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Assessment of Oral Anticoagulant Reversal Strategies in Emergency Surgery: Insights from a Prospective Study

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Abstract **Original Research Article**

Introduction: The management of thrombotic risk in clinical medicine has been a longstanding challenge. Oral anticoagulants, specifically vitamin K antagonists (VKAs) like warfarin, have been used for over fifty years. However, VKAs present significant challenges such as frequent monitoring and dietary interactions. Direct oral anticoagulants (DOACs) were developed to address these limitations, offering simplified dosing and fewer interactions. Both VKAs and DOACs, however, pose challenges in managing major bleeding and urgent surgical interventions. ***Methods***: This prospective study, conducted at Mohammed V Military Hospital in Rabat from January 2022 to January 2023, examined the clinical practice, efficacy, and safety of different treatment strategies in patients on oral anticoagulants (VKAs and DOACs) requiring emergency surgery within 24 hours of hospital admission. Inclusion criteria included being over 18 years of age, on anticoagulant therapy, and requiring emergency surgery. Patients were evaluated for bleeding before and after surgery, use of hemostatic agents, blood loss, transfusions, and adverse events. ***Results***: A total of 69 patients were included, with 48 treated with VKAs and 21 with DOACs. The mean age was 63.8 years (range 36-78), with a mean age of 62.5 years (±10.2) for the VKA group and 66.7 years (±9.1) for the DOAC group (p = 0.44). There was no significant difference in delays to surgery between the VKA (68%) and DOAC (66.6%) groups for surgeries performed within 24 hours. Hemostatic treatment varied significantly, with more VKA patients receiving resh frozen plasma (77% vs. 52%) and more DOAC patients receiving prothrombin complex concentrates (48% vs. 23%). Bleeding complications were observed in 12.5% of VKA patients and 9.5% of DOAC patients. Thromboembolic events were observed in one patient within 30 days, specifically, a pulmonary embolism occurring on day 3 in a patient who underwent surgery for a hip fracture. The mortality rate was 4.35%, with three deaths recorded among the study population. ***Discussion***: Our study highlighted the differences in hemostatic treatment management between VKA and DOAC patients. The findings suggest more frequent use of fresh frozen plasma for VKA patients and prothrombin complex concentrates for DOAC patients, reflecting differences in clinical practices. Despite these differences, there was no significant impact on surgical delays or bleeding complications between the two groups. ***Conclusion***: The study underscores the importance of tailored hemostatic management strategies for patients on anticoagulants requiring emergency surgery. Further large-scale, multicenter studies are needed to validate these findings and improve clinical protocols, ultimately enhancing patient outcomes in emergency surgical settings involving anticoagulant therapy.Decrease medical as well as financial burden, hence improving the management of cirrhotic patients. These predictors, however, need further work to validate reliability.

Keywords: Oral Anticoagulants, Vitamin K Antagonis, Direct Oral Anticoagulants (DOAC), Anticoagulation Reversal, Emergency Surgery, Bleeding Complications.

INTRODUCTION

In the realm of clinical medicine, the management of thrombotic risk has been a longstanding challenge. For over fifty years, clinicians have relied on oral anticoagulants to navigate this delicate balance, with the earliest iterations being vitamin K antagonists (VKAs) like warfarin, initially discovered in spoiled sweet clover during the early 20th century [1]. Despite their efficacy in reducing stroke risk, particularly in patients with atrial fibrillation [2], VKAs have presented clinicians with notable challenges, including the need for frequent monitoring, dietary interactions, and the risk of intracranial hemorrhage (ICH). Responding to these

limitations, the development of Direct oral anticoagulants (DOACs) emerged over the past decade, offering simplified dosing, fewer interactions, and a reduced risk of ICH compared to VKAs [3]. However, both VKAs and DOACs pose significant challenges, particularly in managing major bleeding complications and urgent surgical interventions.

The pursuit of effective anticoagulant reversal strategies has become increasingly urgent, with specific agents approved for VKAs, dabigatran, and more recently, andexanet alfa for Factor Xa inhibitors (FXaIs) [4]. Nevertheless, contextualizing trial results remains complex, given the ethical considerations precluding placebo arms in bleeding patients or those requiring urgent surgery. Moreover, additional challenges arise in the form of logistical hurdles, such as product vailability and clinician understanding of recommended usage, particularly in emergency settings.

Against this backdrop, understanding current clinical practices and institutional protocols surrounding anticoagulant reversal agents becomes crucial. Hence, our study aims to address these gaps by presenting data from a prospective study conducted at the Emergency department of our institution. Focusing on the clinical practice, efficacy, and safety of different treatment strategies in patients on oral anticoagulants, including VKAs and DOACs, who required emergency surgical intervention, our research seeks to shed light on the intricacies of managing anticoagulation in emergency settings. Throughout investigation, we endeavor to provide valuable insights that can inform and enhance clinical decision-making in this challenging yet essential aspect of patient care.

MATERIALS AND METHODS

In our prospective study conducted at the Emergency department, we examined the clinical practice, efficacy, and safety of different treatment strategies in patients on oral anticoagulants, including vitamin K antagonists and direct oral anticoagulants, requiring emergency surgery. The inclusion criteria were as follows: being over 18 years of age, being on anticoagulant therapy with vitamin K antagonists or direct oral anticoagulants, and requiring emergency surgery (not related to major bleeding) within 24 hours of hospital admission. Patients were followed prospectively after hospitalization between January 2022 and January 2023. Clinical evaluation criteria included bleeding before and/or after surgery, as well as the need for hemostatic agents or drug antidotes. Evaluation criteria included bleeding complications, Thrombo embolic events, in hospital mortality, surgeons' satisfaction with perioperative and postoperative hemostasis, outcomes after the use or non-use of reversal agents, and the frequency of adverse events.

RESULTS

- **Demographic Data of Included Patients**

Overall, 69 patients were included in the study, with 48 patients treated with VKA (phenprocoumon) and 21 patients treated with DOACs. In the DOAC group, 52% (11 out of 21) of patients were treated with apixaban, 33.3% (7 out of 21) with rivaroxaban, and 14.2% (3 out of 21) with dabigatran. The mean age of the cohort was 63.8 years (range 36-78 years), with the VKA group having a mean age of 62.5 years (±10.2) and the DOAC group having a mean age of 66.7 years (±9.1), with the difference not reaching statistical significance ($p = 0.44$).In terms of gender distribution, 45% (31/69) of the total patient population were female. Among those treated with VKA, 42% (20/48) were women, compared to 52% (11/21) in the DOAC group ($p = 0.532$, Chi-square test). At the time of admission, the incidence of acute renal failure was similar in both groups, with 6% (3/48) in the VKA group and 10% (2/21) in the DOAC group ($p = 0.428$, Chi-square test). **Table 1**.

- **Surgical Indications**

The indications for emergency surgery exhibited variability among the patient cohort. Trauma-related surgeries constituted the most prevalent type, representing 32% (22/69) of all cases. This distribution was consistent across VKA-treated patients (31%, 15/48) and DOAC-treated patients (33%, 7/21) ($p = 0.721$). Urgent laparotomies were conducted in 29% (20/69) of patients, with similar proportions observed between the VKA (29%, 14/48) and DOAC (29%, 6/21) groups ($p = 0.183$).

Emergent neurosurgeries were relatively infrequent, accounting for only 3% (2/69) of cases, with one case each in the VKA (2%, 1/48) and DOAC (5%, 1/21) groups ($p = 0.821$). Likewise, emergent vascular surgeries occurred in 4% (3/69) of patients, with comparable distribution between the VKA (4%, 2/48) and DOAC (5%, 1/21) groups ($p = 0.531$). There was a singular instance of surgery for an abscess in the VKA group (1%, 1/48), with no corresponding cases in the DOAC group (not calculable due to zero count). Other types of surgeries were performed in 30% (21/69) of patients, with 31% (15/48) in the VKA group and 29% (6/21) in the DOAC group ($p = 0.672$) **Table 2.**

- **Co-Medications, Indication for Anticoagulation, and Bleeding Risk**

Co-medication with antiplatelet drugs was observed in 13% (9/69) of patients, with a distribution of 13% (6/48) in the VKA group and 14% (3/21) in the DOAC group ($p = 0.823$). The use of anti-inflammatory drugs was reported in 4% (3/69) of patients, with 4% (2/48) in the VKA group and 5% (1/21) in the DOAC group ($p = 0.821$). The primary indication for anticoagulation was atrial fibrillation, which accounted for 74% (51/69) of cases. This included 75% (36/48) of patients in the VKA group and 71% (15/21) in the DOAC

group (p = 0.724). Other indications included venous thrombosis (6%, 4/69), postoperative prophylaxis (6%, 4/69), arterial thrombosis (6%, 4/69), artificial heart valve (3%, 2/69), and other reasons (7%, 5/69), with no significant differences between the groups 0.481). The modified HASBLED score, excluding the criterion "stability of INR," was 2 in both groups, with a range of 0 to 5 (p = 0.672). **Table 3.**

- **Hemostatic Treatment Management in Patients Undergoing Emergency Surgery**

The comparison of anticoagulant reversal strategies between patients on VKAs and those on DOACs revealed notable disparities. VKA-treated patients received fresh frozen plasma significantly more frequently than those on DOACs (77% vs. 52%, respectively; p = 0.039). Conversely, DOAC-treated patients were more commonly administered prothrombin complex concentrates (PCC) compared to VKA-treated patients (48% vs. 23%, respectively; p = 0.007). Vitamin K administration was significantly more prevalent among VKA-treated patients than those on DOACs (62% vs. 14%, respectively; p < 0.001). Notably, the need for red blood cell transfusions was higher among VKA-treated patients compared to DOAC-treated patients (52% vs. 33%, respectively), although this disparity did not reach statistical significance (p = 0.156). Platelet concentrates were utilized similarly in both groups, with no statistically significant difference observed (p = 0.728). Remarkably, a substantially higher proportion of DOAC-treated patients received no hemostatic treatment compared to VKA-treated patients (62% vs. 3%, respectively; p < 0.001). It is noteworthy that no patient in our study received a specific antidote, primarily due to its unavailability at the time of recruitment. **Table 4.**

- **Delay in Emergency Surgery**

A comparison was conducted between the two groups of patients to assess delays in emergency surgery. The data are presented at the Table 5.

The analysis reveals that 68% of the VKA group and 66.6% of the DOAC group underwent surgery in less than 24 hours without any delay. In each group, 31% of the VKA group and 33.3% of the DOAC group experienced a delay of more than 24 hours. There was no significant difference in the incidence of delays in emergency surgery between the two groups. In other words, the type of anticoagulation therapy (VKA vs. DOAC) does not significantly affect the likelihood of experiencing a delay in emergency surgery.

- **Bleeding Complications**

Clinically significant bleeding at the surgical site occurred in 9.5% of patients receiving DOACs (2/21) and in 12.5% of patients receiving VKAs (6/48) within 30 days post-admission. Notably, the incidence of bleeding at the surgical site did not significantly differ based on the administration of preoperative hemostatic treatment. Among patients receiving DOACs, 12.5% (1/8) of those who underwent preoperative hemostatic treatment experienced bleeding, compared to 17% (8/47) of patients on VKAs who received similar treatment. Conversely, for patients not receiving preoperative hemostatic treatment, 7.7% (1/13) of those on DOACs experienced bleeding, while none of the patients on VKAs experienced bleeding. The calculated p-value for the difference between these groups was 0.45, indicating no significant distinction.

Among VKA patients with hemorrhagic complications (8/8), all had an INR above 1.5 at admission, but only three of these patients received PCC as preoperative hemostatic treatment.

- **Thrombo Embolic Events TTE and in Hospital Mortality**

Thromboembolic events within 30 days were observed in one patient during this study. We noted a pulmonary embolism occurring on day 3 in a patient who underwent surgery for a hip fracture. This event represents approximately 1.45% (1 out of 69 patients) of our cohort.

In our study, we observed a mortality rate of approximately 4.35% (3 out of 69 patients). One patient, under VKAs therapy, underwent surgical revision for a postoperative intracranial hematoma that re-bled; this patient died 72 hours after the revision. Another patient, also under VKAs, underwent emergency laparotomy for an obstructive syndrome and died due to refractory shock from gastrointestinal bleeding. Lastly, a patient operated for a hip fracture died 4 days after surgery; the cause of death was a pulmonary embolism, a complication potentially linked to oral anticoagulant therapy.

Table 1 : Baseline Characteristics of Patients

Characteristics of patients at baseline	Total (n=69)	VKA (n=48)	DOAC (n=21)	p-Value
Female sex	31 (45%)	20 (42%)	11 (52%)	0.532
Age (years)	63.8 (36–78)	62.5 (±10.2)	66.7 (±9.1)	0.44
Acute renalfailure	5 (7%)	3 (6%)	2 (10%)	0.428

Table 2 : Surgical indications

Surgical Indications	Total (n=69)	VKA (n=48)	DOAC (n=21)	p-Value
Traumatology surgery	22 (32%)	15 (31%)	7 (33%)	0.721
Emrergent laparotomy (EL)	20 (29%)	14 (29%)	6 (29%)	0.183
Emergent Neuro surgery (EN)	2 (3%)	1 (2%)	1 (5%)	0.821

Surgical Indications	Total (n=69)	VKA (n=48)	DOAC (n=21)	p-Value
Emergent Vascular surgery EVS	3 (4%)	2 (4%)	1 (5%)	0.531
Excisio drainage Abscess	1 (1%)	1 (2%)	0 (0%)	--
Other	21 (30%)	15 (31%)	6 (29%)	0.672

Table 3: Co-medication, and Bleeding Risk Factors in AVK and DOAC Treatment Groups

Characteristics of patients at baseline	Total (n=69)	VKA (n=48)	DOAC (n=21)	p-Value
Antiplatele tdrugs	9 (13%)	6 (13%)	3 (14%)	0.823
Anti-inflammatory drugs	3 (4%)	2 (4%)	1 (5%)	0.821
Indication of anticoagulants drugs				
Atrial fibrillation	51 (74%)	36 (75%)	15 (71%)	0.724
Venous thrombosis	4 (6%)	3 (6%)	1 (5%)	0.921
Postoperative prophylaxis	4 (6%)	2 (4%)	2 (10%)	0.235
Arterial thrombosis	4 (6%)	2 (4%)	2 (10%)	0.235
Mechanic Artificial heart valve	2 (3%)	2 (4%)	0 (0%)	--
Bleeding risk				
Other	5 (7%)	4 (8%)	1 (5%)	0.672
CHADS-VASC Score	5 (2–9)	5 (2–9)	5 (2–8)	0.798
HASBLED Score	3 (0–5)	2 (0–4)	3 (0–5)	0.481
Modified HASBLED Score	2 (0–5)	2 (0–4)	3 (0–5)	0.672

Table 4: Comparison of Hemostatic Treatments between Patients on VKAs and DOACs Undergoing Emergency Surgery

Hemostatic Treatment	VKA (n=48)	DOAC (n=21)	p-Value
Freshfrozen plasma	37 (77%)	11 (52%)	0.039
Prothrombin complex concentrates (PCC)	11 (23%)	10 (48%)	0.007
Vitamin K	30 (62%)	6 (14%)	< 0.001
Red bloodcell transfusion	25 (52%)	7 (33%)	0.156
Platelet concentrates	8 (17%)	3 (14%)	0.728
No hemostatic treatment	1 (3%)	13 (62%)	< 0.001

Table 5 : Delay in Emergency Surgery

Delay in Emergency Surgery (hours)	VKA (n = 48)	DOAC (n = 21)	p-value
No delay	33 (68%)	14(66,6%)	0.872
more than 24 hours	15(31%)	7(33,3%)	0.872

DISCUSSION

The management of anticoagulation perioperatively presents a complex challenge, necessitating a delicate balance between minimizing thromboembolic and hemorrhagic risks [5]. Our prospective study, conducted at the Mohammed V Military Teaching Hospital in Rabat, focused on analyzing the utilization of hemostatic agents in patients receiving direct oral anticoagulants (DOACs) or vitamin K antagonists (VKAs) who required emergency surgery within 24 hours of hospital admission. With a median age of 63,8 (Range 36-78) years, our patient cohort primarily received anticoagulation for atrial fibrillation, with traumatic surgery and urgent laparotomy for acute abdomen being common indications for emergency surgery.

While our study shares similar demographic characteristics with those conducted by Godon *et al*., from the GIHP-NACO Registry [7], and Last *et al*., from the RADOA Registry [8], such as gender distribution and incidence of acute renal failure, there is a notable difference in the mean age of the cohorts. But our cohort exhibited a mean age of 63.8 years (Range: 36-78 years), which contrasts with the higher median ages reported in the French and German studies, where the median ages were 79 years and 76 years, respectively. This disparity in age distribution might be attributed to differences in life expectancy between regions, possibly influencing the age composition of the patient populations in each study. Also we noted a lower rate of procedural delays (20% vs. 43% in the French registry) and a reduced incidence of bleeding (7% vs. 13% in the French registry). These differences suggest potentially more effective bleeding management within our cohort, with 70% of DOAC patients receiving hemostatic treatment.

Similarly, contrasting our results with those of Last *et al*., from the RADOA registry [8], significant disparities were evident. While our study reported a 30-day in-hospital mortality rate of 4.35% (3 out of 69 patients)., akin to the German study, our cohort displayed a higher proportion of DOAC-treated patients receiving hemostatic treatment (70% vs. 16% in the German study). In contrast, VKA patients in the German study required more hemostatic agents than DOAC patients. These variations in bleeding management between

cohorts may stem from differences in treatment protocols or distinct clinical practices among our respective institutions.

Throughout our study, we frequently observed the utilization of fresh frozen plasma (FFP) for urgent VKA reversal, contrasting with current guidelines advocating for the primary use of four-factor prothrombin complex concentrates (PCCs) in such instances [9]. Moreover, our study demonstrated a similar proportion of VKA and DOAC patients receiving PCC, diverging from the German study where PCC use was more common in VKA patients. These discrepancies raise questions about the relative effectiveness of different hemostatic treatments in VKA- and DOAC-treated patients, as well as variations in prescribing practices across institutions.

Despite similar patient demographic characteristics, significant differences were observed in the management of surgical emergencies and hemorrhagic complications between our study and previous investigations [7, 8]. These disparities underscore the importance of considering local differences in treatment protocols and clinical practices when managing anticoagulated patients requiring emergency surgery.

Our study had some limitations, including patient selection bias and non-standardized decisions regarding hemostatic treatment management. Additionally, the small sample size limits the generalizability of our results to the corresponding patient population.

For VKA-treated patients experiencing major bleeding events or requiring emergency surgery, various options exist for reversing VKA anticoagulant effects. Prothrombin complex concentrates (PCCs) are an effective option for rapidly restoring hemostasis by providing necessary coagulation factors [10]. In contrast, DOAC-treated patients necessitate specific reversal agents, such as idarucizumab for dabigatran, or andexanet alfa for factor Xa inhibitors, to manage bleeding episodes effectively [12, 13]. Emerging compounds like ciraparantag offer potential effectiveness, though further clinical trials are warranted to assess their utility [14].

Managing anticoagulated patients requiring emergency surgery poses a significant clinical challenge. While hemostatic options like PCCs and specific reversal agents play crucial roles in managing bleeding and preventing thromboembolic complications, further studies are essential to comprehensively understand their effectiveness and safety across diverse clinical scenarios. Larger multicenter studies could provide valuable insights into the comparative effectiveness of different hemostatic agents, while integrating new monitoring and treatment technologies could enhance patient management and mitigate complications associated with perioperative anticoagulation [15-16].

CONCLUSION

Our study underscores the critical importance of tailored hemostatic management for patients undergoing emergency surgery while on anticoagulant therapy. Our findings highlight the imperative for anesthesiologists, surgeons, and emergency physicians to familiarize themselves with standardized protocols that guide the care of these patients.

While our study has limitations, such as patient selection bias and the absence of standardized treatment protocols, it provides valuable insights into optimizing care in these complex clinical scenarios. The observed differences in bleeding management between our study and previous research further emphasize the necessity for these standardized protocols and larger-scale prospective studies to validate and refine our findings.

By establishing evidence-based practices, healthcare providers can better tailor hemostatic strategies to meet the unique needs of patients undergoing emergency surgery while on anticoagulant therapy. Ultimately, the optimization of hemostatic management in these settings holds significant potential to improve patient outcomes and enhance the overall quality of care. Through continued research and collaborative efforts, we can strive towards safer and more effective approaches, ultimately benefiting patient care in emergency surgical settings

Consent: As per international standard or university standard, patient's consent has been collected and preserved by the authors.

Ethical Approval: As per international standards or university standards written ethical approval has been collected and preserved by the author(s).

Competing Interests: Authors have declared that no competing interests exist.

Authors' Contributions

This work was carried out in collaboration among all authors. Authors AB and HH conceptualized the research work, did data curation, software work, performed the methodology validation and wrote the original draft, reviewed and edited. Author MC did data curation, visualization, performing the methodology, writing, reviewing and editing. Authors AB and KA supervised, validated, wrote, reviewed and edited the manuscript. All authors read and approved the final manuscript.

REFERENCES

1. Zirlik, A., & Bode, C. (2017). Vitamin K antagonists: relative strengths and weaknesses vs.

direct oral anticoagulants for stroke prevention in patients with atrial fibrillation. *Journal of thrombosis and thrombolysis*, *43*(3), 365-379.

2. Sommerauer, C., Schlender, L., Krause, M., Weissbach, S., Rieckert, A., Martinez, Y. V., ... & Soennichsen, A. (2017). Effectiveness and safety of vitamin K antagonists and new anticoagulants in the prevention of thromboembolism in atrial fibrillation in older adults–a systematic review of reviews and the development of recommendations to reduce inappropriate prescribing. *BMC geriatrics*, *17*, 73-98.
3. Yao, X., Abraham, N. S., Sangaralingham, L. R., Bellolio, M. F., McBane, R. D., Shah, N. D., & Noseworthy, P. A. (2016). Effectiveness and safety of dabigatran, rivaroxaban, and apixaban versus warfarin in nonvalvular atrial fibrillation. *Journal of the American Heart Association*, *5*(6), e003725.
4. IMS Health. IMS data US National Prescription Audit; MAT (movingannual total) 2017–2018. Availableat: [insert link]. Accessed February 1, 2019.
5. Levy, J. H., Connors, J. M., Steiner, M. E., Douketis, J., & Spyropoulos, A. C. (2020). Management of oral anticoagulants prior to emergency surgery or with major bleeding: A survey of perioperative practices in North America: Communication from the Scientific and Standardization Committees on Perioperative and Critical Care Haemostasis and Thrombosis of the International Society on Thrombosis and Haemostasis. *Research and practice in thrombosis and haemostasis*, *4*(4), 562-568.
6. Kassahun, W. F. T., Wagner, T. C., Babel, J., & Mehdorn, M. (2021). The effects of oral anticoagulant exposure on the surgical outcomes of patients undergoing surgery for high-risk abdominal emergencies. J. *Gastrointest. Surg*, *25*, 2939–2947. DOI: 10.1007/s11605-021-04964-9
7. Godon, A., Gabin, M., Levy, J. H., Huet, O., Chapalain, X., David, J. S., ... & Albaladejo, P. (2022). Management of urgent invasive procedures in patients treated with direct oral anticoagulants: An observational registry analysis. *Thrombosis Research*, *216*, 106-112.
8. Last, J., Herrmann, E., Birschmann, I., Lindau, S., Konstantinides, S., Grottke, O., ... & Lindhoff-Last, E. (2024). Clinical Course and Management of Patients with Emergency Surgery Treated with Direct Oral Anticoagulants or Vitamin K Antagonists—Results of the German Prospective RADOA-Registry. *Journal of Clinical Medicine*, *13*(1), 272.
9. Tomaselli, G. F., Mahaffey, K. W., Cuker, A., Dobesh, P. P., Doherty, J. U., Eikelboom, J. W., ... & Wiggins, B. S. (2017). 2017 ACC expert consensus decision pathway on management of bleeding in patients on oral anticoagulants: a report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways. *Journal of the American College of Cardiology*, *70*(24), 3042-3067.
10. Goldstein, J. N., Refaai, M. A., Milling, T. J., Lewis, B., Goldberg-Alberts, R., Hug, B. A., & Sarode, R. (2015). Four-factor prothrombin complex concentrate versus plasma for rapid vitamin K antagonist reversal in patients needing urgent surgical or invasive interventions: a phase 3b, open-label, non-inferiority, randomised trial. *The Lancet*, *385*(9982), 2077-2087.
11. Steiner, T., Poli, S., Griebe, M., Hüsing, J., Hajda, J., Freiberger, A., ... & Veltkamp, R. (2016). Fresh frozen plasma versus prothrombin complex concentrate in patients with intracranial haemorrhage related to vitamin K antagonists (INCH): a randomised trial. *The Lancet Neurology*, *15*(6), 566-573.
12. Kaide, C. G., & Gulseth, M. P. (2020). Current strategies for the management of bleeding associated with direct oral anticoagulants and a review of investigational reversal agents. *The Journal of Emergency Medicine*, *58*(2), 217-233.
13. Majeed, A., Ågren, A., Holmström, M., Bruzelius, M., Chaireti, R., Odeberg, J., ... & Schulman, S. (2017). Management of rivaroxaban-or apixaban-associated major bleeding with prothrombin complex concentrates: a cohort study. *Blood, The Journal of the American Society of Hematology*, *130*(15), 1706-1712.
14. Singh, T., Maw, T. T., Henry, B. L., Pastor-Soler, N. M., Unruh, M. L., Hallows, K. R., & Nolin, T. D. (2013). Extracorporeal therapy for dabigatran removal in the treatment of acute bleeding: a single center experience. *Clinical Journal of the American Society of Nephrology*, *8*(9), 1533-1539.
15. Ocampo, D. A. M., Cruz, N. S. S., & González, J. E. C. (2023). The Effects on Surgical Gastorintestinal Diseases Urgent Due to the Covid-19 Pandemic. *Asian Journal of Research in Surgery*, *6*(1), 137-137.
16. Kaatz, S., Mahan, C. E., Nakhle, A., Gunasekaran, K., Ali, M., Lavender, R., & Paje, D. G. (2017). Management of elective surgery and emergent bleeding with direct oral anticoagulants. *Current cardiology reports*, *19*, 1-10.