Global Thrombosis Forum

Virtual High School Scholars' Day

Saturday, July 30, 2022

10:00am – 1:00pm

Loyola University Health Science Division

https://luc.zoom.us/j/84826293153

Consistent with The North American Thrombosis Forum objectives, training, and educational initiatives the Global Thrombosis Forum, under the leadership of Dr. Atul Laddu, has continued to make a major impact in inspiring public sectors, in particular younger students to promote awareness of thrombosis and its management at various levels. Such programs have recruited talented young scholars who have participated in educational and translational research programs in an exemplary fashion. Since its foundation in 2011, the Global Thrombosis Forum has worked with Loyola University and other academic institutions on various initiatives in promoting these activities. The summer research scholar's program at various institutions including Loyola University, NorthShore University Systems, Albany College of Pharmacy, PACO Foundation, and Harvard University have provided major platforms for the young students to carry out translational research projects which have resulted in the participation at national and international meetings and publications. This program is now expanded to include international institutions including in countries such as Brazil, India, and China.

The COVID-19 pandemic has made a major impact on our educational and research programs at the Health Sciences Division of Loyola University Chicago. The University is committed to its primary mission in continuing our academic programs. Consistent with our educational mission we have converted our courses and other communication to students to a virtual format. Since 2020, the GTF High School Scholar Summer Research program is planned in the virtual format in which students and faculty contributed with several innovative approaches to carry out assigned projects in an effective manner. This involved periodic group sessions, individual faculty / student interactions and scheduled didactic presentations relevant to assigned biomedical research in an integrated fashion. The concept and implementation of the virtual program was supported by the Vice Provost, Dr. Meharvan Singh who has provided guidance and support. With this advanced communication and the utilization of various platforms such as Zoom students were continually in touch with the faculty and mentors. With this platform this program will continually evolve and will offer students who are not able to physically participate on site the ability to participate.

Dr. Callahan, Provost, Loyola University Chicago, has been extremely supportive of the GTF / Loyola initiatives and has provided guidance and leadership to carry out these missions. Under the strong leadership of Dr. Sam Goldhaber, President of the NATF and Dr. Atul Laddu, President, and CEO of GTF and the faculty participation at various institutions, these programs will continue to expand in various formats. The summer research programs along with other programs which were scheduled at various institutions will also provide flexibility for students to participate in short term research projects. Such programs will be offered to individuals with dedicated time periods pending their availability. This will provide opportunities for young students which will be helpful in their career planning and education to become physicians and scientists to serve healthcare and biomedical research programs.

AGENDA

10:00 – 10:30 Welcome Addresses

Provost Dr. Margaret Callahan
Dr. Atul Laddu
Dr. Meharvan Singh
Dr. Eva Wojcik
Dr. Jawed Fareed
Featured Guest – Professor PL Antignani, President, IUA

Student Presentations

10:30 *Anticoagulation in COVID-19*

Isha Patkar

10:40 *Differentiation Between Apixaban and Rivaroxaban and the Potential Healthcare Impact of a Seemingly Simple Marketing Change— the Power of Science and the Voice of the People*

Neha Koganti

10:50 *Glycemic Indices and Related Biomarkers in Pulmonary Embolism*

Roumika Patil

11:00 *Thrombin generation parameters and biomarkers such as D-dimer, prothrombin fragment F1+2 and thrombin-antithrombin complex*

Priya Ray

11:10 *The relationship between thrombo-inflammatory biomarkers and cellular indices of inflammation in pulmonary embolism patients*

Radhika Kulkarni

11:20 *Vaccine-Induced Immune Thrombotic Thrombocytopenia* **(***VITT)*

Divya Honavar

11:30 *Reversal Agents for DOACs*

Richa Mahajan, Sanika Ainchwar

11:40 *Biomarkers and Thrombosis*

Arav Bongirwar

Posters

11:50 *COVID-19 and D-Dimer*

Aniket Talanki, Isanth Talanki

12:00 *Hypertension and VTE*

Aneesh Natakala

12:10 *Role of Nurses in the Management of VTE*

Krish Raina

12:20 *Presentation of the "Dr. Usha Mathur Excellence in Research Awards"*

Dr. Jawed Fareed

12:30 *Featured Presentation. A tribute to Professor Joseph Caprini*

Dr. Alfonoso Tafur

12:40 *Closing Remarks*

ABSTRACTS

Glycemic Indices and Related Biomarkers in Pulmonary Embolism

Roumika Patil

Introduction: Pulmonary Embolism (PE) is a thrombotic blockage in the pulmonary arteries that is caused often by a detached embolus that has traveled up to the lungs, known as Deep Vein Thrombosis (DVT). This condition can lead to lack of blood flow to vital organ tissue, or even death of the tissue. Additionally, this condition can cause several complications, such as pulmonary hypertension, which can lead to more severe complications such as heart failure and cardiac arrest. Today, DVT/PE is estimated to affect between 350,000-600,000 individuals annually in the United States. The mortality rate is approximately 100,000 people each year. Diabetes mellitus (DM) is one of the most common metabolic disorders resulting from dysregulated glucose metabolism and is a very important risk factor for cardiovascular disease. Several different factors contribute to thrombotic events in DM; these include inflammatory states, primary hemostatic changes, increased levels of various clotting factors, impaired fibrinolysis, increased oxidative stress, and endothelial dysfunction. HbA1c, which is used as an indicator for glycemic control, may be an important measurement in thrombotic events and has also shown positive correlations with thrombo-inflammatory biomarkers. The levels of thrombo-inflammatory biomarkers such as D-Dimer, CRP, PAI-1, tPA, TAFI, and vWF were investigated in several previous studies, however, the relevance of these biomarkers in complex relationships of DM and PE is not completely understood. Additionally, inconsistent results have been published in clinical cohort and epidemiological studies for development of PE in diabetes.

Aim of Study: In this study we aim to find the correlation regarding inflammatory, glycemic, and thrombotic indices in pulmonary embolism by analyzing the data according to various parameters and outcomes.

Hypothesis: Pulmonary embolism patients will have increased levels of inflammatory, glycemic, and thrombotic biomarkers.

Materials and Methods: The PE patient samples (n=87) were collected following the IRB protocols at Loyola University Medical Center and Loyola Heart & Vascular clinics, the levels of thrombo-inflammatory markers (D-Dimer, PAI-1, CRP, tPA, TAFI, vWF, antiPF4 IgG,) were tested by ELISA methods, endogenous glycosaminoglycans (GAGS) with heparin red method.

Statistical Analysis: Statistical analysis has been performed by utilizing IBM SPSS and GraphPad Prism statistical software. Circulating levels of each biomarker in PE patient plasma were compared to control plasma. Continuous variables were analyzed by using non-parametric Mann-Whitney U, Student t-tests and Kruskal-Wallis ANOVA. Categorical variables were tested in Chi square and Fisher exact tests. Survival analysis is formed by using Kaplan Meier method. All analyses performed two-sided P-value < 0.05 were considered statistically significant.

Results: The levels of all the tested biomarkers were elevated in diabetic PE patients in comparison to healthy controls and showed statistical significance, however when biomarker levels correlated with a HbA1c level below and above 7 were compared, the data showed no statistical significance as the p-value was not below 0.05 and the error bars had large overlap. Other factors that did show statistical significance when comparing HbA1c levels below and above 7 were chronic kidney disease (HbA1c <7 8/30 vs HbA1c >7 4/44), age (HbA1c <7 70.33 +- 11.47 vs HbA1c >7 63.68 +- 14.15), BNP (HbA1c <7 568.00 +- 950.47 vs. HbA1c >7 184.57 +- 140.19), smoking status (HbA1c <7 1/30 vs. HbA1c >7 6/44), and hospitalization status of outpatients (HbA1c <7 1/30 vs. HbA1c >7 13/44).

Conclusion: In conclusion, the levels of thrombo-inflammatory biomarkers were elevated in diabetic PE patients compared to healthy controls. However, we were not able to show any difference according to glycemic indices which did not support our hypothesis. Although the results of biomarkers are inconsistent, the patient outcomes, demographics, and clinical risks may show some connection behind this. Additional studies are necessary to understand the influence of glycemic control on thrombo-inflammation and outcomes in diabetic PE patients.

Thrombin generation parameters and biomarkers such as D-dimer, prothrombin fragment F1+2 and thrombin antithrombin complex

Priya Ray

Introduction: Pulmonary embolism (PE) is a serious condition that occurs when an embolus travels to the lungs and causes a blockage in the pulmonary arteries. Usually, the embolism originates from deep vein thrombosis. Common symptoms include sudden shortness of breath, chest pain, and coughing up blood. There are many risk factors, including medical conditions such as heart disease, certain cancers, surgery, prolonged immobility, smoking, obesity, and pregnancy. Thrombin generation tests have been used to identify coagulation and potential thrombosis, which also help in identifying potential PE. Some parameters used in thrombin generation tests are peak thrombin generation (the highest amount of thrombin generated at a given time), endogenous thrombin potential (ETP) (the amount of thrombin that can be generated by the plasma after coagulation starts), and lag time (the amount of time it takes for the thrombin to be generated). Another important aspect of coagulation and thrombosis identification are biomarkers. Some biomarkers are prothrombin fragment F1+2 (made when prothrombin is converted into thrombin and helps diagnose thrombosis), the thrombin antithrombin complex (TAT) (indicates the activation of coagulation), and d-dimer (a protein that is generated after a blood clot is dissolved in the blood).
Purpose: The purpose of this study was to determine the thrombin generation potential in samples obtained from PE patients and its relevance to the thrombin generation markers, such as prothrombin fragment 1+2 (F1+2), thrombin antithrombin (TAT) and d-Dimer.
Hypothesis: The hypothesis of this study was that despite the increase in thrombin generation biomarkers, the thrombin generation potential in PE may be reduced.
Materials and Methods: This study was conducted using 150 samples from patients with PE, collected within 24-72 hours. Sandwich ELISA kits were used to measure the levels of F1+2, TAT, and D-dimer in the PE patients' samples. Fluorogenic Assay was used to measure thrombin generation in the samples. The control group consisted of 50 samples of normal human plasma (NHP) from the vendor.
Statistical Analysis: Statistical tests were run on the data to determine statistical significance and correlation between the parameters and biomarkers. Tests such as the Mann-Whitney U test and Spearman Correlation were conducted using PRISM GraphPad.
Results: The results were compiled using Mean ± Standard Deviation. The peak thrombin levels decrease from 158.46 ± 31.46 nM in NHP to 87.94 ± 88.61 nM in PE patients, as well as ETP levels decreasing from 713.37 ± 199.97 nM*min in NHP to 580.43 ± 539.54 nM*min in PE patients. On the other hand, lag time increases from 2.61 ± 0.62 min in NHP to 4.79 ± 10.18 min in PE patients. For the biomarkers, all three increased in PE patients compared to NHP. The F1+2 levels increase from 294.19 ± 104.99 pmol/L in NHP to 936.36 ± 802.11 pmol/L in PE patients, the TAT levels increase from 2.29 ± 1.13 µg/L in NHP to 40.04 ± 60.76 µg/L in PE patients, and the D-dimer levels increase from 182.55 ± 205.77 ng/L in NHP to 6715.63 ± 5160.73 ng/L in PE patients.
Conclusion: Marked decrease in thrombin generation parameters as studied by the peak thrombin and (ETP) in comparison to NHP is a suggestion of the consumption of the coagulation factors. On the other hand, increase in lag time compared to the NHP is due to the delay in the formation of thrombin. The increase in the thrombin biomarkers (F1+2, TAT, and D-dimer) suggests that there is a continuous activation of the coagulation process in the PE patients.

Anticoagulation in COVID-19

Isha Patkar

In the past few years, ever since severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) was proclaimed a pandemic, the associated effects on the body have been explored in great scrutiny. While it can be easily concluded that Covid-19 results in long-term fatigue or shortness of breath, more recent findings conclude that severe, stage 3, cases of Covid-19 can directly result in thrombotic events. In many of the hospitalized patients with Covid-19, incidence rates for thrombotic disorders were much higher in comparison to

non-hospitalized as studies found the clinical implications to be pulmonary embolism, deep vein thrombosis, arterial thrombosis, myocardial infarction, and death. These events are caused by many coagulation abnormalities occurring when SARS-CoV-2 enters the host cell, such as endothelial dysfunction, increased levels of D-dimer, hyperactivity in platelets, and abnormal activation of coagulation pathways. To mitigate the possibilities of severe consequences from these thrombotic events and prevent them, antithrombotic therapies are the most effective and efficient answer. Anticoagulant and antiplatelet agents that interfere in different steps of the clotting process are popular treatment options in Covid-19 patients. However, the use of them differs depending on the severity of the condition of the patient, any other medications they are on, and additional relevant factors. Thus, researchers and numerous national institutions have prepared recommendations and guidelines to be followed in terms of antithrombotic therapy. This review aims to explain the mechanisms of Covid-19 induced coagulopathy, address its clinical implications, and assess the efficacy of antithrombotic therapies in accordance with the guidelines put henceforth by major societies. The antithrombotic agents that were used in Covid-19 are UFH, LMWH, apixaban, rivaroxaban, warfarin, sulodexide, and aspirin. Their use and dosing depend upon the severity of the Covid-19 and the condition of the patient. More specifically, non-hospitalized, non-critically ill hospitalized, critically ill hospitalized, and discharged from hospital. Covid-19 results in coagulation abnormalities in endothelial dysfunction, hyperactivity in platelets elevated D-dimer, fibrinolytic shut down, abnormal activation of coagulation pathways, and cytokine storm.

The thrombotic events associated with Covid-19 are manifested in many ways with myocardial infarctions (MI), deep venous thrombosis (DVT), pulmonary embolisms (PE), venous thromboembolism (VTE), and arterial thrombosis being the most common events.

Although bleeding is rare in patients with severe, stage 3 Covid-19, especially as opposed to increased rates of coagulation and clotting, there are select cases which have recorded bleeding to have occurred after contraction of Covid-19. These cases are characterized by being difficult to control and having microvascular damage.

The coagulation abnormalities are frequent during COVID-19 and result in thrombotic events in respiratory, cardiovascular, and venous systems. It has been shown that the severity of these coagulation abnormalities was correlated with the severity and the prognosis of the disease. These coagulation abnormalities consisted of diverse findings in individual patients, but the most seen can be listed as: elevated D-dimer levels, prolonged prothrombin time (PT), elevated fibrinogen levels and thrombocytopenia. Based on the changes in these coagulation abnormalities three stages of COVID-19-associated coagulopathy (CAC) have been proposed. In stage 1, patients exhibit mild symptoms and mild localized inflammation and elevated D-dimer. Stage 2 is characterized by more severe symptoms requiring supplemental oxygen, with pulmonary inflammation and intravascular coagulation activation (elevated D-dimer, fibrinogen). Patients who progress to stage 3 require critical care support and demonstrate severe systemic inflammation and coagulopathy with markedly elevated D-dimer and fibrinogen, prolonged PT, and thrombocytopenia.

In conclusion, my research shows that COVID-19 results in major alterations in the coagulation parameters and must be managed effectively using antithrombotic agents such as UFH, LMWH, apixaban, rivaroxaban, warfarin, sulodexide, and aspirin.

Differentiation Between Apixaban and Rivaroxaban and the Potential Healthcare Impact of a Seemingly Simple Marketing Change— the Power of Science and the Voice of the People

Neha Koganti

Introduction: In 2021, one of the major pharmacy distributors in the US (CVS Caremark, CVS) made the decision to have only one DOAC (*D*irect Acting *O*ral *A*nti*C*oagulant), rivaroxaban, available to customers, and removed all other prescribed DOACS from its formulary, including apixaban. Since this decision can have

potentially serious healthcare consequences to the patients, a letter was written by the President of American Society of Hematology (ASH), an organization to which many physicians hold membership. We conducted a literature review to examine the healthcare impact of non-medical switching from apixaban to rivaroxaban and the reversal of CVS's decision, which went into effect on July 1, 2022.

Materials and Methods: Several articles and literature were used to conduct this study. We aimed to examine the similarities and differences between apixaban and rivaroxaban as anticoagulant drugs; demonstrate why apixaban, compared to rivaroxaban, is a more optimal anticoagulant choice in certain patient populations; and discuss the original marketing decision of CVS and its reversal of this decision. To add insight into the reversal of the decision, we interviewed Beth Waldron, a patient advocate who was able to reverse CVS's decision.

Results: Despite their similar mechanisms of action, half-lives, and metabolism, the pharmacology of apixaban and rivaroxaban varies greatly. The most significant difference between them is their excretion methods: apixaban's main excretion method is hepatic metabolism while rivaroxaban's main method is by the kidneys. Apixaban's properties made it a safe candidate to be used in patients with renal disease. In addition, both drugs have an equivalent efficacy in preventing recurrent VTE, but major and minor bleeding occurrences were higher in the rivaroxaban group. Furthermore, the risk of ischemic and hemorrhagic events was increased for patients 65 years or older with atrial fibrillation receiving rivaroxaban. According to Beth Waldron, the strong voices of physicians, patient advocates, pharmacists, and nonprofits resulted in the reversal of the decision by a multibillion-dollar corporation, CVS Caremark.

Conclusions: The drugs' efficacies indicate that there is a lower incidence of brain bleeds in patients treated with apixaban rather than rivaroxaban, which leads many physicians to believe that apixaban is a safer anticoagulant choice. Apixaban also seems to be a better choice than rivaroxaban in patients with increased risk of bleeding, such as chronic kidney disease (CKD) or end-stage renal disease (ESRD) since rivaroxaban needs the kidneys to be in optimal state for excretion to happen, which is not the case in such diseases. Apixaban also appears to be a better choice in patients 65 years or older with atrial fibrillation due to the higher incidence of major ischemic or hemorrhagic events in patients who received rivaroxaban. CVS was pressured to reverse their decision due to the strong power of patients' voices through social media, non-profits, and more. These findings highlight the dangers of non-medical switching as well as the importance of patient advocacy, which Beth Waldron clearly exemplifies.

The relationship between thrombo-inflammatory biomarkers and cellular indices of inflammation in pulmonary embolism patients

Radhika Kulkarni

Introduction: Pulmonary embolism (PE) is the formation of a thrombus within the pulmonary arteries or its branches that leads to impairment of blood flow and oxygen exchange in the lungs. It has previously been established that PEs are associated with a systemic inflammatory response which has been implicated in impacting clinical outcomes, PE resolution, and overall prognosis. Despite this, prognostic thrombo-inflammatory profiling of PE patients for evaluation of risk factors has yet to be done. In this context, we conducted a retrospective analysis of PE patients at our institution.

Materials and Methods: A retrospective analysis of 418 PE patients was conducted. Baseline demographics, comorbidities, and clinical outcomes were assessed. Thrombo-inflammatory profiling was done on all patients via enzyme-linked immunoassays for PAI-1 (ng/ml), D-dimer (ng/ml), XIII-A (%), CRP (ug/ml), Microparticles (nM), vWF (%), Total Protein S (%), uPA (ng/ml), TNF-a (pg/ml), B2GPI (ng/ml), Fibronectin (ug/ml), and Peak Thrombin (nM). Patient complete blood counts were used to calculate cellular indices of inflammation such as neutrophil to lymphocyte, platelet to lymphocyte, platelet to hemoglobin, and platelet to erythrocyte ratios.

Results: The two cohorts demonstrated no differences in terms of demographics or comorbidities. Furthermore, inflammatory

biomarkers and cellular indices of inflammation were elevated in PE patients when compared to healthy controls.

Conclusion: Thrombo-inflammatory profiling of PE patients demonstrated a significant correlation between various metrics of inflammation and PE clinical outcomes and resolution. These findings highlight the importance of the thrombo-inflammatory state exacerbated by PE and warrant further clinical studies in a larger, stratified patient cohort.

PPT Presentations

Vaccine-Induced Immune Thrombotic Thrombocytopenia (VITT)

Divya Honavar

Vaccine-induced thrombotic thrombocytopenia (VITT) is a rare but devastating adverse event following adenoviral vector-based vaccinations for COVID-19 resulting in thrombosis, especially of the cerebral and splanchnic vasculature. The pathogenesis of this condition stems from unregulated, widespread activation and consumption of platelets causing thrombosis in all blood vessels. Diagnosis of the condition is based on the presence of thrombotic symptoms in recently vaccinated patients along with confirmatory laboratory studies. Treatment involves immediate hospitalization, anticoagulation to prevent further thrombosis, and plasma exchange therapy to clear the antibodies from the blood.

Reversal Agents for DOACs

Richa Mahajan, Sanika Ainchwar

Direct Oral Anticoagulants (DOACs) are widely used to treat conditions such as venous thromboembolism (VTE), atrial fibrillation (AF) and acute coronary syndrome (ACS). Bleeding is a major adverse effect of the DOACs. We will review the reversal agents used to treat the adverse effects of DOACs.

Biomarkers and Thrombosis

Arav Bongiwar

A biomarker is a biological molecule found in blood, body fluids, or tissues that is a sign of a normal or abnormal process, or of a condition. Biomarkers such as D-dimer, P-selectin, cardiac enzymes (CPK, MB, troponin, and CRP have been used to see how well the body responds to a treatment for a disease or condition. Several of these biomarkers also have significant links with COVID-19.

Poster Presentations

COVID-19 and D-Dimer

Aniket Talanki, Ishanth Talanki

Covid-19 is caused by Sars CoV- 2 and has now been identified as a global pandemic. The COVID-19 infection can lead to thrombotic complications. D-dimer has been used as a biomarker in COVID-19 during its early stages to prevent and manage thrombosis. Elevated D-dimer levels have been found in patients with COVID0-19. In this research effort, we have tried to understand what D-dimer is, establish it as a biomarker, the role of D-dimer in COVID-19 patients, changes in D-dimer with age and anticoagulation.

Hypertension and VTE

Aneesh Natakala

The relationship between high blood pressure and VTE has been researched in this project. Hypertension (HTN) is a major medical burden throughout the world. In 2000, it was estimated that approximately 1 billion people Worldwide. HTN is often accompanied by thickening of the interior wall of the blood vessels, and results in thrombotic events. It is concluded that there is a direct relationship between hypertension and VTE.

Role of Nurses in the Management of VTE

Krish Raina

This is our effort to look closely at the significant role of a nurse in guiding patients who suffer from VTE. From patient education to various forms of risk assessment, we have studied many factors of the VTE recovery process to conclude how nurses play a crucial role and

are much needed in this process. The nurses use their wide variety of skills and knowledge to ensure patients have a safe recovery. The project idea originated from Ms. Priya Lokasundaram, a nurse and GTF mentor and our association with Dr. Margaret Callahan, the Provost of Loyola University, and a nurse by profession, is a tribute to Florence Nightingale who spearheaded the movement to make the career of nursing the most trusted out of all professions.

Acknowledgements

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