CANCER HISTORY: AN EMERGING RISK FACTOR FOR CARDIOVASCULAR DISEASES IN EMERGENCY DEPARTMENT PATIENTS WITH CHEST PAIN

PART 1 - PROJECT PROPOSAL

A. Abstract (English)

Background. Cancer, either active or previous, is increasingly associated with cardiovascular (CV) diseases, intertwingling with aging, thrombosis, inflammation and immunity. Current diagnostic approach to patients with a suspected acute CV disease, however, is largely based on “classic” atherogenic risk factors, such as diabetes, dyslipidemia, hypertension, and smoking habit. Tailoring of risk-stratification and diagnostic algorithms to cancer patients is therefore a clinical need.
Aim. We will compare the clinical profile and CV outcome of patients with a history of cancer, to those of patients without cancer, after an Emergency Department (ED) visit for acute chest pain. Second, we will compare the accuracy and efficiency of current diagnostic algorithms for acute CV diseases (myocardial infarction, MI, and pulmonary embolism, PE) in cancer *vs* non-cancer patients. Finally, we will estimate the effect of cancer history on outcome prediction models in unselected patients.
Methodology. This will be a retrospective outcome study performed in the Molinette Hospital, hosting both a tertiary ED and a national referral cancer center. All consecutive patients evaluated in the ED for chest pain from December 2021 to December 2024, will be enrolled using hospital software query on triage data. Investigators will collect clinical, diagnostic, biomarker and outcome data, including 30-day and 1-year follow-up, with patient’s informed consent. Collected data will include emerging covariates exploring thrombosis, inflammation, immunity and SARS-CoV2 infection. Outcomes will include vital status and occurrence of MI, PE, heart failure and stroke. Clinical presentation, outcomes and diagnostic protocols will be compared between cancer and non-cancer patients, both in unselected patients and using propensity score matching. Cancer status and covariates will be used for outcome prediction modelling.

Abstract (Italiano)

Background. Il cancro, attivo o pregresso, è sempre più associato alle malattie cardiovascolari (CV), essendo legato all'invecchiamento, la trombosi, l'infiammazione e l'immunità. L'attuale approccio diagnostico nei pazienti con un sospetto di malattia CV acuta, tuttavia, si basa in gran parte sui “classici” fattori di rischio aterogeni, quali diabete, dislipidemia, ipertensione e fumo. L'adattamento della stratificazione del rischio e degli algoritmi diagnostici ai pazienti oncologici è quindi un'esigenza clinica.
Scopi. Confronteremo il profilo clinico e la prognosi cardiovascolare dei pazienti con anamnesi di cancro, rispetto a quelli senza cancro, dopo un accesso nel Dipartimento di Emergenza e Accetazione (DEA) per un dolore toracico acuto. In secondo luogo, confronteremo l'accuratezza e l'efficienza degli attuali algoritmi diagnostici per le malattie CV acute (infarto miocardico, MI, ed embolia polmonare, PE) nei pazienti con cancro rispetto a quelli senza cancro. Infine, valuteremo l'effetto dell'anamnesi di cancro sui modelli di previsione degli esiti, in pazienti non selezionati.
Metodi. Eseguiremo uno studio retrospettivo presso l'Ospedale Molinette, sede di un DEA terziario e di un centro oncologico di riferimento nazionale. Tutti i pazienti consecutivi valutati nel DEA per dolore toracico, da dicembre 2021 a dicembre 2024, saranno arruolati utilizzando un software ospedaliero per l'interrogazione dei dati di triage. Gli sperimentatori raccoglieranno dati clinici, diagnostici, biomarcatori e di esito, e svolgeranno un follow-up a 30 giorni e a 1 anno, con il consenso informato del paziente. I dati raccolti includeranno variabili emergenti che esplorano trombosi, infiammazione, immunità e infezione da SARS-CoV2. Gli esiti includeranno lo stato vitale e l'insorgenza di MI, PE, insufficienza cardiaca e ictus. La presentazione clinica, gli esiti e i protocolli diagnostici saranno confrontati tra pazienti affetti e non affetti da cancro, sia in pazienti non selezionati che utilizzando il propensity score matching. Il cancro e le covariate saranno utilizzati per predire gli outcome con appropriati modelli statistici.

B. Background/state of the art and relevant preliminary results of the proponent in the area

Aging is associated with cancer and cardiovascular (CV) diseases, which represent the leading cause of death worldwide.(Dagenais, Leong et al. 2020) Thanks to the advances in

screening programs and new treatment options, cancer survival has significantly improved in the last decades.(Arnold, Rutherford et al. 2019, Siegel, Miller et al. 2022) At the same time, growing evidence shows that cancer patients and cancer survivors are at greater risk of acute CV events, which include myocardial infarction (MI), pulmonary embolism (PE), heart failure and CV death.(Navi, Reiner et al. 2017, Paterson, Wiebe et al. 2022) In fact, cancer and CV disease share common risk factors, such as age, smoking, diabetes, obesity and sedentary lifestyle. Furthermore, cancer facilitates inflammation, thrombosis, vascular and myocardial damage, and also anti-cancer therapies (including chemotherapeutic agents, biological agents and radiotherapy) can cause CV damage, thrombosis, inflammation and immune suppression.(Gevaert, Halvorsen et al. 2021) History of cancer, previously associated only as a risk factor for PE, has therefore emerged as a newly recognized comprehensive CV risk factor. Frequently, aging and cancer are tangled up with additional emerging modifiers or catalyzers of CV events, such as inflammatory/immune disorders and incident COVID-19.(Ando, Hayashi et al. 2020, Bonaventura, Vecchié et al. 2021) This defines a clinical need to fine-tune current diagnostic algorithms for acute CV events on the evaluation of emerging CV risk factors.

Chest pain is the most common and typical presenting symptom of acute CV events, such as MI and PE, and is one of the main causes of Emergency Department (ED) visits. In patients with chest pain, diagnostic protocols are based on clinical evaluation, blood and imaging tests. A key step is represented by clinical risk stratification, which evaluates risk factors and medical conditions increasing the probability of an acute CV event. With demographic aging and improved cancer survival, the number of patients with a history of cancer evaluated in the ED for chest pain is rising.(Gallaway, Idaikkadar et al. 2021, Gevaert, Halvorsen et al. 2021) Hence, there is a growing need to map the CV outcome of cancer patients evaluated in the ED for chest pain, and to develop diagnostic protocols optimally performing in this patient group. This universal clinical need is even more compelling in the ED of large cancer centers, such as the Molinette Hospital.

The project proponent is the local PI of a large ongoing spontaneous no-profit international study (PRESC1SE-MI) enrolling consecutive ED patients with chest pain, assessing the safety and efficacy of the latest diagnostic algorithm for MI by the European Society of Cardiology (ESC). Since December 2021, the PI's group has established a research pipeline leading to enrollment, data entry, and 30-day follow-up of around 3500 consecutive patients with chest pain visited in the local ED. About 10% of these patients are affected by cancer, and the overall 30-day incidence of MI is 6%. The current project will take advantage of and stream from this preliminary data, prosecuting patient enrolment and implementing new project-focused data collection/analyses.

C. Hypotheses and aims

Hypothesis. History of cancer is associated with specific clinical characteristics, increased incidence of acute CV events (MI, PE), CV diseases (MI, PE, heart failure, stroke), and worse outcome.

Primary aim. To evaluate the clinical characteristics, final diagnoses, 30-day and 1-year outcomes of consecutive patients with a history of active or past cancer presenting to the ED with chest pain. These will be compared to those of consecutive patients without cancer evaluated for chest pain in the same period.

Secondary aims. (a) To evaluate the accuracy and efficiency of current diagnostic algorithms used for diagnosis of MI (troponin algorithm, ESC) and PE (D-dimer algorithm, ESC) in cancer *vs* non-cancer patients. (b) To evaluate the prevalence and association with CV events and outcomes of additional emerging risk factors related to aging and cancer (thrombosis, inflammation, immunity, COVID-19). (c) To evaluate the prevalence and association with CV events and outcomes of diagnostic biomarkers related to cancer and aging.

D. Project plan including experimental design, methods and ethical aspects

Experimental design. This will be a prospective outcome study performed on consecutive outpatients evaluated in the ED for chest pain.

Setting. The study center is a tertiary ED with an average census of 65.000 visits/years of adult patients with non-traumatic, non-pediatric, non-ob/gyn related illnesses.

Enrolment. The study will enroll patients evaluated in the ED from December 2021 to December 2024 for chest pain (=3 years). Consecutive ED visits for chest pain are automatically extracted from the informatic ED database, using a validated automatic query on triage data inputed by trained nurses following approved protocols, independent of the present study. Chest pain is defined by any pain from the chin to the epigastric region, either anterior or posterior. Exclusion criteria are: age <18 years, out-of-hospital cardiac arrest, and end-stage renal disease in chronic dialysis.
Clinical data**.** Clinical data of enrolled patients are obtained by study investigators and trained research personnel from the ED charts and hospital data (when appropriate). Key variables will be: age, gender, chest pain characteristics and associated symptoms, traditional CV risk factors (smoking, hypertension, diabetes, dyslipidemia), thrombosis risk factors and signs of deep vein thrombosis, cancer (defined as previous or active, including type and treatments), immune diseases (*e.g.* organ transplant, immunosuppression drugs), recent SARS-Co2 infection, ECG findings, performance/results of chest computed tomography angiography (lungs, aorta, coronary vessels), final ED diagnosis and disposition (home discharge, hospital admission), performance of cardiovascular interventions.
Biomarker data. Blood test results obtained during the index visit, including biomarkers of CV damage (troponin, BNP), inflammation (white blood cells, C-reactive protein, procalcitonin), thrombosis (D-dimer), and SARS-CoV-2 infection status (molecular/antigenic nasopharyngeal swab), are automatically imported in the study database from the hospital laboratory database, using patient code matching. Selected timing of sampling and processing are also recorded.
Follow-up data. The research personnel will collect outcomes through telephone calls and acquisition of hospital charts. Patients will be contacted after 30 days and 1 year from the index visit, using a pre-defined questionnaire exploring vital status, new ED visit/hospital admission, diagnosis of CV diseases (MI, PE, heart failure, stroke). Vital status will also be checked on public repositories. Data will be registered only for patients providing informed consent.
Data registry. Data will be registered on a secure REDCap anonymized electronic database, accessible only to investigators. This is a secure web application for building and managing study databases.
Ethical requirements. The local Ethic Committee has already authorized collection of patient data regarding outcomes, traditional CV risk factors, and biomarkers (0037598/06-Apr-2021), with patient's consent recorded during follow-up contact. Patients refusing participation will be excluded. An amendment requesting inclusion of further cancer/immunity and clinical variables will be obtained for this project.
Expected numerosity. Based on preliminary results, we expect enrolment of about 10.000 consecutive patients with chest pain over a 3-year enrolment period. Estimating a prevalence of active or past cancer in 10% of patients, the study is expected to yield a main cancer study group of 1.000 patients, and a main no-cancer control group of 7.000.
Data analyses. Clinical presentation, outcomes and diagnostic protocols will be compared between cancer and non-cancer patients, both in unselected patients and using propensity score matching. Cancer status and covariates will be used for outcome prediction modelling, using multivariate logistic and Cox-regression analysis, to explore and quantify the effect on CV outcome of these new CV risk factors. Subgroup analysis will be performed to evaluate the consistency of the results in selected patient subgroups (*e.g.* active/inactive cancer, male/female, age, anemia/normal hemoglobin groups).
Multicenter extension. Using active collaboration with other large EDs already participating to the PRESC1SE-MI study (University Hospital Basel [CH], Careggi Hospital in Firenze [IT], Hospital Clinic in Barcelona [Spain]), the PI will operate to build a multicenter dataset, to increase external validity and scientific impact of project results.

E. Expected results and contingency plans and local impact for the National Health System

The project will provide a valuable map of CV events and outcomes of patients evaluated for chest pain in our large ED, presenting emerging risk factors: primarily cancer, but also disease modifiers such as inflammation, immunity and SARS-CoV-2 infection. In addition, data will allow us to assess the overall accuracy and efficiency of the diagnostic pathways routinely used for chest pain evaluation in the ED in relevant populations such as cancer and immunosuppressed patients, as compared to unselected patients. The following Gantt chart shows the milestones of the project:

Milestones	2023				2024				2025				2026			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Recruitment	■	■	■	■	■	■	■	■								
Creating new RedCap database			■													
Data entry	■	■	■	■	■	■	■	■	■	■						
30-day and 1-year follow-up completion	■	■	■	■	■	■	■	■	■	■	■	■				
Data cleaning and corrections						■	■	■	■	■	■	■				
Statistical analysis											■	■	■	■	■	
Results diffusion													■	■	■	■

By informing on most common causes of chest pain in cancer patients and on their prognosis, results will provide instrumental data for development/tailoring of patient-specific clinical decision rules or additional clinical pathways. These results will lead to a better understanding of the healthcare needs of cancer patients, in turn helping the ED physicians to fine-tune treatments, including their escalation or de-escalation according to patient's prognosis, and to disposition decisions. For instance, identification of increased risk of MI in cancer patients may suggest to lower decision thresholds for ischemia tests, coronary imaging or revascularization, or to increase observation, in patients with cancer history. This is of particular importance in a setting like the Molinette Hospital, a tertiary university hospital hosting both a large ED and a national referral cancer center providing both innovative diagnosis and treatments, and standard oncological care, to a large patient population of the Piemonte region.

PART 2 - PROPONENT'S CV AND TEAM

A. Positions and Honors

Dr. Enrico Lupia is the Director of the Emergency Department – Medical Area and of the High Dependency Unit Division (S.C. Medicina d'Urgenza U) of the Molinette Hospital, and Associate Professor of Internal Medicine at the University of Turin, Department of Medical Sciences. In 2005, he was "visiting researcher" and "visiting instructor of Medicine" at the University of Miami. He is the Director of the School of Specialization in Emergency Medicine of the University of Turin. His research group is active in multiple projects focusing on inflammation, thrombosis, platelet activation, ED diagnostic/prognostic protocols for CV diseases and COVID-19.

B. Publications

- Total number of indexed publications: 113
- H index (from Web of Science): 34
- Total number of publications in the last 5 years (2018-2022): 43
- Average 2021 impact factor of the publications in the last 5 years: 11,8

Selected publications in the last 5 years:

1. Pivetta E, Moretto F, […], **Lupia E**. Comparison between standard and ultrasound-integrated approach for risk stratification of syncope in the emergency department. Intern Emerg Med. 2022 Jan 22. doi: 10.1007/s11739-021-02909-3. Epub ahead of print. IF 5,47 (2021)
2. **Lupia E**, Capuano M, […], Montrucchio G. Thrombopoietin participates in platelet activation in COVID-19 patients. EBioMedicine. 2022 Nov;85:104305. doi: 10.1016/j.ebiom.2022.104305. Epub 2022 Oct 13. IF 11.21 (2021)
3. Nazerian P, Mueller C, […], **Lupia E**, […], Morello F. Integration of transthoracic focused cardiac ultrasound in the diagnostic algorithm for suspected acute aortic syndromes. Eur Heart J. 2019 Jun 21;40(24):1952-1960. doi: 10.1093/eurheartj/ehz207. IF: 35,855.
4. Pivetta E, Goffi A, […], **Lupia E**; Study Group on Lung Ultrasound from the Molinette and Careggi Hospitals. Lung ultrasound integrated with clinical assessment for the diagnosis of acute decompensated heart failure in the emergency department: a randomized controlled trial. Eur J Heart Fail. 2019 Jun;21(6):754-766. doi: 10.1002/ejhf.1379. Epub 2019 Jan 28. IF: 18,174.

5. Nazerian P, Mueller C, […], **Lupia E**, […], Morello F; AdvISED Investigators. Diagnostic Accuracy of the Aortic Dissection Detection Risk Score Plus D-Dimer for Acute Aortic Syndromes: The ADvISED Prospective Multicenter Study. Circulation. 2018 Jan 16;137(3):250-258. doi: 10.1161/CIRCULATIONAHA.117.029457. Epub 2017 Oct 13. IF: 39,922.

C. Conferences

"Hot topics in renal transplantation. New diagnostic tools in kidney tranplant rejection and recurrent glomerular diseases. CISEF GASLINI, Genova, 1 Apr 2017.

Congresso regionale SIMEU Piemonte – Valle d'Aosta, Novara, 17 Mar 2017.

Trombosi venosa profonda ed embolia polmonare. Stato dell'arte ed applicazione pratica. Torino, 15 Mar 2018.

Paziente settico: terapie di supporto integrate e classificazione. Torino, 4 May 2018.

10 anni di procalcitonina e nuovi biomarcatori. Torino, 21 Jun 2018.

Appropriatezza terapeutica nelle infezioni gravi. IgM-PIRO SCORE: dalla teoria alla pratica. Torino, 4 Jun 2019.

Progetto PDTA: quali step per una gestione adeguata della sepsi nel 2019. Torino, 16 Sep 2019.

Linee guida e paziente asmatico acuto. Torino, 11 Dec 2019.

HF ward in Città della Salute. Torino, 6 Oct 2021.

III Congresso Nazionale IVAS. Torino, 5 Nov 2021.

Medicina Interna 2022. Ricerca e clinica si incontrano. Verduno (CN), 7 Oct 2022.

D. Current and anticipated grant support

EL receives economic support by the University of Basel for the PRESC1SE-MI trial (consisting in grant support for scholarship of a study nurse until 2024) and local university funding. A national university funding (PRIN) is currently under evaluation.

E. Previous experience in collaborative research

EL has a long and ongoing experience in collaborative multicenter research focusing on the diagnosis of acute conditions and cardiovascular emergencies in the ED: MI (PRESC1SE-MI trial, international, proponent/coordinating center University of Basel, CH), acute aortic syndromes (ADvISED, PROFUNDUS trials, international, proponent/coordinating center University of Turin/Lupia's group), COVID-19 (CODED study, national, proponent/coordinating center University of Turin/Lupia's group), acute heart failure (international, proponent/coordinating center University of Turin/Lupia's group).

F. Team

1. Dr. Paolo Bima, emergency physician, background in clinical research (cardiovascular diseases, sepsis, COVID-19)
2. Dr. Emanuele Emilio Pivetta, emergency physician and Assistant Professor (University of Torino), background in clinical research (cardiovascular diseases, COVID-19, ultrasonography)
3. Dr. Silvia Tarditi, research assistant and data manager
4. Research assistant/study nurse to be hired with grant resources.