varies depending on procedure-based factors, including patient age, prior DVT, malignancy, surgical procedure, and duration of bed rest. For instances, patients with hip fractures and long bone fractures have higher risk of DVT compared to other surgical procedures. The Caprini assessment model can be used to predict higher-risk patients based on specific patient characteristics and medical history.[1,6]

To diagnose DVT, objective tests are required due to the nonspecific symptoms of DVTs and PEs. Although D-dimer is sensitive, it has low specificity and cannot be used alone. Less invasive diagnostic tests include compression ultrasound, computed tomography pulmonary angiography, and ventilation perfusion scans. The Wells score can be used to stratify clinical presentation and probabilities, and ultrasound with Doppler is the imaging test of choice. Additionally, the ratio of neutrophils to lymphocytes (NLR) can be used as an additional diagnostic tool.[7,8] This study will assess laboratory findings of DVT after major surgery and provide DVT epidemiology data in Indonesia.

MATERIAL AND METHODS

Subjects and design

This retrospective analysis was conducted using data collected from medical records at Dr. Sardjito General Hospital, Yogyakarta, Indonesia. The study was approved by the Medical and Health Research Ethics Committee of the Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada/Dr. Sardjito General Hospital, Yogyakarta with reference number KE/FK/0612/EC/2022.

Procedure

The medical records with ICD10 codes for venous thromboembolism (VTE) were selected. Patients who underwent major surgery and diagnosed with VTE from 2016 to 2021 were included. The exclusion criteria were patients with incomplete medical records, those who had a history of anticoagulant prophylaxis before and after surgery, those with disseminated intravascular coagulation (DIC), and those with DVT diagnosed more than 12 mo after cardiac and orthopedic prosthesis placement and more than one month after other major surgeries (FIGURE 1). The subjects were then grouped based on the type of surgery, and data was collected for each patient, including the length of stay, mortality (all causes of death), DVT onset, wells score, location of thrombus, laterality of thrombus, and degree of occlusion. Laboratory data, including complete blood count characteristics monthly after post-surgery day and DVT presentation when it occurred at the diagnostic day were also collected.

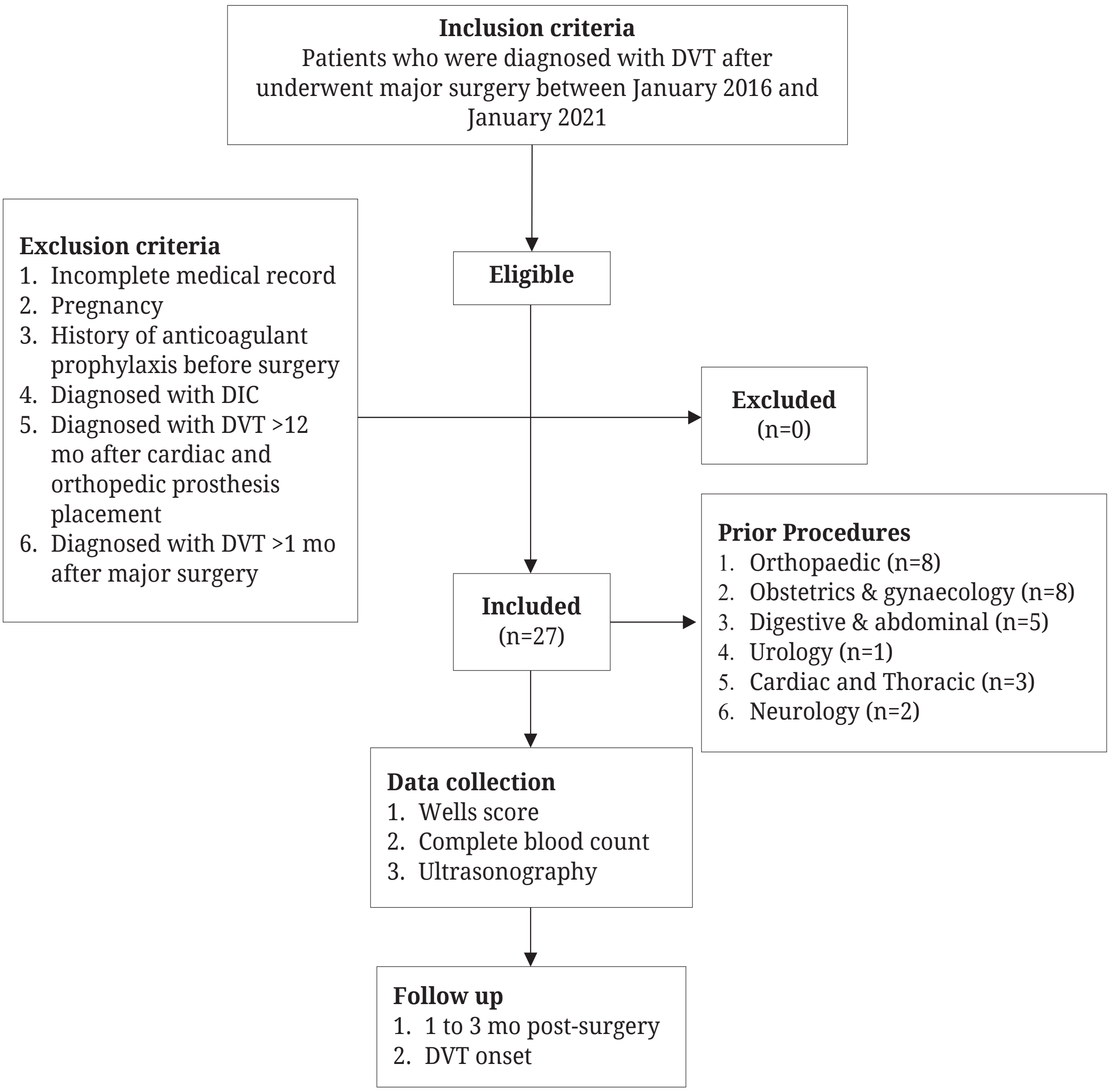

FIGURE 1. Selection criteria for eligible patient

Statistical analysis

Data were presented as mean ± standard of deviations (SD) or frequency or median (min. – max.). Kruskal Wallis or Mann Whitney tests were applied to analyze differences among groups. A p value of <0.05 was considered significant. All statistical analyses were performed using MedCalc software (version 19.6).

RESULTS

A total of 27 subjects were included in this study. The demographic information of the subjects are presented in TABLE 1. The mean age of male subjects is higher than that of female subjects (54.71±8.72 vs 51.10±20.15 y.o.). Risk stratification for surgery indicates that a greater proportion of female subjects are classified as grade 3 compared to male subjects (64.7 vs 22.2%; p=0.060). When stratified by organ systems, the majority of post-surgery VTE cases in female subjects occurred in surgeries involving the digestive and obstetric gynecology system (41.2 and 29.4%), while in male subjects, most post-surgery VTE cases were associated with surgeries involving the nervous and cardiovascular system (44.4 and 22.2%). The percentage of subjects with a Well Score ≥3 was higher in female subjects than in male subjects (82.4 vs 40%; p=0.058). The duration of VTE therapy was longer in female subjects compared to male subjects (65.50±46.51 vs 39.60±41.04 d; p=0.172). Regarding the presentation of VTE, a higher proportion of cases were unilateral in male subjects compared to female subjects (90.9 vs 56.3%; p=0.070). Meanwhile, the location of thrombus formation indicates a higher proportion of proximal thrombus in female subjects compared to male subjects (87.5 vs 80%; p=0.625). Male subjects also exhibit a higher proportion of total occlusion compared to female subjects (60 vs 37.5%; p=0.422).

The haematological laboratory characteristics 3 months post-surgery are presented in TABLE 2. The complete blood examination in the first month post-surgery showed a median erythrocyte count of 3.79 (2.77-5.19) x10^3 cells/mL, median hemoglobin of 10.70 (7.80-14.30) g/dL, and median hematocrit of 32.40% (23.60-44.40). The D-dimer result in the first month post-surgery shows a median value of 5269.50 (709-11320) ng/mL (TABLE 2). There is a significant difference in the results of the leucocyte differential count (p<0.05), despite the leucocyte count showing no significant difference (p=0.133). The platelet count demonstrates a median increase from the first to the second month (215.5 vs 401.0 x10^3 cells/mL; p=0.061), followed by an insignificant median decrease from the second to the third month (401.0 vs 266.5 x10^3 cells/mL; p=0.508). The neutrophil to lymphocyte ratio (NLR) exhibits a notably high median value in the first month, which decreases significantly in the second month (10.52 vs 3.64; p=0.009), followed by an insignificant increase in the third month (3.64 vs 3.98; p=0.878). Additionally, it is noteworthy that there is a significant difference in erythrocyte count, which was higher in unilateral compared to bilateral VTE (4.02 ± 0.61 vs 3.51 ± 0.41 x10^3 cells/mL; p=0.031). This pattern is mirrored in hemoglobin value (11.21 ± 1.71 vs 9.84 ± 1.34 g/dL; p=0.051), hematocrit value (34.22 ± 5.02 vs 29.88 ± 3.98%; p=0.039), and lymphocyte count, which was higher in unilateral compared to bilateral VTE (11.52 ± 7.13 vs 6.91 ± 2.73 x10^3 cells/mL; p=0.045), as presented in TABLE 3.

TABLE 1. Patient baseline characteristics and demographic data

Variables	Quantity
Age (mean ± SD yr)	53.37 ± 13.80
Sex [n (%)]	
• Male	10 (37.0)
• Female	17 (63.0)
Risk stratification [n (%)][a]	
• 1	1 (3.7)
• 2	12 (44.4)
• 3	14 (51.9)
Surgery classification [n (%)]	
• Endocrine	1 (3.7)
• Reproductive	8 (29.6)
• Digestive	5 (18.6)
• Cranial and nerve system	2 (7.4)
• Cardiovascular	2 (7.4)
• Musculoskeletal	8 (29.6)
• Renal and urinary system	1 (3.7)
Post-surgery length of stay (mean ± SD d)	12.15 ± 11.04
DVT onset (d)	20 ± 18.30
Well score [n (%)]	
• 1	3 (11.1)
• 2	6 (22.2)
• 3	12 (44.4)
• 4	4 (14.8)
• 5	2 (7.4)
Therapy duration (mean ± SD d)	54.71 ± 45.29
DVT presentation [n (%)]	
• Unilateral	18 (69.23)
• Bilateral	8 (30.77)
Location of thrombus [n (%)]	
• Proximal	22 (84.62)
• Distal	4 (15.38)
Degree of occlusion [n (%)]	
• Partial	14 (53.85)
• Total	12 (46.15)

During the initial one-month follow-up of laboratory patients, the NLR was found to be significantly higher in proximal thrombus compared to distal thrombus (14.82 ± 9.77 vs 3.15 ± 0.86; p<0.0001). Additionally, the neutrophil count demonstrated an elevated value in proximal thrombus compared to distal thrombus (85.99 ± 5.69 vs 66.63 ± 4.65 x10^3 cells/mL; p=0.007). Conversely, the lymphocyte count was lower in proximal thrombus compared to distal thrombus (7.95 ± 3.99 vs 21.87 ± 3.97 x10^3 cells/mL; p=0.015). Furthermore, the eosinophil count was reduced in proximal thrombus compared to distal thrombus (0.91 ± 1.59 vs 2.17 ± 0.64 x10^3 cells/mL; p=0.044), as presented in TABLE 4.

TABLE 2. Hematological laboratory characteristics 3 months post-surgery

Variable	1st month	2nd month	3rd month	p
Leucocyte (x10^3 cells/mL)	12.15 (3.02-25.55)	8.15 (1.15-28.16)	9.74 (5.66-20.55)	0.133
Erythrocyte (x10^3 cells/mL)	3.79 (2.77-5.19)	4.01 (2.77-5.21)	3.775 (2.37-4.84)	0.362
Platelet (x10^3 cells/mL)	215.5 (62-745)	401.0 (16-707)	266.5 (116-657)	0.103
Hemoglobin (g/dL)	10.7 (7.8-14.3)	10.9 (7.4-14)	10.85 (6.4-12.5)	0.677
Hematocrit (%)	32.4 (23.6-44.4)	33.7 (22.5-43.3)	32.5 (18.9-39.2)	0.413
Neutrophil (%)[a,b]	85.65 (63.1-94.9)	67.9 (30.7-91.3)	70.15 (59.9-87.4)	0.001
Lymphocyte (%)[a,b]	8 (2.5-25)	19.2 (5.2-43.9)	17.95 (7.1-28.4)	0.001
Monocyte (%)[b]	5.65 (1.4-11.4)	7 (1.5-18.1)	8 (3.1-17.5)	0.029
Eosinophil (%)[a,c]	0.35 (0-6.4)	2.2 (0-8.5)	0.85 (0.1-4.5)	0.008
Basophil (%)[a]	0.2 (0.1-0.8)	0.4 (0.2-1.9)	0.45 (0-0.9)	0.014
NLR[a,b]	10.52 (2.59-38.31)	3.64 (0.7-17.27)	3.98 (2.14-12.35)	0.001

Note: p-value was analyzed using Kruskal-Wallis and Wilcoxon test for post hoc; [a] significantly different between 1st and 2nd month ($p<0.05$); [b]significantly different between 1st and 3rd month ($p<0.05$); [c]significantly different between 2nd and 3rd month ($p<0.05$); NLR: neutrophil to lymphocyte ratio

TABLE 3. Hematological laboratory characteristics based on VTE presentation in the first month

Variable	Unilateral	Bilateral	p
Leucocyte (x10^3 cells/mL)	10.76 (3.02-25.55)	12.98 (6.11-16.48)	0.839
Erythrocyte (x10^3 cells/mL)	3.91 (3.11-5.19)	3.52 (2.77-4.04)	0.031*
Platelet (x10^3 cells/mL)	215.50 (62-745)	261.50 (183-635)	0.593
Hemoglobin (g/dL)	11.05 (8.10-14.30)	10.35 (7.80-11.20)	0.051*
Hematocrit (%)	33.70 (25-44.40)	31.45 (23.60-34.10)	0.039*
Neutrophil (%)	83 (63.10-92)	87.40 (81.50-94.90)	0.059*
Lymphocyte (%)	10.65 (2.50-25)	6.60 (2.50-10.90)	0.045*
Monocyte (%)	6.20 (1.40-11.40)	4.65 (2.50-8.20)	0.373
Eosinophil (%)	0.45 (0-6.40)	0.25 (0-2.30)	0.200
Basophil (%)	0.20 (0.10-0.80)	0.20 (0.10-0.70)	0.802
NLR	7.98 (2.59-36.46)	13.34 (7.56-38.31)	0.381

Note: number of sample p-value was analyzed using Mann-Whitney; *significantly different ($p < 0.05$); NLR: neutrophil to lymphocyte ratio.

TABLE 4. Hematological laboratory characteristics based on thrombus location in the first month

Variable	Proximal	Distal	p
Leucocyte (x10^3 cells/mL)	12.52(3.02-25.55)	9.96 (6.24-11.33)	0.131
Erythrocyte (x10^3 cells/mL)	3.79(2.77-5.19)	3.89 (3.33-4.36)	0.937
Platelet (x10^3 cells/mL)	214(62-745)	220 (216-252)	0.231
Hemoglobin (g/dL)	10.60(7.80-14.30)	11.80 (9.90-12.20)	0.459
Hematocrit (%)	32.30(23.60-44.40)	34.90 (28.90-39.10)	0.594
Neutrophil (%)	86.80(74.80-94.90)	64.90 (63.10-71.90)	0.007*
Lymphocyte (%)	6.90(2.50-15.90)	23.20 (17.40-25)	0.015*
Monocyte (%)	5.20(1.40-8.20)	8.70 (6.40-11.40)	0.100
Eosinophil (%)	0.30(0-6.40)	1.80 (1.80-2.90)	0.044*
Basophil (%)	0.20(0.10-0.70)	0.50 (0.20-0.80)	0.272
NLR	12.55(5.05-38.31)	2.72 (2.59-4.14)	<0.0001*

Note: number of sample p-value was analyzed using Mann-Whitney; *significantly different ($p < 0.05$); NLR: neutrophil to lymphocyte ratio.

TABLE 5. Hematological laboratory characteristics based on VTE occlusion degrees

Variable	Partial	Total	p
Leucocyte (x10^3 cells/mL)	11.30 (3.02-25.55)	12.52 (9.82-16.48)	0.618
Erythrocyte (x10^3 cells/mL)	3.79 (2.77-4.75)	3.80 (3.20-5.19)	0.196
Platelet (x10^3 cells/mL)	252 (62-745)	192 (98-583)	0.219
Hemoglobin (g/dL)	10.30 (7.80-14.20)	11.10 (7.80-14.30)	0.283
Hematocrit (%)	32.20 (23.60-40.50)	32.70 (24-44.40)	0.278
Neutrophil (%)	86.10 (63.10-94.90)	85.20 (64.90-92.30)	0.986
Lymphocyte (%)	9 (2.50-23.20)	7.70 (4-25)	0.820
Monocyte (%)	5.70 (1.40-11.40)	5.60 (2.50-8.20)	0.867
Eosinophil (%)	0.30 (0-3.40)	0.60 (0-6.40)	0.517
Basophil (%)	0.20 (0.10-0.70)	0.20 (0.10-0.80)	0.564
NLR	9.79 (2.72-38.31)	11 (2.59-22.44)	0.648

Note: p-value was analyzed using Mann-Whitney; NLR: neutrophil to lymphocyte ratio.

The hematological laboratory characteristics based on VTE occlusion degrees were not significantly different (TABEL 5). The erythrocyte count was found to be lower in cases of partial occlusion when compared to total occlusion VTE, with values of 3.68 ± 0.49 vs 4.05±0.69 x10^3 cells/mL, respectively (p=0.196). Similarly, hemoglobin levels exhibited a decrease in instances of partial occlusion compared to total occlusion VTE, registering values of 10.38 ± 1.63 vs 11.20 ± 1.76 g/dL, respectively (p=0.283). Additionally, the hematocrit also demonstrated a lower value in partial occlusion VTE cases compared to total occlusion, with measurements of 31.58 ± 4.36 vs 34.17 ± 5.82%, respectively (p=0.278).

The median of neutrophil differential count significanlty decreased in the 2nd month (85.65 vs. 67.9%; p=0.003), however it not significanlty increased in the 3rd month (67.9 vs. 70.15%; p=0.386). In contrast, the median of lymphocyte differential count significanlty increased in the 2nd month (8% vs. 19.2%; p=0.006), and not significantly decreased in the 3rd month (19.2% vs. 17.95%; p=0.919). The monocyte differential count also significantly increased in the 2nd month (5.65% vs. 7%; p=0.05), followed by a non significantly increased in the 3rd month (7% vs. 8%; p=0.878). Similarly, the eosinophil differential count it significantly increased in the 2nd month (0.35% vs. 2.2%; p=0.003), followed by a significantly decrease in the 3rd month (2.2% vs. 0.85%; p=0.013). Lastly, the basophil differential count significantly increased in the 2nd month (0.2% vs. 0.4%; p=0.001), however not significantly increased in the 3rd month (0.4% vs. 0.45%; p=0.235), as presented in FIGURE 2.

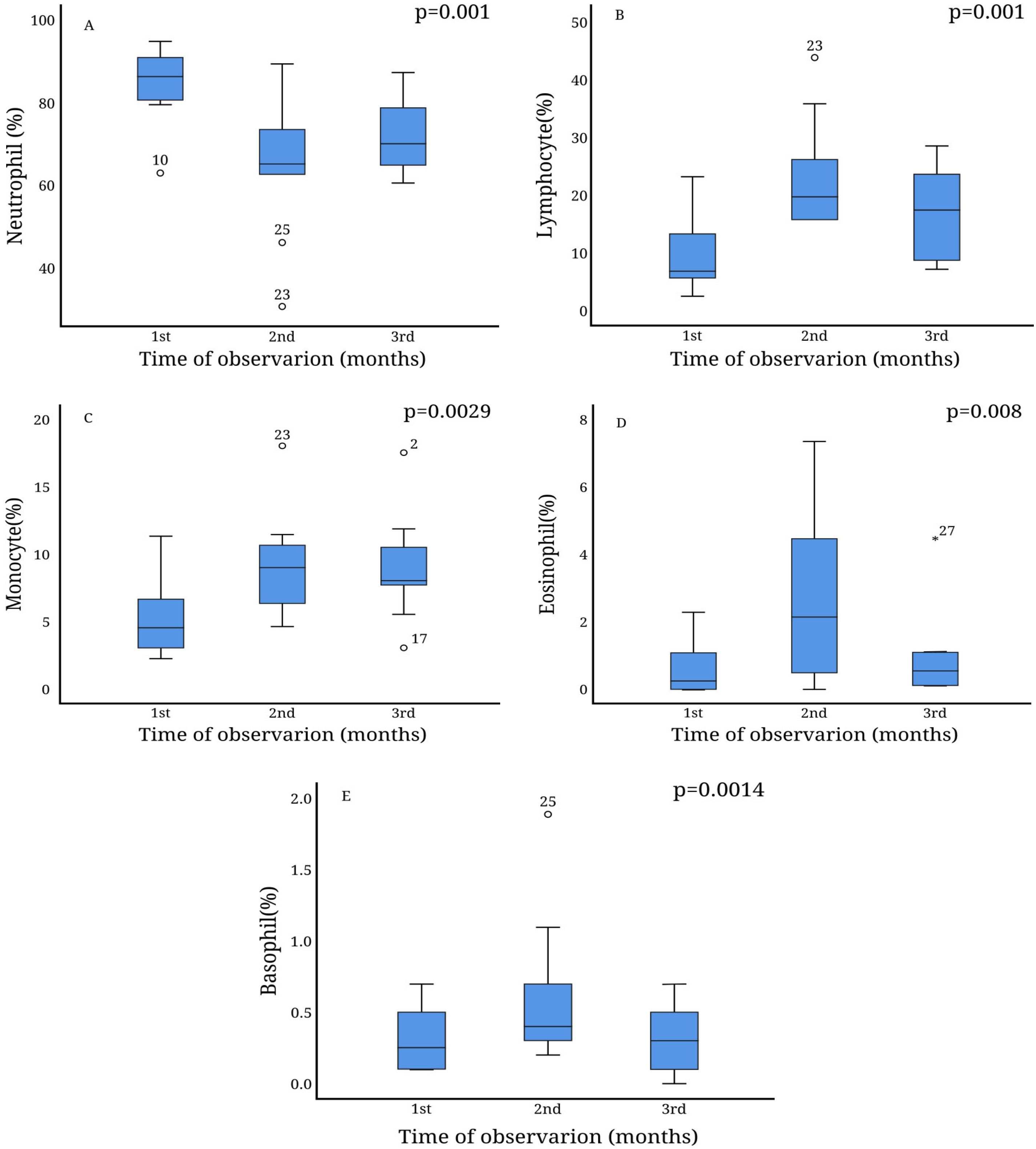

FIGURE 2. Box plot comparison of differential leucocyte count between months. A) neutrophil [n (%)]; B) lymphocyte, [n (%)]; C) monocyte [n (%)]; D) eosinophil [n (%)]; E) basophil [n (%)].

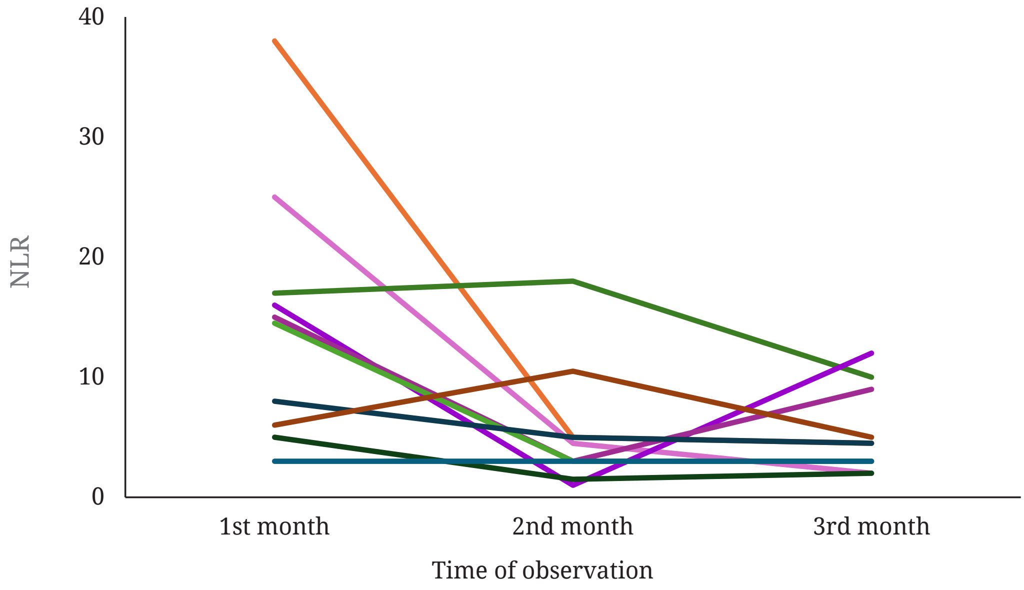

FIGURE 3. NLR kinetic between subjects

Moreover, among all study subjects, only two individuals—those who underwent surgery on the gastrointestinal and urinary systems—experienced an increase in NLR during the 2nd month of post-surgery examination. Despite these isolated cases, overall the NLR decresed in the 2nd month examination (FIGURE 3).

DISCUSSION

In this study, 27 (0.21% of cases) out of 12681 postoperative patients since 2016 were diagnosed with DVT. This result is consistent with a previous cross-sectional study that reported a VTE incidence of 2.1% among patients who underwent major orthopaedic or abdominal surgery, with DVT and PE accounting for 1.3% and 0.8% of cases, respectively.[5] On patients with acute medical illness in Indonesia, the rate of DVT was 37 - 40%.[4] Another Asian study revealed that after total knee replacement and total hip replacement, the incidence of asymptomatic DVT was 17 and 24%, respectively, which is comparatively lower than the incidence rates of 36-84% in Western populations. The study also found that the overall postoperative DVT rate without pharmacologic thromboprophylaxis was 7.5% in Asia, where thromboprophylaxis is less commonly used due to the lower probability of VTE development among Asians compared to Caucasians and African Americans. Additionally, racial and ethnic differences in incidence rates have been observed, with Hispanics and Asians having significantly lower rates than Caucasians or African Americans.[9] Another study found that VTE tended to develop after a median of 16 d following non-oncologic general surgery, with a higher incidence of events occurring within the first week compared to those occurring after 30 d. This delayed presentation may increase the likelihood of symptomatic PE, which was observed in half of the patients with VTE, and lead to unfavourable outcomes.[10]

Although age is a major risk factor for VTE and incident VTE is more common in older individuals due to higher blood coagulability potency, as well as a higher prevalence of provoking risk factors for VTE such as cancer, immobility, hospitalization, and surgery, this study did not find age and sex to be significantly related to VTE incidences. However, gender influences VTE risk, with men having a higher age-adjusted incidence rate of VTE than women (130 per 100,000 and 100 per 100,000 population, respectively). Nevertheless, in young adulthood, women have a slightly higher annual incidence of VTE due to hormonal exposures such as pregnancy, the postpartum period, and oral contraceptive use. The use of exogenous hormones such as oral contraceptive therapy has been positively linked with a 1.5-fold greater risk of incident VTE in women.[11,12] Besides, surgery duration, perioperative immobilization, and the development of postoperative complications may impact the risk of VTE in patients after surgery.[13]

Majority of patients who develop VTE after surgery are women, and 29.4% of them undergo obstetric and gynecologic surgeries. The incidence of VTE following gynecologic surgery depends on whether the patient has benign or malignant disease, with hysterectomy being the most commonly performed major gynecologic surgical procedure. The prevalence of DVT after gynecologic surgery varies, with reported rates of 14% for benign gynecologic and 38% for malignant disease. The surgical approach may also impact the rate of VTE, as more women undergo minimally invasive surgery. Minimally invasive surgery is thought to offer benefits such as early ambulation and decreased VTE risk.[14] Patients with gynecologic cancer have an estimated VTE risk that is approximately 14 times higher than those without cancer. Studies have reported DVT incidence ranging from 17-40% and PE incidence ranging from 1-2.6% in these patients.[15] This is suspected to be related to the decrease in antithrombin III, protein C, and protein S activity post-open surgery patients are also at a higher risk due to increased dysfibrinogenemia.[16]

Venous thromboembolism in this study occurred on average 20 d after surgery. This result is consistent with previous research indicating that VTE events generally occur within the first 4 wk after surgery. The influence of preoperative factors is a major predisposition to postoperative VTE events. Endothelial damage commonly occurs during surgery, suspected to increase procoagulant activity in patients with high initial risk.[16,17]

The majority of subjects had a Well score of 3, and only 6 subjects had a Well score >3 (22.2%). A higher Well score is associated with a higher risk of VTE events. However, the sensitivity and specificity of the Well score in predicting VTE events are uncertain[19,20] Some researchers have attempted to find other indices to predict VTE events, including hematological results. A study showed that red blood cell count, hemoglobin, and hematocrit are risk factors for VTE events in the general population. Hematocrit is one of the determinants of blood viscosity, and an increase in hematocrit may trigger clot formation by increasing the contact time between platelets and coagulation factors in circulation, which is adjacent to dysfunctional endothelium. Increased hematocrit can also promote platelet transport to the vessel wall, thereby increasing interaction with the vascular wall and raising the risk of VTE.[16,17]

The relationship between the NLR and thromboembolic events is believed to be influenced by various systemic factors such as inflammation, endothelial dysfunction, and oxidative stress. Inflammation causes damage to the endothelial layer through interactions between neutrophils and the endothelium. During ischemic conditions, inflammation becomes a dominant process, and leukocytes play a crucial role in this process.[18]

Inflammation triggers the release of chemical compounds from damaged cells or tissues, including prostaglandins, leukotrienes, histamine, bradykinin, and other pro-inflammatory compounds. This leads to the infiltration of leukocytes, particularly neutrophils and lymphocytes. Neutrophils and macrophages are the first types of leukocytes to appear in the inflammatory response. They release pro-inflammatory cytokines and chemokines, which stimulate T cells, a type of lymphocyte.[19]

During the acute phase of inflammation, the number of lymphocytes decreases due to the release of cortisol from the adrenal cortex. Conversely, in chronic inflammation, impaired cortisol function leads to an increase in lymphocyte count. In the acute phase, stress responses during inflammation activate the HPA axis, leading to the release of corticotropin-releasing hormone (CRH) from the hypothalamus. This stimulates the release of adrenocorticotropic hormone (ACTH), which triggers the release of cortisol. Cortisol inhibits lymphocytes, resulting in a decrease in their count during the acute phase. In the chronic phase, excessive cortisol levels bind to glucocorticoid receptors, causing dysregulation and glucocorticoid receptor resistance, leading to decreased cortisol levels and an increase in lymphocyte count.[20]

Neutrophil to lymphocyte ratio, which can be easily calculated from a complete blood count test, serves as a readily obtainable marker for indicating inflammation in the body. While the exact mechanism of using NLR as an inflammation marker is not fully understood, it is commonly employed for this purpose. Neutrophil to lymphocyte ratio reflects the balance between the innate immune response (neutrophils) and the adaptive immune response (lymphocytes). Severe systemic inflammatory conditions, such as sepsis and septic shock, result in increased NLR compared to mild systemic inflammation conditions.[18]

Otasevic *et al.*[21] reported that NLR, PLR, ESR, CRP, and LDH levels were significantly higher in lymphoma patients with VTE compared to those without VTE. Conversely, TP and albumin levels were significantly lower in lymphoma patients with VTE. Curve of ROC analysis indicated that NLR, PLR, and CRP demonstrated acceptable sensitivity and specificity in predicting VTE in lymphoma patients. The study also revealed that NLR and CRP were independent prognostic factors influencing the development of VTE in lymphoma patients. Previous studies have also suggested that NLR and PLR can be used as predictors of VTE development, although conflicting results have been reported. Additionally, the study found that lymphoma patients who did not respond well to therapy were more susceptible to VTE development, aligning with published data highlighting the association between aggressive lymphoma, advanced disease stage, lower survival rates, and higher mortality rates.[21]

Earlier research has demonstrated a significant increase in the number of neutrophils in the blood of patients with PE. Autopsy findings have also indicated neutrophil infiltration in most right ventricle samples from individuals who died from PE, suggesting a potential link between high NLR and VTE. This corresponds to the theory that neoplastic cells activate the coagulation and fibrinolysis systems to expedite angiogenesis, cell growth, and invasive properties of cancer cells.[22] As NLR rises, the risk of morbidity and mortality in patients experiencing organ damage and failure also increases.

Several previous studies have indicated that NLR exhibits moderate diagnostic accuracy for VTE, demonstrating moderate sensitivity and specificity. Meta-analyses conducted earlier have shown that high NLR predicts short-term mortality. In another meta-analysis, NLR has been independently demonstrated to predict both overall mortality and short-term mortality. While D-dimer exhibits high sensitivity in diagnosing VTE, its specificity is low due to potential influences from various pathophysiological factors. Consequently, D-dimer is commonly utilized to rule out VTE diagnosis.[23]

Several laboratory tests, including the NLR, D-Dimer, and platelet to lymphocyte ratio (PLR), are used as predictors of thromboembolic events. Neutrophil to lymphocyte ratio is calculated by dividing the number of neutrophils by the number of lymphocytes. An increased neutrophil count indicates systemic inflammation, while a decreased lymphocyte count indicates sustained stress due to illness. Neutrophils have been implicated in blood clot formation through the release of neutrophil extracellular traps (NETs). This suggests the potential use of NLR as a biological marker for DVT.[24] Compared to D-dimer, NLR is easier to assess and widely available in healthcare facilities as it does not require specialized testing.

D-dimer is a commonly used marker for diagnosing DVT, and its measurement improves sensitivity and specificity in DVT and PE diagnosis. Guidelines from the American Society of Haematology recommend using D-dimer as an initial test to reduce the need for diagnostic imaging in low-risk VTE patients. D-dimer concentration increases shortly after surgery but returns to normal levels within a week. However, D-dimer tests are only useful for ruling out acute VTE and are not specific enough to confirm the diagnosis.[25,26]

D-dimer levels increase in patients with conditions such as heart attacks, pneumonia, sepsis, cancer, and post-surgery, as well as during the second or third trimester of pregnancy. As a result, D-dimer is not very useful in hospitalized patients since its levels often rise due to other systemic diseases. Therefore, it is important to incorporate other more specific markers in diagnostic assessments.[25,26]

In a study conducted by Rinaldi *et al.*[26], the diagnostic abilities of the NLR and D-dimer for DVT were compared. The study found that in individuals with a low probability of DVT based on the Wells score, NLR exhibited higher sensitivity than D-dimer (65 vs 60%). However, for individuals with a high probability of DVT, NLR showed higher specificity than D-dimer (69.2 vs 53.8%). Due to its superior sensitivity in the low probability group, NLR could serve as an additional and more effective screening tool. Additionally, NLR is easily accessible and does not require specialized testing, enabling quick evaluation of symptomatic patients suspected of having DVT and reducing the need for ultrasound in patients with a low probability of DVT.[26] These findings contrast with a study by Kadek, which reported that D-dimer had higher sensitivity than NLR, and NLR exhibited better specificity than D-dimer in DVT cases.[27]

Recent studies have also considered the PLR as a predictor of VTE in cancer patients and after surgery. According to Yamagata *et al.*[28] the platelet count is higher in the group with VTE compared to the group without VTE, and the platelet count is significantly associated with cancer patients. Platelet count is related to the risk of symptomatic VTE in cancer patients but not in subjects without cancer. Platelet to lymphocyte ratio is recommended for VTE diagnosis instead of relying solely on platelet count or lymphocyte count because it encompasses the inflammatory values of both blood cell types.[27]

Moreover, both thrombocytosis (elevated platelet count) and lymphocytopenia (low lymphocyte count) are associated with increased systemic inflammation, and PLR has been identified as an independent risk factor for high inflammatory processes, serving as a novel marker that combines these two haematological indices.[27] Grilz *et al.*[29] observed a significant relationship between PLR and the occurrence of VTE in 1469 cancer patients. Kurtipek *et al.*,[19] reported higher PLR values in 71 patients with acute PE compared to healthy controls, suggesting that PLR may be linked to impaired arterial endothelial function in the lungs. Their study demonstrated that PLR values above 260 are an independent predictor of VTE cases in cancer patients.[19,30]

The combination of NLR and PLR yields sensitive, specific, and accurate results in identifying DVT events. Recent findings also indicate a moderate and significant association between the combination of NLR and PLR and the occurrence of DVT.[31] However, it is still recommended to use D-dimer followed by Doppler ultrasonography in the lower extremities as the primary diagnostic approach. This is because research results demonstrate that D-dimer has higher sensitivity compared to NLR, PLR, or the combination of NLR and PLR.[27]

Farah *et al.*[32] suggested that mean platelet volume (MPV) serves as an important inflammatory marker in lung and pancreatic cancer patients. Platelets play a significant role in clot formation, which is relevant to the development of VTE. Mean platelet volume, along with other markers related to platelet function and count, is commonly used in haematological assessments. Evidence indicates that MPV can reflect platelet turnover, as larger platelets tend to be younger and more reactive compared to smaller platelets. The association between increased MPV and the risk of VTE and cardiovascular risk has been well-established.[32]

McLeod *et al.*[33] reported that NLR levels at the time of DVT diagnosis are associated with a higher risk of thromboembolic and the occurrence of proximal DVT, which refers to thrombosis in veins closer to the heart. Proximal DVT includes thrombosis in the popliteal vein or above, while distal DVT refers to thrombosis in the calf veins.[33] These findings align with previous study, which indicated that NLR levels above the 95th percentile is associated with a 2.4 times higher risk of VTE.[34] Furthermore, the study suggests that NLR values in the highest quartile (>2.6) are linked to the development of post-thrombotic syndrome (PTS), supporting the notion that inflammation plays a significant role in the pathophysiology of PTS.[33]

Although the levels of white blood cells (WBC) were similar between the healthy control group and DVT patients, patients with DVT exhibited statistically higher levels of MPV, D-dimer, platelets, and NLR. Specifically, in the subgroup of patients with extensive DVT involving the iliac and femoral veins, there were significant increases in WBC levels, platelets, NLR, and the fibrinogen-to-albumin ratio (FAR). No significant differences were observed for other variables between the two groups. However, when considering the extent of DVT (proximal DVT and distal DVT), postoperative NLR and WBC levels were significantly higher in the proximal DVT group compared to the distal DVT group, which is consistent with previous research.[35] The underlying mechanism explaining this phenomenon is still unknown.

Kuplay *et al.*[36] showed that patients with distal thrombus had higher values of lymphocytes, monocytes, eosinophils, and basophils compared to proximal thrombus. Meanwhile, proximal thrombus had significantly higher neutrophil values compared to distal thrombus. As for NLR values, there was a significant difference, where proximal NLR was higher than distal NLR ($p<0.0001$). Previous research indicated that patients with proximal thrombus had a higher mean NLR compared to patients with distal thrombus (4.40 ± 4.28 vs 3.54 ± 3.55; p=0.05). This indicates the presence of increased inflammation in patients with DVT with a more proximal thrombus location.[36]

This study brings forth several innovations, particularly in its thorough depiction and assessment of VTE occurrences in Indonesia. Notably, earlier research on VTE in the country concentrated solely on observing the incidence and characteristics of VTE patients over a two-year period, while this study extends this observation to encompass a five-year timeframe.[4] Furthermore, an analysis of NLR parameters and trends were conducted, serving as markers for VTE patients. In contrast to previous studies, which focused on the general VTE population, this study specifically addresses VTE events occurring post-surgery.[8] This study covers the period from 2016 to 2021, reflecting advancements and further developments in VTE detection in Indonesia. The limitations of this study stem from the reliance on electronic medical records, which were only widely implemented in this center from the beginning of 2016. Consequently, there is a possibility of overlooking some data. Researchers attempted to address this issue by expanding the scope of diagnosis codes searched (from I82 extended to I80), but the risk remains.

CONCLUSION

In conclusion, VTE occurs in 0.21% of post-operative patients in Dr. Sardjito General Hospital, with the highest incidence observed in post-gynecological surgery patients. The NLR can serve as a diagnostic tool for VTE in extremities, as an elevated NLR indicates the presence of a more proximal thrombus.

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