Panacea Journal of Medical Sciences 2024;14(2):573–578

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Panacea Journal of Medical Sciences

Journal homepage: http://www.pjms.in/

Original Research Article

A study on thrombotic microangiopathy spectrum disorders in snake bite

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ARTICLE INFO

Article history:
Received 14-02-2023
Accepted 15-06-2023
Available online 13-08-2024

Keywords:
Hemotoxic toxin syndrome
Venom induced Consumptive coagulopathy (VICC)
Thrombotic microangiopathy
Microangiopathic hemolytic anemia (MAHA)

ABSTRACT

Background: Hemotoxic toxin syndrome, carry a high risk of hemorrhage and death. Snake venom have toxins that cause coagulopathy in a two different mechanism of actions. The snake toxins act as anticoagulant which inhibit clotting cascade or act as procoagulant toxins which activate the clotting cascade and consume clotting factors. The consumption coagulopathy in snake bite is referred to as Venom Induced Consumptive Coagulopathy (VICC). VICC is marked by prolonged clotting time and clotting factor deficiencies and an elevated d-dimer. VICC has a rapid onset and resolves with inactivation of toxins and synthesis of new clotting factors. A subset of VICC develops Thrombotic Microangiopathy (TMA). TMA is different and poorly understood hemotoxic syndrome.

Materials and Methods: We performed a prospective analytical study of all consenting adult patients presenting to Thanjavur medical college, Tamil Nadu with suspected or with clear snake bite history within 24 hours and all Patients with thrombocytopenia less than 1.5 lakh in the first 3 days of hospital stay. All patients with Pre-existing kidney disease with serum creatinine more than 1.4 prior to snake bite and ultrasound evidence of chronic kidney disease were excluded. The study was done from January 2021 to January 2022.

Results: TMA spectrum disorders, including isolated thrombocytopenia, MAHA, and renal failure, are primarily hematological and renal, with severe presentations involving thrombocytopenia, MAH, schistiocytes, and renal failure. Clinicians should monitor tests, administer ASV early, and anticipate further TMA evidence to prevent complications.

Conclusion : Thrombotic microangiopathy should be anticipated in all Hemotoxic snake bite. So early recognition and appropriate management will save the patient lives.

1. Introduction

Snake bite envenomation leads to significant life threatening toxin mediated clinical syndromes.[1–5] Early access to medical care is important and antivenom is the standard of care for envenomed patients. Many victims do not attend health care centers or hospitals but rely on traditional and native treatments, which in turn increase the burden of the disease by increasing the mortality. Available data shows 4.5 to 5.4 million people[6–9] get bitten by snake annually. Of this 1.8 to 2.7 million severely affected. Snake bite is classified as category A neglected tropical disease by WHO. They affect over 1 billion people in resource limited setting carrying significant economic cost for low to middle income countries. There may be limited access to antivenom, blood products, specialized hospital and intensive care and ventilators. WHO set a global target for 50% reduction[10] in snake bite associated mortality and morbidity. Hemotoxic toxin syndrome,[11] carry a high risk of hemorrhage and death. Snake venom have toxins that cause coagulopathy in a two different mechanism of actions. The snake toxins act as anticoagulant[12–17] which inhibit clotting cascade or act as procoagulant[12–18] toxins which activate the clotting

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https://doi.org/10.18231/j.pjms.2024.103

cascade and consume clotting factors. The consumption coagulopathy in snake bite is referred to as Venom Induced Consumptive Coagulopathy (VICC).[1,2,19–27] VICC is marked by prolonged clotting time and clotting factor deficiencies and an elevated ddimer. VICC has a rapid onset and resolves with inactivation of toxins and synthesis of new clotting factors. A subset of VICC develops Thrombotic Microangiopathy (TMA).[1,2,19,28–30] TMA is different and poorly understood hemotoxic syndrome.

2. Materials and Methods

2.1. Study design

Prospective analytical study

2.2. Study period

January 2021 to January 2022.

2.3. Study setting

Department of general medicine, Thanjavur.

2.4. Participants

All consenting adult patients presenting to Thanjavur medical college with suspected or with clear snake bite history within 24 hours and Patients with thrombocytopenia less than 1.5 lakh in the first 3 days of hospital stay. 91 patients both males and females with history or suspected history of snake bite is taken for the study. Pre-existing kidney disease with serum creatinine more than 1.4 prior to snake bite and ultrasound evidence of chronic kidney disease are excluded.

2.5. Study procedure

After explaining the purpose, procedure, benefits and risks involved in the study, patient's information study was handed over to the study subjects. After obtaining informed written consent, the patients with snakebite who fits into the eligibility criteria enter into the study. The study subjects were subjected to through clinical history examination and necessary laboratory investigations were done. Data was collected using pre- structured proforma.

2.6. Study variables

1. Admission characteristics- nature of bite, symptoms, signs
2. Clinical syndrome – local swelling, pure hemotoxicity, neurotoxicity and Acute Renal Failure Clinical findings- signs of bleeding, confusion, headache, aphasia, dysarthria, breath holding time, neck holding time, fever, jaundice, haematuria, oliguria
3. Laboratory parameters- complete blood count, prothrombin time, activated partial prothrombin time, platelets count, peripheral smear for schistiocytes, retic count, serum lactate dehydrogenase level, serum bilirubin, d- dimer.

3. Results

TMA spectrum disorders include isolated thrombocytopenia, thrombocytopenia with MAHA, thrombocytopenia, MAHA and renal failure. The most severe presentation is with thrombocytopenia, MAHA, schistiocytes and renal failure associated with significant mortality. TMA spectrum disorders affect predominantly the hematological system and renal system and the neurological finding are very low. Clinicians need to have a very high suspicion of TMA in snake envenomation syndromes. Easily available tests including complete blood count, platelet count, schistiocytes, hemoglobin, lactate dehydrogenase, creatinine, bilirubin and d-dimer should be monitored for first few days as the patient enters VICC. Early and appropriate administration of ASV helps in preventing the complications. And anticipation for the further evidence of TMA must be kept.

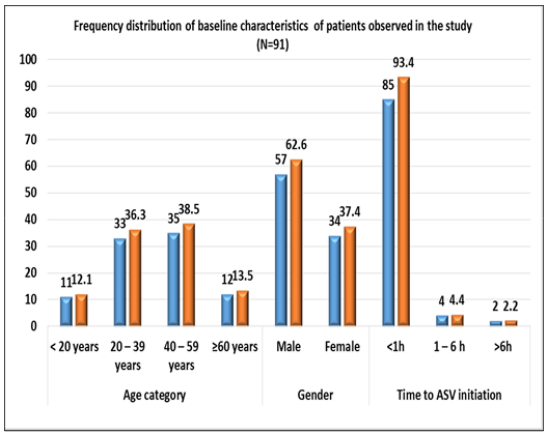

Figure 1: Frequency distribution of baseline characteristics of patients in this study

A total of 91 patients were taken for study. Blue bar diagram denotes absolute count and red bar diagram shows percent of patitents. 93.4% of studied population were given ASV within 1 hr of hospital admission.

Out of the studied population, approximately 49.5 % developed AKI. 31.9 % needed ICU stay same population need to undergo dialysis. 52.7 % had to undergo blood transfusion during the course of treatment and 40.7% developed venom induced DIC.

4. Discussion

In our study most of the patients have reached health care facility either primary or tertiary heath care centre within 24 hours. And in most of the patients the mean time between

Table 1: Various outcomes in snake bite cases among study population

S.No	Parameter	N	%
	Acute kidney injury		
1	Yes	45	49.5
	No	46	50.5
	Dialysis		
2	Yes	29	31.9
	No	62	68.1
	ICU stay		
3	Yes	29	31.9
	No	62	68.1
	Blood transfusion		
4	Yes	48	52.7
	No	43	47.3
	Venom induced consumptive coagulopathy		
5	Yes	37	40.7
	No	54	59.3

the time of bite and suspected history of bite is less than 1 hour. About 93.4% of patients (85 patients out 0f 91 patients studied) have received their antisnake venom within 1 hour of bite history. In a study conducted by ESLAMAIAN ET AL, it showed the mean time period between the bite and reaching first health care facility was about 6 hours. In the past, people used to rely on the natural medications and had superstitious believes which delay the arrival to health centre after bite. This mean hour of 1 hours shows that there is an increasing awareness among the people across the country.

Study by PADHIYAR ET AL, showed 62.5 % of patient had received.

ASV at primary health centre itself before arriving to the tertiary health care hospital. In my study the similar findings were observed. This shows the better availability of antisnake venom even at small health centres. This very much helps in preventing the mortality and the complications of snake bite that occurs due to delay in antisnake venom. The mean antisnake venom vials administered in my study is around 3 vials.

Almost more than 50 studies have been carried out in various countries across the world to bring out the prevalence of thrombotic Microangiopathy (TMA) spectrum disorders that occurs following snake bite. These cases are predominantly distributed in countries like India, Srilanka followed by Australia and from few other countries. The species studied are mainly Vipers, Elapids and few others.

In our study 33% of patients had, deranged INR at presentation and around 40% of patients had platelets count less than 1 lakh 50000 cells/cu.mm at presentation. Among this 40.7% of patients developed venom induced consumptive coagulopathy and 53.7% of patients have received blood and blood products transfusion and around 3.9% patients had ICU stay. In a study done by Demple et al, showed normalization of coagulation profile occurs within 48 hours of antisnake venom administration.

Another study by Aggarwal et al, showed 51 patients out of 53 studied showed who had abnormal coagulation profile at presentation after 12 hours of intravenous antisnake venom administration their coagulation profile become normal. In our study this time interval between the normalization of coagulation profile and antisnake venom administration was difficult to analyse.

The majority of the studies that are done prior to the systemic review, suggested that thrombotic Microangiopathy spectrum disorders are uncommon. However the systemic review of the previous studies published in December 8, 2020 by TINN NOUTOUSE et al found that there is a significant incidence of TMA spectrum disorders following snakebite. Our study also supports the fact, that TMA [1,2,19,28–30] disorders following snakebite usually occurs in the background of coagulopathy in the presence of thrombocytopenia is significant. In most of the cases the platelet count is usually between 50,000 cells/cu.mm to 1, 00,000 cells/cu.mm and in severe cases it is less than 50,000cells/cu.mm.

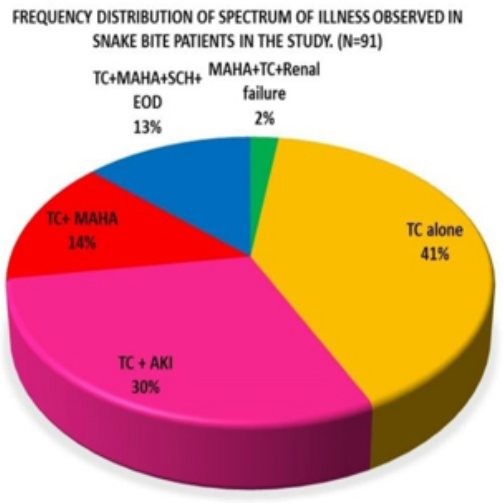

Figure 2: Distribution of spectrum of illness

Mechanism of coagulation are typically in favour of venom induced consumptive coagulopathy, with coagulation factor consumption as evidenced by prolonged INR and APTT. Anemia and thrombocytopenia present in almost in many cases as seen in other TMAs such as hemolytic uremic syndrome (HUS). [1,4,31–41] In our study the full spectrum of illness Microangiopathy haemolytic anemia, thrombocytopenia and renal failure was seen in 2.2 % of study patients. Thrombocytopenia and acute kidney injury was observed in 29.7 % of patients. Thrombocytopenia, Microangiopathy haemolytic anemia,

schistiocytes, end organ damage seen in 13.2%. Out of this 67.6% developed acute kidney injury and about 45(% had the need for dialysis. These patients were intensively treated with hemodialysis and transfusion, out of which around 14.3% developed acute kidney injury managed conservatively without the need for renal replacement therapy.

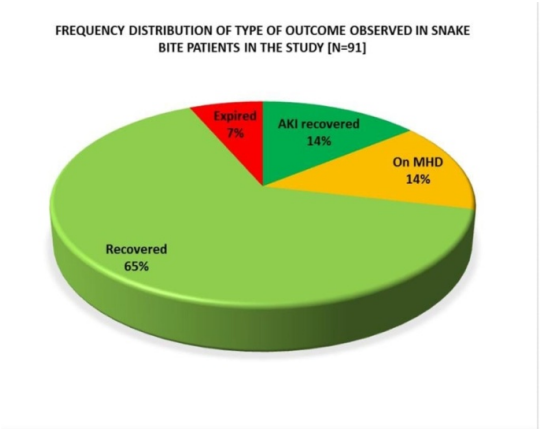

Figure 3: Outcome of patients in tma spectrum disorders

Around 64.8% needed renal replacement therapy and recovered. And 14.3 % patients were put on maintenance hemodialysis and was on further follow up. And around 6.6% of patients expired in spite of effective treatment.

The predominant clinical organ affected is renal system. AKI occurring in almost more than 90% of cases with TMA. And the majority of cases required dialysis for AKI and recovered over days to weeks. Very few cases were put on maintenance HD. The clinical studies available has provided little evidence whether timing of antivenom has benefit against TMA prevention. In animal studies the antivenom administered before envenomation developed few complications. And supported the hypothesis that fewer manifestation such as TMA, VICC occurs following the timely administration of ASV within the critical period. This study also shows non correlation the time of ASV administration and the clinical course particularly TMA.

The platelet count at admission, the presence of schistiocytes and the development of VICC, the need for dialysis and outcome are very much interrelated and has effect. The aetiology of TMA following snake bite remains unclear. The pattern of end organ renal injury TMA in the previous studies are mostly in the pattern of HUS than TTP as evidenced by lack of neurological manifestation. It is found that the development of full spectrum disorder was associated with higher antisnake venom dose, blood products, dialysis, ICU stay, longer duration of hospital stay and mortality. The treatment modality used in the patients with TMA were blood and blood products transfusion and dialysis.

The main limitation of this study is we could not able to do renal biopsy and the clinical correlation of severity with it. Herein, from this study it is found that there is a reasonable risk in the development of TMA spectrum disorders following snakebite. Antivenom in the corner stone in the management of snakebite, and it is found that there is no evidence for ASV protective effect against the development of TMA after snake bite. Further studies has to be carried out to show the benefit of plasma exchange for TMA spectrum disorders that occur following snake bite. This will helps to formulate the protocol for the management of TMA and its complications following bite.

5. Conclusion

TMA spectrum disorders include isolated thrombocytopenia, thrombocytopenia with MAHA, thrombocytopenia, and renal failure. The most severe presentation is with thrombocytopenia, MAHA, schistiocytes and renal failure associated with significant mortality. TMA spectrum disorders affect predominantly the hematological system and renal system.

Easily available tests including complete blood count, platelet count, schistiocytes, hemoglobin, lactate dehydrogenase, creatinine, bilirubin and d-dimer should be monitored for first few days as the patient enters VICC.

Early and appropriate administration of ASV helps in preventing the complications. Patients with full blown TMA should be managed adequately with good supportive care and individualized transfusions with blood and blood products has to be done if needed.

6. Source of Funding

None.

7. Conflict of Interest

None.

References

1. Jameson J, Fauci AS, Kasper DL, Hauser SL, Longo DL, Loscalzo J, et al. Harrison's Principles of Internal Medicine. 20th ed. McGraw Hill; 2018. [April 19, 2020.22-Oct-2021].
2. Isbister GK, Little M, Cull G, Mccoubrie D, Lawton P, Szabo F, et al. Thrombotic microangiopathy from Australian brown snake (Pseudonaja) envenoming. *Int Med J*. 2007;37(8):523–8.
3. Dhanapriya J, Dineshkumar T, Sakthirajan R, Thirumalvalavan K, Kurien AA, Balasubramaniyan T, et al. Thrombotic microangiopathy due to Viperidae bite: Two case reports. *Indian J Nephrol*. 2017;27(2):161–4.
4. Rathnayaka RN, Ranathunga PAN, Kularatne SA. Hemolytic Uremic Syndrome, and Thrombotic Thrombocytopenic Purpura Following Hump-nosed Pit Viper (Genus: Hypnale) Envenoming in Sri Lanka. *Wilderness Environ Med*. 2019;30(1):66–78.
5. Enjeti AK, Lincz LF, Seldon M, Isbister GK. Circulating microvesicles in snakebite patients with microangiopathy. *Res Pract Thromb Haemost*. 2019;3(1):121–5.
6. Mohapatra B, Warrell DA, Suraweera W, Bhatia P, Dhingra N, Jotkar RM, et al. Snakebite mortality in India: a nationally

representative mortality survey. *PLoS Negl Trop Dis*. 2011;5(4):1018. doi:10.1371/journal.pntd.0001018.
7. Kasturiratne A, Wickremasinghe AR, De SN, Gunawardena NK, Pathmeswaran A, Premaratna R, et al. The Global Burden of Snakebite: A Literature Analysis and Modelling Based on Regional Estimates of Envenoming and Deaths. *PLOS Med*. 2008;5(11):218. doi:10.1371/journal.pmed.0050218.
8. Mackessy SP, Kini RM, Clemetson KJ, Markland FS, Mclane MA, Morita T, et al. Thrombin-Like Enzymes in Snake Venoms. In: Toxins and Hemostasis [Internet]. Dordrecht: Springer Netherlands; 2010. p. 519–57. [cited 2018 Sep 26].
9. Harshavardhana HS, Pasha I, Prabhu NCS, Ravi P. Snake Bite Induced Coagulopathy:A Study of Clinical Profile and Predictors of Poor Outcome. *Int J Sci Stud*. 2014;2:2–5.
10. Chippaux JP. Snakebite envenomation turns again into a neglected tropical disease! *J Venom Anim Toxins Incl Trop Dis*. 2017;23:38. doi:10.1186/s40409-017-0127-6.
11. Alirol E, Sharma SK, Bawaskar HS, Kuch U, Chappuis F. Snake bite in South Asia: A review. *PLoS Negl Trop Dis*. 2010;4(1):603. doi:10.1371/journal.pntd.0000603.
12. Ohno M, Chijiwa T, Oda-Ueda N, Ogawa T, Hattori S. Molecular evolution of myotoxic phospholipases A2 from snake venom. *Toxicon*. 2004;42(8):841–54.
13. Kini RM. Serine proteases affecting blood coagulation and fibrinolysis from snake venoms. *Pathophysiol Haemost Throm*. 2018;34(4-5):200–4.
14. Marsh NA. Snake venoms affecting the haemostatic mechanism–a consideration of their mechanisms, practical applications and biological significance. *Blood Coagul Fibrinolysis*. 2018;5(3):399–410.
15. Marsh NA. Diagnostic uses of snake venom. *Haemostasis*. 2001;31(3-6):211–7.
16. Bradford HN, Krishnaswamy S. Meizothrombin Is an Unexpectedly Zymogen-like Variant of Thrombin. *J Biol Chem*. 2012;287(36):30414–25.
17. Lövgren A. Recombinant snake venom prothrombin activators. *Bioengineered*. 2013;4(3):153–7.
18. Marsh N, Williams V. Practical applications of snake venom toxins in haemostasis. *Toxicon*. 2005;45(8):1171–81.
19. Isbister GK. Snakebite doesn't cause disseminated intravascular coagulation: coagulopathy and thrombotic microangiopathy in snake envenoming. *Semin Thromb Hemost*. 2005;36(4):444–51.
20. Berling I, Isbister GK. Hematologic Effects and Complications of Snake Envenoming. *Transfus Med Rev*. 2015;29(2):82–9.
21. Valenta J, Stach Z, Michálek P. Snakebite Envenoming by Sochurek's Saw-scaled Viper EchisCarinatusSochureki. *Prague Med Rep*. 2016;117(1):61–7.
22. Ratnayake I, Shihana F, Dissanayake DM, Buckley NA, Maduwage K, Isbister GK, et al. Performance of the 20-minute whole blood clotting test in detecting venom induced consumption coagulopathy from Russell's viper (Daboiarusselii) bites. *Thromb Haemost*. 2017;117(3):500–7.
23. Suchithra N, Pappachan JM, Sujathan P. Snakebite envenoming in Kerala, South India: clinical profile and factors involved in adverse outcomes. *Emerg Med J*. 2008;25(4):200–4.
24. Isbister GK, Buckley NA, Page CB, Scorgie FE, Lincz LF, Seldon M, et al. A randomized controlled trial of fresh frozen plasma for treating venom-induced consumption coagulopathy in cases of Australian snakebite (ASP-18). *J Thromb Haemost*. 2013;11(7):1310–8.
25. https://journals.plos.org/plosntds/issue?id=10.1371/issue.pntd.v08.i02.
26. Moon JM, Chun BJ, Cho YS, Kim JC, Koo YJ, Park KH, et al. Coagulopathy after snake envenomation in South Korea. *Clin Toxicol (Phila)*. 2021;59(10):905–12.
27. Kasturiratne A, Wickremasinghe AR, De SN, Gunawardena NK, Pathmeswaran A, Premaratna R. The Global Burden of Snakebite: A Literature Analysis and Modelling Based on Regional Estimates of Envenoming and Deaths. *PLOS Medicine*. 2008;5(11):218–218.
28. Noutsos T, Currie BJ, Wijewickrama ES, Isbister G. Snakebite Associated Thrombotic Microangiopathy and Recommendations for Clinical Practice. *Toxins*. 2022;14(1):57. doi:0.3390/toxins14010057.
29. Isbister GK. Snakebite Doesn't Cause Disseminated Intravascular Coagulation: Coagulopathy and Thrombotic Microangiopathy in Snake Envenoming. *Semin Thromb Hemost*. 2010;36(4):444–51.
30. Noutsos T, Currie BJ, Lek RA, Isbister GK. Snakebite associated thrombotic microangiopathy: a systematic review of clinical features, outcomes, and evidence for interventions including plasmapheresis. *PLoS Negl Trop Dis*. 2020;14(12):e0008936. doi:10.1371/journal.pntd.0008936.
31. Winters JL. Plasma exchange in thrombotic microangiopathies (TMAs) other than thrombotic thrombocytopenic purpura (TTP). *Hematology Am Soc Hematol Educ Program*. 2017;2017(1):632–8.
32. Snake-bite-induced acute renal failure in India. *Kidney Int*. 1989;35(3):891–907.
33. Ho WK, Verner E, Dauer R, Duggan J. ADAMTS-13 activity, microangiopathic haemolytic anaemia and thrombocytopenia following snake bite envenomation. *Pathology*. 2010;42(2):200–2.
34. Menon JC, Joseph JK, Whitaker RE. Venomous Snake Bite in India - Why do 50,000 Indians Die Every Year? *J Assoc Physicians India*. 2017;65(8):78–81.
35. Viravan C, Looareesuwan S, Kosakarn W, Wuthiekanun V, Mccarthy CJ, Stimson AF, et al. A national hospital-based survey of snakes responsible for bites in Thailand. *Trans R Soc Trop Med Hyg*. 1992;86(1):100–6.
36. Weinstein S, Warrell DA, White J, Keyler DE. Venomous Bites from Non-Venomous Snakes: A Critical Analysis of Risk and Management of "Colubrid Snake Bites. 1st ed. Elsevier Science; 2011.
37. Ohno M, Chijiwa T, Oda-Ueda N, Ogawa T, Hattori S. Molecular evolution of myotoxic phospholipases A(2) from snake venom. *Toxicon*. 2004;42(8):841–54.
38. Dhananjaya BL, Nataraju A, Gowda CDR, Sharath BK, D'Souza CJM. Vanillic acid as a novel specific inhibitor of snake venom 5'-nucleotidase: a pharmacological tool in evaluating the role of the enzyme in snake envenomation. *Biochemistry (Moscow)*. 2009;74(12):1315–9.
39. Mccleary RJR. Evolution of Venom Variation in the Florida Cottonmouth, Agkistrodon Piscivorus Conanti. University of Florida; 2009.
40. Girish KS, Jagadeesha DK, Rajeev KB, Kemparaju K. Snake venom hyaluronidase: an evidence for isoforms and extracellular matrix degradation. *Mol Cell Biochem*. 2002;240(1-2):105–115.
41. Tan NH, Fung SY, Sim SM, Marinello E, Guerranti R, Aguiyi JC, et al. The protective effect of Mucunapruriens seeds against snake venom poisoning. *J Ethnopharmacol*. 2009;123(2):356–8.

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Cite this article: Sundararajan C, Vetrivel S, Abirami S, Charulatha R. A study on thrombotic microangiopathy spectrum disorders in snake bite. *Panacea J Med Sci* 2024;14(2):573-578.