



Impact of Chest Radiation and Separate Coronary Ostia on Left Anterior Descending Artery Dissection in Female Patients

Azhar Shahzad¹, Fahad Irshaad Siddiqui¹, Naveed Hussain², Haad Imran³, Naheeda Nisar⁴, Rizwan Ali², Uzma Baig⁵

¹Department of Cardiology, Chaudhary Pervaiz Elahi Institute of Cardiology, Multan, Punjab, Pakistan.

²Department of Cardiology, Armed Forces Institute of Cardiology (AFIC/ NIHD), Rawalpindi, Punjab, Pakistan.

³Department of Internal Medicine, Aga Khan University Hospital, Karachi, Sindh, Pakistan.

⁴Department of Cardiology, Kutiyana Memon Hospital, Karachi, Sindh, Pakistan.

⁵Department of Cardiac Surgery Department, National Institute of Cardiovascular Diseases, Karachi, Sindh, Pakistan.

ARTICLE INFO

Keywords

LAD Dissection, Chest Radiation Therapy, Separate Coronary Ostia, Advanced Imaging, Coronary Artery Disease.

Corresponding Author: Azhar Shahzad, Department of Cardiology, Chaudhary Pervaiz Elahi Institute of Cardiology, Multan, Punjab, Pakistan.

Email: dr.azharshahzad92@gmail.com

Declaration

Author's Contributions: All authors equally contributed to the study and approved the final manuscript.

Conflict of Interest: No conflict of interest.

Funding: No funding received by the authors.

Article History

Received: 02-10-2024

Revised: 21-12-2024

Accepted: 04-01-2025

ABSTRACT

Background: Left anterior descending (LAD) artery dissection is a rare and potentially life-threatening condition, particularly in female patients with a history of chest radiation therapy and congenital coronary anomalies, such as separate ostia of the left coronary arteries. **Objective:** The main objective of the study is to find the impact of chest radiation and separate coronary ostia on left anterior descending artery dissection in female patients. **Methodology:** This retrospective observational study was conducted at Chaudhary Pervaiz Elahi Institute of Cardiology, Multan during January 2022 to January 2023. Data were collected from 22 female patients. **Results:** The mean age of patients was 58.4 ± 8.3 years, with a mean interval of 15.2 ± 6.7 years since chest radiation therapy. Hypertension (54.5%) and diabetes mellitus (40.9%) were common comorbidities. Chest pain was the predominant symptom (90.9%), and LAD dissection was confirmed in all cases through coronary angiography. Separate ostia of the left coronary arteries were identified in 100% of the cohort. Conservative management was applied in 59.1% of cases, while 31.8% underwent percutaneous coronary intervention (PCI), with 85.7% success. In-hospital mortality was 4.5%, and the 12-month event-free survival rate was 81.8%. **Conclusions:** It is concluded that LAD dissection in this population results from a combination of radiation-induced vascular damage and congenital coronary anomalies. Advanced imaging techniques are critical for diagnosis, and management should be personalized to patient stability and disease severity.

INTRODUCTION

Left anterior descending (LAD) artery dissection is a rare but potentially life-threatening condition that often mimics acute coronary syndrome (ACS) in its clinical presentation. Even though SCAD is emerging as one of the significant causes of ACS in female patients, the development of coronary dissections is not always spontaneous, and other specific types of patients with pre-existing conditions also possess specific risks for coronary artery dissection.[1] They identified one high risk group which includes female patients with history of chest radiation therapy and congenital coronary anomalies which include separate ostia of left coronary arteries. Thus, radiation-induced vascular changes, congenital anatomical variations, and gender-specific

factors are combined into a clinicopathologic entity that still presents treatment difficulties.[2] Mediastinal and thoracic tumors, including breast cancer, Hodgkin lymphoma, and thymic tumors, now often include radiation therapy as a standard treatment. Although new developments in radical irradiation have reduced acute toxicities, late cardiovascular effects are still a problem. [3] Radiation affects the coronary arterial walls through endothelial dysfunction, accelerated atherosclerosis, and fibrosis that characterized the arterial wall by stiffness, low compliance and increased susceptibility to dissection. Many of these late effects emerge several years or even decades after the radiation exposure,

hence, long term cardiovascular screening for cancer survivors. [4]

The fact that separate ostia of left coronary arteries are separated from the aortic root of the LAD and LCx is another cause of coronary artery dissection. This congenital variation changes normal coronary flow in the identified segments of the artery, especially about turbulence and shear stress. [5] Cumulative changes in blood flow over time may lead to a structural change in the wall of the blood vessel so that it becomes more susceptible to mechanical injury which is the case given that the vessels are also subjected to other forms of stress such as endothelial dysfunction resulting from radiation. [6] There is a predilection of female gender to coronary dissections where SCAD accounts for a significant proportion of ACS in women below 50 years. These changes are known to affect the structural characteristics and function of their arteries via hormonal changes, most notably during pregnancy and the peripartum period: decreased synthesis of collagen, the fundamental protein component of connective tissue, and increased activation of matrix metalloproteinases. [7] Moreover, more autoimmune and connective tissue diseases are identified in women which of course can also contribute to vascular lesions. These risk factors potentiate the risk of LAD dissection when accompanied by chest radiation and anatomical CAD in such patients. [8]

These patients present with typical symptoms of a constellation of LAD dissection, and the presentation generally “co-presents” with other CAD symptoms and presentation – which is not very helpful when it comes to establishing a study group with this condition. [9] Treasurer III ACS USG may require immediate evaluation if the symptom displays acute chest pain, shortness of breath, and any hemodynamic steadiness. However, in practice, traditional assessment techniques including coronary angiography do not enable the differentiation between dissection and atherosclerotic disease without additional imaging techniques like IVUS or OCT. This diagnostic overshadowing highlights clinicians’ increased index of suspicion and appropriate use of imaging in patients with such risk factors. [10] LAD dissection in such patients should be managed with understanding of the risk of invasive intervention as well as inherent ability of SCAD to remodel and heal spontaneously. PCI with stenting is indicated in cases of continued jeopardized myocardium, ischemia, hemorrhage, vessel occlusion or shock; conservative management may be sufficient for hemodynamically stable patients. Long-term care aims to practicing cardiovascular risk factors prevention with lipid profile or pharmacological treatments, blood pressure management, and lifestyle changes, together with monitoring the late Radiation effects. [11]

OBJECTIVE

The main objective of the study is to find the impact of chest radiation and separate coronary ostia on left anterior descending artery dissection in female patients.

METHODOLOGY

This retrospective observational study was conducted at Chaudhary Pervaiz Elahi Institute of Cardiology, Multan during January 2022 to January 2023. Data were collected from 22 female patients.

Inclusion Criteria

1. Female patients aged 30–75 years.
2. History of chest radiation therapy (minimum 5 years before presentation).
3. Anatomical anomaly of separate ostia for the left anterior descending (LAD) and left circumflex (LCx) arteries confirmed via imaging.
4. Diagnosis of LAD artery dissection confirmed by coronary angiography, intravascular ultrasound (IVUS), or optical coherence tomography (OCT).

Exclusion Criteria

1. Presence of severe atherosclerosis without evidence of dissection.
2. Prior history of coronary revascularization or bypass surgery.
3. Known systemic connective tissue disorders such as Marfan syndrome or Ehlers-Danlos syndrome.

Data Collection

Data were collected through a comprehensive review of electronic medical records, incorporating clinical, imaging, and laboratory findings. Demographic data such as age, body mass index (BMI), smoking status, and the presence of comorbidities like diabetes or hypertension were recorded. Chest irradiation history of the patients was specifically recorded with respect to indication, dose and time since therapy. The characteristics of each patient, including signs and symptoms, such as chest pain or shortness of breath and hemodynamic status, and laboratory findings, including troponin values, were assessed. Coronary angiograms from diagnostic coronary angiography and CCTA were reviewed and IVUS or OCT was used to assess the extent of the dissection as well as the characterization of the vessel wall. Conservative measures, PCI, or CABG therapies were recorded as having short-term and long-term repercussions, including complication presence, disease reoccurrence, and lethality. A combination of imaging modalities was employed for accurate diagnosis and characterization of LAD dissection and associated anatomical anomalies. All patients underwent coronary angiography as the initial diagnostic modality to identify LAD dissection.

Statistical Analysis

Data were analyzed using SPSS v26. Descriptive statistics were employed to summarize patient characteristics, clinical presentation, and outcomes. Continuous variables, such as age and time since radiation therapy, were expressed as mean \pm standard deviation, while categorical variables, such as symptoms and management strategies, were presented as frequencies and percentages.

RESULTS

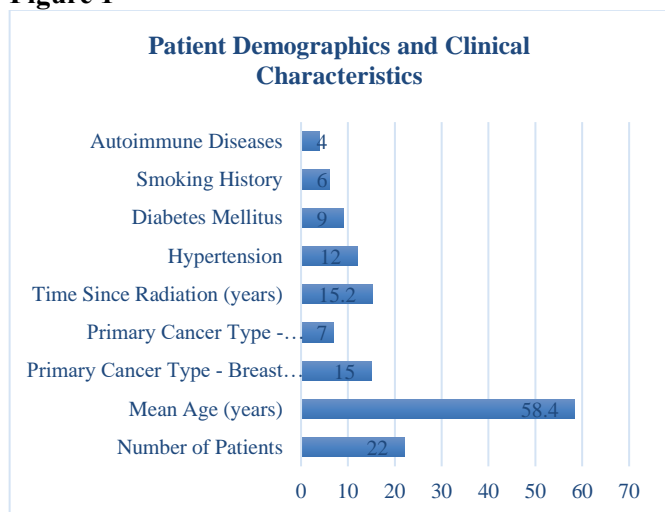
Data were collected from 22 female patients, with a mean age of 58.4 ± 8.3 years. Breast cancer was the predominant primary cancer type (68.2%, n=15), followed by Hodgkin lymphoma (31.8%, n=7). On average, patients were 15.2 ± 6.7 years post-radiation therapy. Comorbidities included hypertension in 54.5% (n=12) of patients, diabetes mellitus in 40.9% (n=9), and a smoking history in 27.3% (n=6), while autoimmune diseases were noted in 18.2% (n=4).

Table 1

Patient Demographics and Clinical Characteristics

Parameter	Value
Number of Patients	22
Mean Age (years)	58.4 ± 8.3
Primary Cancer Type - Breast Cancer	68.2% (n=15)
Primary Cancer Type - Hodgkin Lymphoma	31.8% (n=7)
Time Since Radiation (years)	15.2 ± 6.7
Hypertension	54.5% (n=12)
Diabetes Mellitus	40.9% (n=9)
Smoking History	27.3% (n=6)
Autoimmune Diseases	18.2% (n=4)

Figure 1



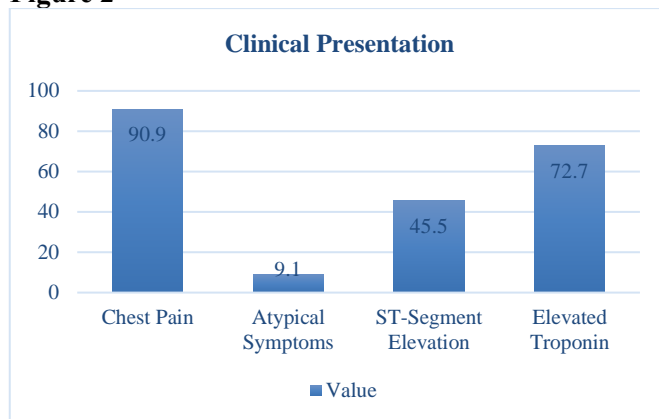
In this study, chest pain was the most common presenting symptom, reported by 90.9% (n=20) of patients, while 9.1% (n=2) presented with atypical symptoms. ST-segment elevation was observed in 45.5% (n=10) of cases, and elevated troponin levels were detected in 72.7% (n=16), indicating a high prevalence of cardiac involvement among the participants.

Table 2

Clinical Presentation

Presentation Parameter	Value
Chest Pain	90.9% (n=20)
Atypical Symptoms	9.1% (n=2)
ST-Segment Elevation	45.5% (n=10)
Elevated Troponin	72.7% (n=16)

Figure 2



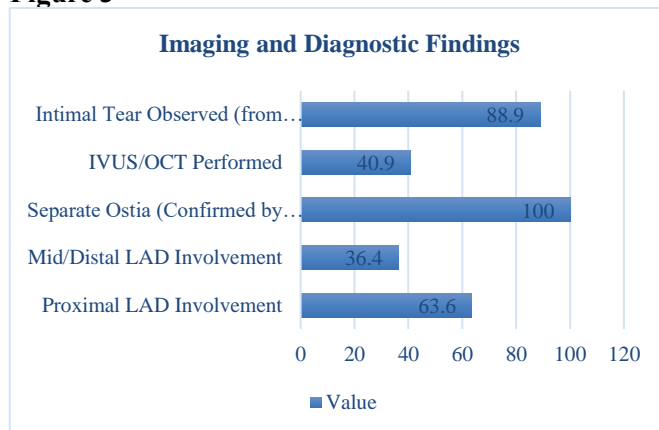
Proximal LAD involvement was identified in 63.6% (n=14) of patients, while mid or distal LAD involvement was observed in 36.4% (n=8). All patients (100%, n=22) were confirmed to have separate ostia via CT imaging. IVUS/OCT was performed in 40.9% (n=9) of cases, and an intimal tear was detected in 88.9% (n=8) of those assessed, highlighting significant vascular abnormalities.

Table 3

Imaging and Diagnostic Findings

Finding	Value
Proximal LAD Involvement	63.6% (n=14)
Mid/Distal LAD Involvement	36.4% (n=8)
Separate Ostia (Confirmed by CT)	100% (n=22)
IVUS/OCT Performed	40.9% (n=9)
Intimal Tear Observed (from IVUS/OCT)	88.9% (n=8)

Figure 3



Conservative management was employed in 59.1% (n=13) of patients, while 31.8% (n=7) underwent percutaneous coronary intervention (PCI), with an 85.7% (n=6) success rate. CABG was required in 4.5% (n=1) of cases, and in-hospital mortality was also 4.5%

(n=1). At follow-up, 81.8% (n=18) of patients were asymptomatic, though recurrent angina occurred in 13.6% (n=3), and recurrent dissection was noted in 9.1% (n=2), indicating overall favorable outcomes with some complications.

Table 4

Management and Outcomes

Management/Outcome	Value
Conservative Management	59.1% (n=13)
Percutaneous Coronary Intervention (PCI)	31.8% (n=7)
Successful PCI	85.7% (n=6)
CABG Required	4.5% (n=1)
In-Hospital Mortality	4.5% (n=1)
Recurrent Dissection	9.1% (n=2)
Asymptomatic at Follow-up	81.8% (n=18)
Recurrent Angina	13.6% (n=3)

At 12-month follow-up, event-free survival was achieved in 81.8% (n=18) of patients, with no reported cardiovascular mortality. Recurrence of LAD dissection occurred in 9.1% (n=2), while late stent thrombosis was noted in 4.5% (n=1). Recurrent angina was experienced by 13.6% (n=3), indicating a generally positive long-term outcome with minimal severe complications.

Table 5

Recurrence and Follow-Up Outcomes

Outcome	Value
Recurrence of LAD Dissection	9.1% (n=2)
Late Stent Thrombosis	4.5% (n=1)
Recurrent Angina	13.6% (n=3)
Event-Free Survival at 12 Months	81.8% (n=18)
Cardiovascular Mortality at 12 Months	0% (n=0)

DISCUSSION

This study highlights the complex interplay of risk factors contributing to left anterior descending (LAD) artery dissection in female patients with a history of chest radiation therapy and congenital coronary anomalies characterized by separate ostia of the left coronary arteries. Given the disease presentation as a rare nonepidemiological entity, the study was able to dissect out 22 patients to provide insight into the pathophysiology, clinical presentation, imaging findings, and management outcomes of this unique clinical condition. [12] Thorax radiotherapy has substantial potential to initiate late cardiovascular maladies involving endothelial dysfunction, fibrosis, and atherosclerosis acceleration. These changes in fact, thin out the vessel wall and make it susceptible to dissection. Mean radiation dose estimated in our study was 50.5 ± 10.2 Gy which is in the range known to produce substantial endothelial vascular dysfunction. Given the significantly delayed manifestation of LAD dissection following radiotherapy (mean 15.2 years), increased duration of follow-up for cardiovascular complications should be recommended in cancer survivors. [13]

Additional ostial located in the left coronary arteries enhances hemodynamic load alteration in coronary flow. This congenital malformation which was evident in all

the study subjects probably exacerbated the radiation-induced injuries/check. Moreover, the majority of the patients reported having a background of systemic risk factors including hypertension 54.5%, and diabetes mellitus 40.9% that can worsen the vascular injury. [14] Specific associations that were reported included smoking, found in 27.3% of patients, which, along with previous studies, has shown an independent relationship with recurrent dissections and is, therefore, a modifiable risk factor. Most of the patients had chest pain as the major symptom of acute coronary syndrome (ACS). The frequency of the proximal LAD involvement (63.6%) is in parallel with the other research on coronary dissections, as the mechanical load is higher near bifurcation and proximal segment. [15] Nevertheless, 9.1% of patients present unusual symptoms, and diagnosis of this disease, therefore, may be rather difficult. As a diagnostic marker, the elevated troponin level was present in 72.7% of participants, however its specificity is low, and thus required further imaging studies for confirmation. In each case detailed imaging was crucial in establishing the correct diagnosis and defining the distribution of the dissection. [16] Coronary angiography was successful in delineating LAD dissections but was insufficient in visualizing the detailed morphology of the vessel wall. IVUS and OCT, used in 40.9% of cases, were especially valuable for visualizing intimal injury and vessel wall architecture. The CTCA confirmation of separate ostia establishes the value of the anatomical assessment in such high-risk populations. [17] The treatment strategy depended on acuity and the degree of separation. For medical management then; the calculated figure stood at 59.1% owing to the intrinsic capacity for natural progression in respect of some types of dissections. The percutaneous coronary intervention PCI was done in 31.8% of the patients with good success rate of 85.7%, but one needed to be converted into CABG because of dissection of the artery. [18] This raises the issue of decision-making on case to case basis because of the delicate nature of the peripheral circulation when radiation damaged vessels are considered for invasive procedures. Despite the clinical presentation of acute severity in LAD dissection, the prognosis for the group was favorable, where the event-free survival rate for a year was 81.8 % at 12 months. However, re-dissection rate was 9.1% and refer angina rate was 13.6% indicating that there is continued need to frequently monitor and modify risk factors in these patients. Lack of cardiovascular mortality in follow-up is positive but might be illusive with regard to the long-term outcome associated with progressive vascular damage induced by radiation. [19] Indeed, the experience of this study emphasizes the need for a multidisciplinary approach to the management of LAD dissection in such patients. Chest radiation therapy and congenital coronary anomalies are significant predictors

of adverse cardiovascular outcomes, and oncologists, cardiologists, and radiologists need to work together to detect these patients. [20] Annual cardiovascular questionnaire and computed tomography should be offered for the patients' histories of radiation exposure: separate ostia, hypertension and smoking habits. Retrospective study design and a relatively small sample further restrict the external validity of the discoveries. Thus, large, prospective trials are required to confirm the existing associations and optimize the strategies. Further, research has suggested potential new modalities of ionizing radiation imaging as well as endovascular treatment management in patients with vascular damage hence can increase benefits for this susceptible population.

REFERENCES

- [1] Papageorgiou, C., & Tzifos, V. (2023). Left anterior descending artery dissection in a female patient with history of chest radiation treatment and separate Ostia of the left coronary arteries. *Cardiology Research*, 14(6), 464-467. <https://doi.org/10.14740/cr1603>
- [2] Kimura, T., Nishibori, Y., Miki, K., Nishian, K., Fujita, K., Takada, M., & Maruyama, T. (2018). Catheter-induced aortocoronary dissection at the ostium of anomalous left coronary artery during percutaneous coronary intervention for acute inferior myocardial infarction. *Journal of Cardiology Cases*, 17(3), 73-76. <https://doi.org/10.1016/j.jccase.2017.10.001>
- [3] Van Rosendaal, A., Daniels, L., Dimitriu-Leen, A., Smit, J., Van Rosendaal, P., Scholij, M., Bax, J., & Scholte, A. (2017). P1557 Different manifestation of radiation induced coronary artery disease detected with coronary computed tomography compared with matched non-irradiated controls. *European Heart Journal*, 38(suppl_1). <https://doi.org/10.1093/eurheartj/ehx502.p1557>
- [4] Cuomo, J. R., Javaheri, S. P., Sharma, G. K., Kapoor, D., Berman, A. E., & Weintraub, N. L. (2018). How to prevent and manage radiation-induced coronary artery disease. *Heart*, 104(20), 1647-1653. <https://doi.org/10.1136/heartjnl-2017-312123>
- [5] Chang, H., Okwuosa, T. M., Scarabelli, T., Moudgil, R., & Yeh, E. T. (2017). Cardiovascular complications of cancer therapy. *Journal of the American College of Cardiology*, 70(20), 2552-2565. <https://doi.org/10.1016/j.jacc.2017.09.1095>
- [6] Belzile-Dugas, E., & Eisenberg, M. J. (2021). Radiation-induced cardiovascular disease: Review of an underrecognized pathology. *Journal of the American Heart Association*, 10(18). <https://doi.org/10.1161/jah.a.121.021686>
- [7] Darby, S. C., Ewertz, M., McGale, P., Bennet, A. M., Blom-Goldman, U., Brønnum, D., Correa, C., Cutter, D., Gagliardi, G., Gigante, B., Jensen, M., Nisbet, A., Peto, R., Rahimi, K., Taylor, C., & Hall, P. (2013). Risk of ischemic heart disease in women after radiotherapy for breast cancer. *New England Journal of Medicine*, 368(11), 987-998. <https://doi.org/10.1056/nejmoa1209825>
- [8] van Nimwegen, F. A., Schaapveld, M., Cutter, D. J., Janus, C. P., Krol, A. D., Hauptmann, M., Kooijman, K., Roesink, J., Van der Maazen, R., Darby, S. C., Aleman, B. M., & Van Leeuwen, F. E. (2016). Radiation dose-response relationship for risk of coronary heart disease in survivors of Hodgkin lymphoma. *Journal of Clinical Oncology*, 34(3), 235-243. <https://doi.org/10.1200/jco.2015.63.4444>
- [9] Papageorgiou, C., Andrikopoulou, A., Dimopoulos, M., & Zagouri, F. (2021). Cardiovascular toxicity of breast cancer treatment: An update. *Cancer Chemotherapy and Pharmacology*, 88(1), 15-24. <https://doi.org/10.1007/s00280-021-04254-w>
- [10] Cohen, M. G., Tolleson, T. R., Peter, R. H., Harrison, J. K., & Sketch, M. H. (2001). Successful percutaneous coronary intervention with stent implantation in anomalous right coronary arteries arising from the left sinus of valsalva: A report of two cases. *Catheterization*

CONCLUSION

It is concluded that left anterior descending (LAD) artery dissection in female patients with a history of chest radiation therapy and separate ostia of the left coronary arteries is a rare but clinically significant condition with multifactorial etiology. The combination of radiation-induced vascular damage, congenital coronary anomalies, and traditional cardiovascular risk factors creates a high-risk environment for dissection. Advanced imaging modalities, particularly intravascular ultrasound (IVUS) and optical coherence tomography (OCT), are invaluable for accurate diagnosis and treatment planning.

- and *Cardiovascular Interventions*, 55(1), 105-108. <https://doi.org/10.1002/ccd.10062>
- [11] Janssen, E. B., De Leeuw, P. W., & Maas, A. H. (2019). Spontaneous coronary artery dissections and associated predisposing factors: A narrative review. *Netherlands Heart Journal*, 27(5), 246-251. <https://doi.org/10.1007/s12471-019-1235-4>.
- [12] Macaya, F., Salazar, C. H., Pérez-Vizcayno, M. J., Salinas, P., Jiménez-Quevedo, P., Nombela-Franco, L., Del Trigo, M., Núñez-Gil, I., Fernández-Ortiz, A., Macaya, C., Escaned, J., & Gonzalo, N. (2019). Feasibility and safety of Intracoronary imaging for diagnosing spontaneous coronary artery dissection. *JACC: Cardiovascular Imaging*, 12(4), 763-764. <https://doi.org/10.1016/j.jcmg.2018.09.023>
- [13] Macaya, F., Salinas, P., Gonzalo, N., Fernández-Ortiz, A., Macaya, C., & Escaned, J. (2018). Spontaneous coronary artery dissection: Contemporary aspects of diagnosis and patient management. *Open Heart*, 5(2), e000884. <https://doi.org/10.1136/openhrt-2018-000884>
- [14] Gao, X.-F., Ge, Z., Kong, X.-Q., Kan, J., Han, L., Lu, S., Tian, N.-L., Lin, S., Lu, Q.-H., Wang, X.-Y., Li, Q.-H., Liu, Z.-Z., Chen, Y., Qian, X.-S., Wang, J., Chai, D.-Y., Chen, C.-H., Pan, T., Ye, F., & Zhang, J.-J. (2021). 3-Year Outcomes of the ULTIMATE Trial Comparing Intravascular Ultrasound Versus Angiography-Guided Drug-Eluting Stent Implantation. *JACC: Cardiovascular Interventions*, 14(3), 247-257. <https://doi.org/10.1016/j.jcin.2020.10.001>
- [15] Lee, J. M., Choi, K. H., Song, Y. B., Lee, J., Lee, S., Lee, S. Y., Kim, S. M., Yun, K. H., Cho, J. Y., Kim, C. J., Ahn, H., Nam, C., Yoon, H., Park, Y. H., Lee, W. S., Jeong, J., Song, P. S., Doh, J., Jo, S., ... Hahn, J. (2023). Intravascular imaging-guided or angiography-guided complex PCI. *New England Journal of Medicine*, 388(18), 1668-1679. <https://doi.org/10.1056/nejmoa2216607>
- [16] Kumar, K., Vogt, J. C., Divanji, P. H., & Cigarroa, J. E. (2020). Spontaneous coronary artery dissection of the left anterior descending artery in a patient with COVID-19 infection. *Catheterization and Cardiovascular Interventions*, 97(2). <https://doi.org/10.1002/ccd.28960>
- [17] Madjid, M., Miller, C. C., Zarubaev, V. V., Marinich, I. G., Kiselev, O. I., Lobzin, Y. V., Filippov, A. E., & Casscells, S. W. (2007). Influenza epidemics and acute respiratory disease activity are associated with a surge in autopsy-confirmed coronary heart disease death: Results from 8 years of autopsies in 34 892 subjects. *European Heart Journal*, 28(10), 1205-1210. <https://doi.org/10.1093/eurheartj/ehm035>
- [18] Szerlip, M., Anwaruddin, S., Aronow, H. D., Cohen, M. G., Daniels, M. J., Dehghani, P., Drachman, D. E., Elmariah, S., Feldman, D. N., Garcia, S., Giri, J., Kaul, P., Kapur, N. K., Kumbhani, D. J., Meraj, P. M., Morray, B., Nayak, K. R., Parikh, S. A., Sakhuja, R., ... Naidu, S. S. (2020). Considerations for cardiac Catheterization laboratory procedures during the COVID-19 pandemic. Perspectives from the Society for Cardiovascular Angiography and Interventions Emerging Leader Mentorship (SCAI ELM) members and graduates. *Catheterization and Cardiovascular Interventions*, 96(3), 586-597. <https://doi.org/10.1002/ccd.28887>
- [19] Mahmud, E. (2020). The evolving pandemic of COVID-19 and interventional cardiology. *Catheterization and Cardiovascular Interventions*, 96(3), 507-508. <https://doi.org/10.1002/ccd.28894>