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DEVELOPMENT AND VALIDATION OF AN ECHOCARDIOGRAPHY SCORE FOR DIAGNOSIS OF CARDIAC MASSES

TESI DI DOTTORATO

Presentata da:
Dott. Andrea Rinaldi

Supervisore:
Chiar.mo Prof Nazzareno Galiè

Coordinatore Dottorato:
Chiar.mo Prof Gaetano Gargiulo

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SUMMARY

Abbreviations List

Cardiac Mass = CM

Cardiac Magnetic Resonance = CMR

Cardiac Computed Tomography = c-CT

C-Reactive Protein = CRP

Diagnostic Echocardiographic Mass Score = DEM Score

Endomyocardial Biopsy: EMB

Early Gadolinium Enhancement = EGE

Fédération Nationale des Centres de Lutte Contre le Cancer = FNCLCC

Internation Normalized Ratio = INR

Late Gadolinium Enhancement = LGE

Papillary fibroelastomas = PFE

Positron emission tomography with 18F-fluorodexyglucose = 18F-FDG PET

Transthoracic echocardiography = TTE

Transesophageal echocardiography = TEE

Two-dimensional = 2D

Three-dimensional = 3D

ABSTRACT

Background

Echocardiography is the cornerstone in the evaluation of cardiac masses and provides accurate information on its characteristic and localization, without subjecting patients to radiation exposure. Despite, its accuracy in diagnosis of cardiac masses remains challenging and, up to date, no validated diagnostic algorithm is validated.

Purpose

The aim of our study was to evaluate the diagnostic accuracy of echocardiography, to identify the echocardiographic predictors of malignancy and to develop and then validate a multiparametric echocardiographic score that could be used to estimate the likelihood of the histological nature of a CM, in order to address the need for further diagnostic imaging.

Materials and methods

The final sample consisted of 273 consecutive patients who had a complete 2D-echocardiographic evaluation and a definitive histologic diagnosis or in case of cardiac thrombi, with radiological evidence of thrombus resolution after an appropriate anticoagulant treatment. Logistic regression was performed to evaluate the ability of echocardiographic findings to discriminate benign versus malignant masses, then a scoring system was developed and validated in a separate test cohort.

Results

Of the 322 patients initially included in the Bologna Cardiac Masses Registry, 13 with a poor acoustic window, 27 with no histological examination patients and 9 extra-cardiac masses were excluded. In the remaining 273 patients, classical 2-D echocardiogram identified 249 masses with a diagnostic accuracy of 88%. A weighted score [Diagnostic Echocardiographic Mass (DEM) Score] ranging from 0 to 9 was obtained from these 6 variables: infiltration, polylobate mass, moderate-severe pericardial effusion: 2 points; inhomogeneity, sessile, non-left mass localization: 1 point each, in order to predict the nature of the mass. The AUC for the score was 0.965 (95% CI [0.938-0.993]). In a logistic

regression analysis using the DEM score as a predictor, the likelihood of malignant CM increased more than 4 times for a 1-unit increase in the score (OR=4.468; 95% CI 2.733-7.304). A score < 3 denoted a high probability of a benign diagnosis, and a score ≥ 5 points corresponded to a higher risk of malignancy. An intermediate score between 3 and 4 points, identifies a "gray zone". The predictive validity of the score was determined as its ability to predict survival during the follow-up by Kaplan-Meier survival curves (Log-rank test = 102.4, p<0.001, all significant pairwise comparisons), with a median survival of 15 months (95% CI 2.4-10.2) among patients scoring 5 to 9, a median survival of 25 months (95% CI 7.3-10.7) among patients with a score of 3 to 4 and a median survival of 104 months (95% CI 59.6-168.0) among those scoring < 3.

Conclusion

2D-Echocardiography provides a high diagnostic accuracy in identifying cardiac masses and our multiparametric echocardiographic score could be useful to predict the histological nature of cardiac masses without the constant need of a second-level imaging confirmation.

Key words: cardiac masses, pseudotumour, primary benign tumours, primary malignant tumours, secondary malignant tumours.

BACKGROUND

Cardiac masses are a rare and heterogeneous disease entity that frequently present subtle symptoms with, consequently, important diagnostic and therapeutic delay with poor consequences for patients.

Cardiac masses are classified into benign masses (primary tumours and pseudotumours) and malignant ones (primitive tumours and, more frequently, metastasis). Their low prevalence and mixed clinical presentation make the diagnosis of cardiac masses challenging. In fact, they can remain asymptomatic for a long time and provoke more specific symptoms only in an advanced stage (flow obstruction, embolization, conduction system abnormalities)[1].

For clinicians, the diagnosis of cardiac mass is a common diagnostic dilemma with a subsequent diagnostic and therapeutic pathway that has still not be standardized.

Even if most cardiac masses are benign and with a good prognosis, it is important that clinicians are aware of the principal imaging characteristics of cardiac masses to reach an earlier diagnosis and to optimized patients' diagnostic and therapeutic pathway[2].

Definition

A cardiac mass is defined as an abnormal mass of tissue, the growth of which exceeds and is uncoordinated with that of the surrounding cardiac structures. Its diagnosis can be reached through various imaging tests (echocardiography, cardiac computed tomography, cardiac magnetic resonance or positron emission tomography (PET)) or directly, during surgery or post-mortem autopsy.

Epidemiology

The estimated prevalence for primary cardiac tumors is 1:2000 autopsies and for secondary tumors 1:100 autopsies, with a secondary/primary ratio of 20:1[3].

Approximately 75% of cardiac tumours are benign (mostly myxomas)[4], while the other are malignant tumours, usually sarcomas. Angiosarcomas and unclassified sarcomas account for approximately

76% of all cardiac sarcomas, of which angiosarcomas are the most common. Rhabdomyosarcoma is the most common form of cardiac sarcoma in children. Leiomyosarcoma, synovial sarcoma, osteo- sarcoma, fibrosarcoma, myxoidsarcoma, liposarcoma, mesen- chymal sarcoma, neurofibrosarcoma, and malignant fibrous histiocytoma are other cardiac sarcomas observed. While primary cardiac tumors are extremely uncommon, secondary tumors are more frequently encountered since the heart can theoretically be a site of metastasis by any malignant neoplasm [3,5,6]. The exact incidence of cardiac metastatic disease is unknown.

Pseudotumours are the most frequent cardiac masses encountered and are defined as lesions not originating from a neoplastic transformation of a specific cell type[7]. Among these, thrombi are the most common and their diagnosis is confirmed by the evidence of imaging resolution after appropriate anticoagulant treatment. Other masses defined as pseudotumours are infective vegetations, pericardial cysts and anatomical variants.

Cardiac masses in pediatric patients are usually fibromas and rabdomyomas and malignant tumours are rare[3].

Classification

Due to their heterogeneity and rarity, a univocal classification of cardiac masses lacks.

According to histology, cardiac masses can be classified as:

- Primary benign cardiac tumours,
- Primary malignant cardiac tumours,
- Metastasis,
- Pseudotumours.

Cardiac masses can be intracardiac or can involve pericardial structures or the great vessels. Cardiac masses may growth into cardiac chambers and eventually, involve valvular apparatus or intramurally, with myocardial involvement[8].

Anatomo-pathological characteristics

WHO Classification of Tumours of the Heart and Pericardium classifies cardiac tumours as follows:

- According to their biological behaviour: benign tumors, tumors of uncertain biologic behavior, germ cell tumors, and malignant tumors
- According to localization: heart, pericardium, great vessels.
- According to cell line of origin [9].

Table 1 Adapted from A.Burke, F. Tavora. The 2015 WHO Classification of Tumors Of The Heart

Heart Tumours (WHO 2015)

Benign Tumors and Tumor-Like Conditions
Histiocytoid cardiomyopathy
Hamartoma of mature cardiac myocytes
Adult cellular rhabdomyoma
Cardiac myxoma
Papillary fibroelastoma
Hemangioma
Capillary hemangioma
Cavernous hemangioma
Arteriovenous malformation
Intramuscular hemangioma
Cardiac Fibroma
Lipoma
Cystic tumor of the atrioventricular node
Granular cell tumor
Schwannoma

Tumors of uncertain biologic behavior
Inflammatory myofibroblastic tumor
Paraganglioma

Germ cell tumors
Teratoma, mature
Teratoma, immature
Yolk sac tumor

Malignant tumors
Angiosarcoma
Undifferentiated pleomorphic sarcoma
Osteosarcoma
Myxofibrosarcoma
Leiomyosarcoma
Rhabdomyosarcoma
Synovial sarcoma
Miscellaneous sarcomas
Cardiac lymphomas

Metastatic tumors

Tumors of the pericardium
Solitary fibrous tumor
Malignant
Angiosarcoma
Synovial sarcoma
Malignant mesothelioma
Germ cell tumors
Teratoma, mature
Teratoma, immature
Yolk sac tumor

Benign primary cardiac tumors

The majority of primary cardiac tumors are benign in nature[11,12,13]. Of these benign cardiac tumors, cardiac myxomas by far are the most common entities in adults and rhabdomyomas in the pediatric population.

- **Myxoma**: Cardiac myxomas are the most common primary cardiac tumor in adults, typically affected women with a mean age at diagnosis of 50 years old. They are usually located in the the left atrium, characteristically originating from the mid-portion of the atrial septum by a narrow stalk; 15–20% originate within the right atrium. It is very rare to find a myxoma on the cardiac valves or within the left or right ventricle [2,5]. Myxomas origins from endocardium. There are a few myxoma syndromes (10% of cases) in which a genetic disorder is present, resulting in multiple tumors [5,6,9]:

  a) The Carney complex is one such syndrome, inherited in an autosomal dominant pattern, in which atrial and noncardiac myxomas, schwannomas and various endocrine tumors are present, along with various skin pigmentation abnormalities[20]). The myxomas in this syndrome occur at an earlier age and tend to recur more frequently[21].
  b) LAMB syndrome
  c) NAME syndrome

  On echocardiogram, a myxoma presents as a heterogeneous mobile mass with one of the two basic appearances. These patients also tend to exhibit laboratory abnormalities such as anemia and elevations in inflammatory markers[2,6,1]. Patients with myxomas may report constitutional symptoms, such as fever and weight loss or symptoms related to tumor embolization or flow obstruction.

  Due to the intrinsic risk of embolization, cardiovascular complications and sudden death, surgical resection is indicated and surgery is associated with a low operative mortality and good longterm outcome.

- **Papillary fibroelastoma**: Papillary fibroelastomas (PFE) can arise from endocardium and have a highly mobile stalk. They are usually singular, small (2 to 40 mm) and commonly affect the aortic valve followed by the mitral valve mainly in the downstream side [11,5,6].They are usually too small to provoke valve dysfunction. These tumors are more common in women and older patients. Echocardiographic features of a PFE are small size, with independent motion and attachment to an endocardial surface. Especially on TEE, the borders appear stippled or shimmering, which is due to the vibration at the tumor–blood interface due to the finger-like projections. The latter has been likened to a 'sea anemone' due to the frond-like arms attached to a central pedicle, best seen when the tumor is viewed under water.

  PFE, as well as myxoma, can cause embolic events: either the tumor itself or thrombi that have formed on the tumor embolize, most commonly causing a transient ischemic attack or stroke. Surgical excision is recommended for larger (≥1 cm), left-sided PFEs in patients who are deemed appropriate surgical candidates (young age, low surgical risk) or at the time of cardiac surgery for another cardiovascular condition. Right-sided PFEs should be removed only if large or mobile and associated with hemodynamically significant obstruction or risk of embolism such as can be seen with a patent foramen ovale with right-to-left shunting. Excision significantly decreases the risk of stroke from a PFE [11,5,6,1].

- **Rhabdomyoma**: Rhabdomyomas are the most common primary cardiac tumor in children, typically associated with tuberous sclerosis and, in these cases, tend to be multiple. They are usually located into the ventricular walls or on the atrioventricular valves. At the echocardiogram they appear as small, well-circumscribed (multiple) nodules or a pedunculated mass. Myocardial embedding is possible, emerging as a lobulated, homogeneous and hyperechogenic mass (often brighter than the surrounding myocardium)[1]. Most of these tumors regress spontaneously and so serial echocardiographic follow-up may be sufficient. Resection may be required if the cardiac mass causes obstructive symptoms or arrhythmias [3,6,5,9,12].

- **Fibroma**: cardiac fibromas are the second most common benign cardiac tumor in the pediatric population. On the echocardiogram, they usually appear as a distinct, demarcated, non-contractile and solid, highly echogenic mass within the myocardium. They are commonly located in the left ventricular free wall, anterior free wall or ventricular septum. Only in rare cases they can lead to obstruction and heart failure symptoms due to extension into the cavity. Otherwise, the myocardial location can lead to arrhythmias. These tumors do not spontaneously regress and surgical resection is frequently required [2,5,12,6,9].
- **Lipoma**: Lipomas are composed of benign adipose tissue. The majority of these arise in the subendocardium. Tumor size can range from a few to several centimeters. On echocardiography, lipomas tend to be broad based, immobile, without a pedicle and well circumscribed. They are hyperechoic in the cavity but hypoechoic in the pericardium, homogenous without calcification. Typically lipomas are asymptomatic, but may cause arrhythmias or valvular dysfunction. Compression of the coronary arteries may be caused by subepicardial lipomas. Due to the progressive growth of lipomas along with the potential symptom profile, excision may be required [4,5,9,6,14]
- **Other benign primary cardiac tumors**: Hemangiomas, atrioventricular node tumors and teratomas are even rarer benign tumors that may occur within the heart. Hemangiomas are made up of dilated vascular channels; thus, their echocardiographic appearance is one of an echogenic mass with echolucencies. They can be located within the endocardium, myocardium, epicardium or pericardium, and are commonly seen in the right ventricular free wall or the left ventricular lateral wall. Teratomas, which are extremely rare in adults, arise in the pericardium and can cause tamponade or extrinsic compression of the heart[1].

Malignant primary cardiac tumors

Malignant cardiac tumors constitute 15% of primary cardiac tumors and are usually right-sided or have pericardial or great vessels involvement. Rapid growth, local invasion and hemorrhagic pericardial effusion are all additional signs of malignancies.

- **Sarcomas**: sarcomas are the most common malignant cardiac tumors, typically diagnosed in individuals in their mid-40s. Any type of sarcoma may develop in the heart, but the most common is the angiosarcoma. The predilection site is the right side of the heart, particularly the right atrium. Echocardiographically they emerge as lobulated masses, distinctly heterogeneous with an area of necrosis or hemorrhage. They have no stalk. These tumors tend to have direct pericardial involvement and they may cause pericardial effusions, with or without tamponade. Interestingly, cytology on the pericardial fluid is frequently unrevealing. The signs and symptoms related to a cardiac angiosarcoma therefore often include pericardial chest pain, obstruction, congestion, dyspnea and fatigue. At the times of diagnosis they are usually already metastatic with lung involvement. The prognosis is poor, and without resection, 90% of patients die within one year of diagnosis and even with metastatic disease, surgical debulking does have a survival advantage. Rhabdomyosarcomas are the second most common primary cardiac sarcoma and can arise from any cardiac structure. These tumors occur in multiple sites within the heart and can cause obstruction at multiple levels. The growth is very rapid and the pericardium is early invaded. Leimyosarcomas, osteosarcomas, fibrosarcomas and undifferentiated sarcomas are other rare primary cardiac sarcomas. Adjuvant chemotherapy and radiation have been attempted to improve the poor overall survival; however, no randomized trials have been undertaken. Radiation typically is used for metastatic disease [1,2,5,7,14,15]
- **Lymphoma**: Cardiac lymphomas are less common than sarcomas. On autopsy, 16% of patients with Hodgkin disease and 18% of patients with non-Hodgkin lymphoma had notable cardiac involvement at a median of 20 months after initial diagnosis. In immunocompromised

patients such as post-transplant or HIV patients, primary cardiac lymphomas are more frequent than in general population. These tumors are most commonly diffuse large B-cell lymphomas. On echocardiography, they appear as homogeneous, infiltrating masses leading to 'wall thickening' and restrictive hemodynamics or as nodular masses intruding into the heart chambers, referentially the right heart chambers and especially the right atrium[1]. The AV groove can be affected as well, encasing the right coronary artery, as well as the pericardium with effusion or enfacement. Lymphomas' symptoms are strongly related to the localization, dimensions and infiltration. Diagnosis can be made with cytology testing of pericardial fluid or by transvenous biopsy under echocardiographic guidance. This is a key step as the prognosis of lymphomas is generally much better than that of other primary cardiac masses if patients are eligible for suitable chemotherapy. Radiation therapy is less favorable, and surgical resection is rarely indicated [5,6,9,13,16].

- **Mesothelioma**: malignant mesotheliomas account for half of the primary pericardial tumors. The other half of primary pericardial tumors is benign (teratomas, fibromas and lipomas). These tumors form bulky nodules within the pericardial cavity, encircling the heart, mimicking pericarditis, tamponade or pericardial constriction. Echocardiography typically reveals a pericardial effusion and a tumor encasing the heart; a discrete mass may not be seen. Prognosis is poor, although surgery plus radiation can provide some palliative benefit[1].
- **Metastatic cardiac tumors**: Metastatic involvement of the heart is not rare. Metastases may occur through direct invasion of a nearby tumor, hematogenous spread, transvenous extension through the inferior vena cava or lymphatic spread. The most common tumors with metastatic potential to the heart are lung carcinoma, breast carcinoma, esophageal carcinoma, malignant lymphoma, leukemia and malignant melanoma. Malignant melanoma, due to its hematogenous spread, has the highest propensity to have cardiac involvement. The pericardium tends to be most commonly involved. Renal cell carcinoma reaches the heart by extension through the inferior vena cava, but hematogenous metastases can also be seen.

Cardiac involvement should be suspected in any patient with a known malignancy, who develops new cardiovascular signs or symptoms. Echocardiography should then be undertaken as the initial diagnostic test to evaluate for the presence of cardiac metastatic disease.

Pseudotumours

Pseudotumours are associated with a significant morbidity and mortality even if they do not have an intrinsic malignant potential. In fact, due to their localization and intrinsic characteristics, pseudotumours can cause valve or conduction system disfunction, pulmonary or systemic embolization and flow impairment[7]. Their treatment and prognosis differ from those of other neoplastic lesions. Among pseudotumours are classified:

- **Cardiac thrombi**: cardiac thrombi are the most frequent pseudotumours [4,13]. Thrombi are usually left-sided and are observed in patients with an history of ischemic cardiopathy, atrial fibrillation, mitral valve significative stenosis or dilatative cardiomyopathy. Left atrial thrombi can be wrongly diagnosed as myxomas, in particular, if pedunculated. However, most atrial thrombi are right-sided, nearby central lines or in patients with coagulation abnormalities. Their diagnosis is confirmed by the evidence of imaging resolution after appropriate anticoagulant treatment.
- **Cystic Tumor of the Atrioventricular Node:** cystic tumors of the atrioventricular node are rare choristomatous lesions composed of ectopic glands that occur in the area of the atrioventricular node and the atrial septum[5,9]. Ten percent of patients have other midline defects. Because of these tumors' location, congenital heart block is a typical manifestation. Histologically, the cysts are benign and lined by flattened cuboidal or squamous epithelium. Sudden death is the most common initial manifestation of disease. Most patients are female (in a ratio of 3:1), with the diagnosis being made in the fourth decade of life. Most atrioventricular nodal tumors are diagnosed incidentally at autopsy, with a history of heart

problems or as the cause of sudden death. There are a few case reports of successfully resected atrio- ventricular nodal tumors[9].

- **Pericardial Cysts**: pericardial cysts are formed by incomplete coalescence of fetal lacunae during pericardial development. The estimated incidence of these congenital abnormalities is very low, 1 : 100,000, and they account for up to 7% of mediastinal masses reported in the literature. They typically do not communicate with the pericardial space and are asymptomatic in more than half of the cases. They contain transudate clear serous fluid and are unilocular and lined by endothelium or mesothelium. They are rarely found in children and discovered more commonly in the third or fourth decade of life and have no gender preference. They are usually asymptomatic and found incidentally on chest X rays and can easily be characterized by cardiac CT or MRI.
- **Valvular Vegetations**: Valvular vegetatins are distinguished in:
    a) Infective endocarditis is defined as an infection of the endocardial surfaces of the heart—primarily of 1 or more heart valves, the mural endocardium, or a septal defect. In infective endocarditis, valve lesions are usually irregular and mobile and can cause intracardiac complications - valve perforation, abscesses or pseudoaneurisms, conduction defect and valve function impairment with consequent heart failure – or systemic complications – systemic or pulmonary embolization with intraparenchymal infarcts and abscesses.
    b) Non-infective endocarditis is a non-infective lesions frequently observed in patients in advanced neoplasm or connective tissue diseases as systemic lupus erythematosus. Their pathogenesis is still not clear but seems to be associated with sterile platelets aggregations on damaged endothelium as a consequence of systemic inflammations. Libman-Sacks endocarditis is a type of sterile nonbacterial thrombotic endocarditis secondary to inflammation often see in LES. The condition most commonly involves

the surface of the mitral and aortic valves, but all four cardiac valves and endocardial surfaces such as the chordae tendinae and endocardium surface can be involved. Another form of non-infective endocarditis is marantic endocarditis which usually affects neoplastic or septic patients.

- **Lambl's excrescences**: Lambls's excrescenses are small, filiform strands that are up to 10 mm in length with a thickness of up to 1.5 mm usually in aortic position. They are frequently seen in older patients and do not seem to be related to a significant embolic risk.
- **Anatomical variants**: normal structures that can be wrongly diagnosed as cardiac masses at echocardiogram. Among these, there are the crista terminalis, the Eustachian valve, the pectinate muscles, the Coumadin or Warfarin ridge, the moderator band and others.

Clinical Presentation

Clinical presentation of cardiac masses depends of the size, location, propensity to embolization, invasiveness, and relation with other cardiac structures. Some intracavitary cardiac tumors as lipomas are frequently asymptomatic. Others, like myxomas, represent the paradigm of clinical presentation: symptoms are mostly related to location, morphological characteristics, and cytokine production (particularly IL-6) resulted from mitral valve obstruction which may cause syncope, dyspnea, and pulmonary edema followed by embolic manifestations.

Patients may also present with nonspecific symptoms such as fatigue, cough, fever, arthralgia, myalgia, weight loss, erythematous rash, and laboratory findings of anemia, an increased erythrocyte sedimentation rate, and increased levels of C-reactive protein and gamma globulin (especially in lymphoma). Less common findings are thrombocytopenia, clubbing, cyanosis, or Raynaud phenomenon. In case of intramural masses, symptoms are associated with conduction disturbances and arrhythmias or sudden cardiac death, and, as for fibroma, symptoms may be related to the growth of the mass which may cause vascular obstruction and heart failure. Usually hamartomas, tumors affecting mainly young children, can present with unremitting ventricular tachycardia [13,14,18,19,20].

Diagnostic Work Up

A clear recommendation about diagnostic pathway of cardiac masses is lacking. Cardiac masses should be evaluated throughout non-invasive multimodal imaging in order to define size, morphology, implant site, location, mobility, extension, invasiveness, relationships and tissue characteristics of the lesions.

The non-invasive multimodal diagnostic approach to a patient with a cardiac mass should include:

- Trans-thoracic echocardiography (TTE).
- Transesophageal echocardiography (TEE).
- Cardiac Magnetic Resonance (CMR).
- Computed Tomography (CT).
- Positron Emission Tomography (PET).

Echocardiography represents the first diagnostic approach to a cardiac mass, while CMR, CT, and PET are second and third-level investigations. Each method has different sensitivity and specificity, but their integrated use allows an increase in diagnostic yield.

Overall, the diagnostic algorithm of a cardiac mass should include the following steps:

1. Identification and localization of the mass.
2. Differentiation between benign and malignant nature.
3. Suspicion of the histology or at least differentiation into the 4 sub-groups.

However, it is important to underline that the definitive diagnosis histological or eventually, for cardiac thrombi, the radiological evidence of thrombus resolution after an adequate period of anticoagulation therapy.

Echocardiography

Echocardiography is the first non-invasive diagnostic tool used for the identification of a cardiac mass. It is a low-cost investigation and can easily be performed both in hospital and outpatient settings [3,14,28]. In addition, cardiac masses are often found incidentally during the echocardiography examination. This method allows a dynamic evaluation and visualizes the anatomical extension and pathophysiological impact of the intracardiac mass [26,29].

Echocardiography gives information about:

- Location, extension, and site of implantation of the mass orienting in the diagnosis. For example, myxomas are usually located in the left atrium, while right atrium is usually the site of implant for angiosarcomas[29];
- Morphology and dimensions;
- Mobility;
- Hemodynamic consequences as valve dysfunction and flow obstruction[1,29];
- Presence of multiple masses[5];
- Associated findings: pericardial effusion, cardiac tamponade and constrictive pericarditis;
- Vascularization of the lesion with contrast echocardiography[1].

Echocardiographic also offers the possibility to plan surgery, to follow-up the patient in order to an early identification of a relapse or a progression/regression of the disease[29] and to monitor patients at risk (subjects with a family history of cardiac neoplasia or suffering from syndromes that predispose to the development of cardiac neoplasms).

During the execution of echocardiography, the examinator should evaluate the following characteristics:

- Localization of the masses, with particular attention to ultrasound artifacts (such as refraction or reverberation phenomena) that can be mistakenly considered masses. Multiple echocardiographic windows and special transducers can limit the error [26,28].

- Distinction of a neoplasm from a pseudotumor. After excluding the presence of the so-called normal anatomical variants, it is important to be able to distinguish neoplasm, thrombus, or vegetation[26,28].
- Distinction between benign and malignant neoplasms: benign primary neoplasm (mainly myxomas) should be suspected when the mass implants at the level of the left atrial septum, is pedunculated and protrudes into the left ventricle during diastole. A primary malignant neoplasm can be hypothesized when the mass infiltrates the myocardial wall, is associated with pericardial effusion and is right-sided. Secondary malignant neoplasm is a likely diagnosis in a patient with known malignant neoplasm elsewhere. Pericardial effusion is the most frequently identified manifestation of secondarisms. If present, it should lead to suspicion of cardiac involvement in a patient with known malignancy[30].

Although echocardiography is recognized as the first-line examination in the diagnosis of cardiac masses, it nevertheless has some limitations:

- It is highly operator dependent and relies on the proper acquisition and interpretation of results.
- Provides little information about pericardial infiltration or cardiac masses tissue characterization[3]
- It has important limitations in patients with inadequate acoustic windows [13,14,30].
- It does not allow a global evaluation of cardiac and extracardiac structures.

The echocardiographic evaluation can be performed in 3 ways:

- Trans-thoracic echocardiography (TTE);
- Trans-esophageal echocardiography (TEE);
- Echocardiography with contrast medium.

Transthoracic echocardiography is the first level investigation for the evaluation of cardiac masses. The image quality depends on the level of tissue penetration of the ultrasounds, the transducer frequency, the instrumental settings, and the operators 'skills. Tissue penetration depends on the patient's habits. The TTE allows identifying ventricular and atrial masses, but it is less suitable for small and localized masses in the atrial appendage [32]. It has a sensitivity of 95% and a specificity of 85-90% in the detection of a left ventricular thrombus[30]. Instead, it has a specificity of 99% but a sensitivity <50% in the identification of a left atrial thrombus[30,33]. The left atrial appendage, the site of most atrial thrombi, is difficult to view through a trans-thoracic approach [30,34]. For endocarditis, however, the sensitivity ranges from 58 to 80% and the specificity is 98% [30,32,35].

Trans-esophageal echocardiography has better image resolution and definition than TTE due to the reduced distance between the heart and the transducer, the absence of excessively reflective tissues (lung and bone tissue), and the use of higher frequency transducers. It allows better image quality especially for the posterior cardiac structures (pulmonary veins, left atrium, atrial appendages, and mitral valve) [30,32]. However, it represents a more invasive method than TTE. The TEE is therefore a method to be used where the trans-thoracic one is not conclusive. The advantages in identifying a cardiac mass are represented by the better resolution of the tumor, its implantation site, and the greater ability to visualize tumors located in the right atrium[26]. In the case of ventricular thrombi, trans-esophageal echocardiography is rarely helpful. Despite having a specificity of 96%, it has a sensitivity of 40%. The apex is often not displayed correctly due to the distance from the transducer, representing an obstacle for the resolution of structural details. However, it may be required in patients in whom transthoracic echocardiography is limited by COPD or obesity. TEE has a sensitivity and specificity of 99% in the diagnosis of thrombi in the left atrium. In fact, from the trans-esophageal approach, the left atrium is close to the transducer and the auricle can be visualized[30]. TEE has a sensitivity of 96.8% in identifying cardiac masses, while it has a sensitivity of 97% and a specificity of 91% in identifying valve vegetations[30,32,35].

Echocardiography with contrast medium can be useful to confirm the presence of a mass, evaluate its vascularization and make a differential diagnosis between a malignant tumor, richly vascularized, and a thrombus, that is a non-vascularized mass[3,31]. Benign heart tumors, such as myxomas, have poor vascularization, so differential diagnosis can be more difficult[3,14]. The examination is performed by injecting substances that increase the echogenicity of the myocardial blood flow, increasing the opacification of the heart chambers or the echo density of the signal. The contrast medium is different depending on the heart chambers to be explored. For the right sections, microbubbles (saline solution mixed with air) are used, which remain trapped at the level of the pulmonary capillary bed.

However, this method has numerous limitations that make it currently still little used in clinical practice. The main ones are:

- need for high experience on the part of the operator;
- adverse effects to contrast administration (nausea, vomiting, headache, flushing, confusion)[30].

Cardiac magnetic resonance (CMR)

CMR is now considered the gold standard for non-invasive soft tissue characterization. This due to the different behavior that the signal assumes when, in a magnetic field, it is returned by tissues exposed to specific sequences of radiofrequency pulses. The intensity of the signal relating to a particular tissue depends mainly on its proton density (DP) and its relaxation times, namely T1 and T2. The post-contrast acquisitions also allow further analysis through the enhancement of the signal (early and late) and the study of perfusion through the venous and arterial phase of the contrast medium (MDC)[14]. Compared to CT, CMR allows a dynamic assessment without exposing the patient to ionizing radiation[13].

Cardiac magnetic resonance provides information about:

- Presence and localization of cardiac masses: T1-weighted sequences allow a first macroscopic localization of the lesion, especially if associated with a cancellation of the blood signal (black-blood imaging);
- Definition of the main characteristics of a mass: morphology, size, mobility, infiltrating nature, margins, and relationships with myocardium, pericardial and pericardiac structures14;
- Evaluation of the effects of a mass on myocardial and myocardial structures function using cine sequences (obstruction of the heart chambers, alterations in contractility, or flow turbulence);
- Tissue characterization of a mass: different tissues have different T1 and T2 relaxation times due to their different biochemical composition. The signal differences captured are therefore used to discriminate the composition of the various tissues. Cancer cells are larger than normal, contain more free intracellular water, and are usually associated with the presence of an inflammatory reaction or interstitial edema. The high content of free water results in longer T1 and T2 relaxation times, therefore a greater contrast between the tumor mass and normal tissue. Furthermore, tumors contain lipomatous or fibrous material that has signal characteristics peculiar to MRI[13]. Based on this:
    - low-protein liquid masses, such as pericardial cysts, appear markedly hypointense on T1-weighted images.
    - Thrombus, hemorrhagic lesions, and cysts with blood content are instead characterized by hyperintensity of the signal during the acute phase, and then become hypointense with the progressive degradation of hemoglobin.
    - Tissues consisting predominantly of fat are hyperintense in both T1 and DP sequences. In the suspicion of a lipid-containing lesion, confirmation can be obtained with sequences that selectively cancel the signal returned by fat, such as Fat Saturation (Fat-sat). The latter allows the diagnosis of the lipoma by comparing the unsaturated images (T1, hyperintense fat) with those in which the fat is saturated and appears black.

Liposarcoma, on the other hand, is often more undifferentiated than a benign histotype[14].

- Histological characterization of the mass through the evaluation of early gadolinium enhancement (EGE) and late gadolinium enhancement (LGE): high enhancement in T1-weighted images after gadolinium injection is suggestive of a highly vascularized and malignant lesion, even if 40-50% of benign lesions have moderate contrast. The principle of LGE lies in the fact that in the normal myocardium there is a progressive "wash-out" of gadolinium, while in the presence of fibrosis or tumors with extensive areas of acute inflammation there is a persistence of the signal for about 20 minutes later injection of the gadolinium-based contrast agent. Furthermore, gadolinium accumulates intracellularly in cells damaged by direct tumor invasion, ensuring the persistence of the signal in the damaged myocardium[13]. Intracavitary thrombi are not perfused during the first passage and show neither early enhancement nor LGE. Malignant lesions usually have neo-angiogenesis and therefore present enhancement at the first passage of the contrast medium. Finally, necrotic tumors have slow impregnation (wash-in) during the first pass of gadolinium, which will highlight a perfusion defect and a delayed wash-out of the contrast medium[14].
- Evaluation of any associated signs of malignancy:
    - invasion of extracardiac structures and infiltrating aspects, appreciable as a loss of continuity between the interfaces of the tissues.
    - Involvement of multiple chambers or the right side of the heart.
    - Inhomogeneity of the signal, both before and after administration of the contrast medium, due to the presence of hemorrhages, calcifications, and necrosis.
    - Irregular margins.
    - Diameter> 5 cm.

- Hemorrhagic areas (which appears hyperintense in T1) or pleural/pericardial effusion.
- Heterogeneity in T1 and T2.
- Enhancement during the first perfusion pass and LGE[14,36].

However, cardiac CMR has limitations:

- Need for electrocardiographic gating: the presence of arrhythmias or a high basal heart rate could cause artifacts or low-quality image acquisition.
- Need for breath holding: this can be a problem in patients with important comorbidities. However, respiratory "navigator-tracking" methods can improve image quality even during free breathing.
- Contraindicated in patients with non-MR compatible pacemakers and implantable cardioverter device[13].
- Limitations in the evaluation of small lesions (<2cm) and valvular vegetations (as they are highly mobile).

One of the main advantages of MRI in oncology is the ability to distinguish between neoplasms and pseudotumors, as well as between benign and malignant cardiac neoplasms with an accuracy of 90-95% [37].

Computed tomography (CT)

CT is the second level investigation most often used in oncology14. It has the advantage of rapid acquisition times, as well as a better spatial resolution regarding the involvement of the lungs, pleura, and mediastinum, especially in patients in whom cardiac metastases or primary extracardiac malignancies are suspected[3]. Although, it has a lower ability to characterize lesions and evaluate their infiltration than MRI. CT allows to evaluate the presence of calcifications, which lead to suspect a myxoma, a fibroid or a teratoma, and fat, assuming the hypothesis of a lipoma[14]. It can identify very small lesions, representing a great resource in staging in the case of malignant tumors[3,14]. Like MRI,

CT can distinguish a hemorrhagic pericardial effusion from a serous one, moreover is able to evaluate coronary involvement or obstruction and to distinguish thrombus from cardiac tumors through the use of contrast media.

However, it has several limitations:

- It does not allow the evaluation of heart valves or heart function[3,14];
- High heart rates or arrhythmias can alter image acquisition[3];
- It requires the use of contrast media with the risk of contrast nephropathy [14];
- It exposes the patient to ionizing radiation[3];

A study conducted by D'Angelo et al.[39] highlighted the diagnostic accuracy of CT the diagnosis of primary or secondary malignancy through the evaluation of the following CT parameters:

- irregular margins;
- pericardial effusion;
- invasiveness;
- solid nature, defined based on the density of the mass for the normal heart muscle;
- dimensions;
- MDC uptake, defined as an increase in mass density from baseline;
- pre-contrast features.

The co-presence of 5 or more of the previous CT signs perfectly predicts the presence of a malignant mass (PPV = 100%). A cut-off < 2 CT marks certainly excludes the presence of malignant lesions (NPV = 100%). On the other hand, the presence of 3 or 4 of the previous CT signs does not allow to accurately discriminate the nature of the mass (PPV = 87%) and requires an additional diagnostic modality. In the latter case, the use of PET increases the diagnostic accuracy, reaching a specificity and a VPP of 100% (Figure 2).39.

18-Fluorodeoxyglucose (FDG) Positron Emission Tomography (PET)

PET with 18F-FDG is usually not included in the diagnostic pathway of cardiac masses despite its ability to provide additional information about the benignity or malignancy of a lesion[4,40]. 18-FDG-PET evaluate SUV (standardized uptake value), ie the uptake of glucose by the tissues in proportion to their metabolic activity[4]. Malignant lesions show higher SUV than benign ones because of a more pronounced glucose metabolism[13,41]. PET also allows the tumours staging, to assess the onset of metastases or to confirm the recovery of the disease after surgery or chemotherapy[3,4]. This method, however, still has some limitations:

- Poor anatomical characterization: PET is a functional investigation and does not provide morphological details relating to the mass or its precise location. For this reason, it is often performed in combination with a CT method (CT / PET), or, more rarely, with an MRI (MRI / PET);
- Metastasis identification: the uptake of the radiotracer by the mass does not allow to distinguish a primary cardiac malignant neoplasm from a metastasis;
- Conditions interfering with the evaluation of the SUV: alterations in the acquisition time, plasma glucose level, insulin therapy, can alter the uptake of the radiotracer by tumor cells42.

The study of D'Angelo et al.[39] evaluated the diagnostic accuracy of PET in predicting a diagnosis of primary or secondary cardiac malignancy, taking into account the following parameters: SUVmax, SUVmean, MTV (metabolic tumor volume) and TLG (total lesion glycolysis), activity and tumor volume indicators. It has been shown that these parameters are significantly higher in malignant lesions than in benign ones, with no difference between primary and secondary malignant lesions. The threshold value that emerged is represented by a SUV^3 [4,9]. No benign tumors demonstrated a higher value than this, while most of the malignant tumors had a $SUVmax^3 > 4,9$. This study also highlighted that the SUV is an independent predictor of mortality risk[39].

Only two other studies, one retrospective (Rahbar et al.[42]) and one prospective (Nensa et al.[41]), evaluated the diagnostic accuracy of PET with 18F-FDG in the diagnosis of malignancy. They showed a sensitivity of 100%, taking as a benchmark an SUV equal to 3.5 and 5.2 respectively.

Endomyocardial biopsy (EMB)

Endomyocardial biopsy (EMB) is a commonly performed procedure for the evaluation of cardiac tissue and, according to the "Consensus statement on endomyocardial biopsy from the Association for European Cardiovascular Pathology and the Society for Cardiovascular Pathology", the study of cardiac masses represents one of its fields of application[43]. Biopsy specimens are usually obtained from the right ventricle, through a jugular or femoral venous access, or from the left ventricle, through a transseptal puncture of the interatrial septum or a femoral or brachial arterial access. Left ventricular biopsy, however, is performed only in a few specialized centers, due to the risk of systemic embolization. Standard protocols require the removal of at least 3-5 tissue fragments, each at least 1-2 mm in length. Multiple sampling reduces the risk of false negatives.

The total complication rate is low and ranges between 1-2%; among these, hematoma of the access site, vaso-vagal reaction, arrhythmias, damage of the tricuspid valve, pulmonary or systemic embolization, perforation of a heart chamber with possible cardiac tamponade are the most frequent. However, EMB isn't a risk-free procedure, so it is advisable to carefully select the patients. In particular, this method should be used:

- In the context of a sequential diagnostic process, after the execution of other appropriate non-invasive methods.
- If EBM's result can affect the clinical and therapeutic management of the patient. Although the clinical diagnosis of cardiac masses is mainly carried out through echocardiography, CMR, and/or CT, histology remains a crucial element in determining the histotype, with the help of immunohistochemistry and molecular biology. EBM, therefore, provides crucial information for the treatment and prognosis of cardiac masses and can be a useful tool for pre-

operative diagnosis of intracardiac masses. It is especially indicated in the diagnostic pathway of right-sided cardiac masses that show an infiltrative or obstructive growth pattern, as well as in the differential diagnosis between sarcomas, lymphomas, and metastatic tumors. In addition, non-resectable cardiac masses can benefit from EBM for planning a therapeutic or palliative strategy[43].

INTRODUCTION

Cardiac masses (CM) are a common diagnostic dilemma in daily cardiology clinical practice due to their rarity and heterogeneity. This term includes benign masses (primary tumours and pseudotumours) and malignant ones (primitive tumours and, more frequently, metastasis)[9,44]. Their low prevalence and mixed clinical presentation make the diagnosis of cardiac masses challenging. In fact, they can remain asymptomatic for a long time and provoke symptoms only in an advanced stage. CM's natural history and prognosis depend on their histology, dimensions and localization and clinicians must be able to decide how to manage such patients[45,46]. Thus, a correct diagnosis is pivotal as treatment options differ greatly.

Endomyocardial biopsy (and cardiac surgery) had traditionally been the gold standard for diagnosis of CM, but their invasive nature, cost and technical complexity has reduced their use for routine evaluation, leading to a more extensive request for a second-level cardiac imaging, and reserved it for situations in which diagnosis remains uncertain after non-invasive tests[3]. Two-dimensional (2D) echocardiography is nowadays the first-line imaging method for the initial assessment of CM in order to define their nature and management[31]. Furthermore, with improved echocardiographic resolution due to higher frequency transducers and new imaging modalities, echocardiography, typically performed for other indications, may be the first imaging modality alerting the clinician to the presence of a cardiac mass[47]. Echocardiography can delineate multiple cardiac structures and characteristics of a CM such as its size, morphology, attachment site, extension and hemodynamic effects. Transesophageal echocardiography (TEE), as well as contrast echocardiography and three-dimensional (3D) echocardiography, are frequently used to complement TTE with an improved detection and characterization of CM. These techniques allow for serial imaging over time without the need for radiation, iodine or gadolinium contrast agents[47].

Unfortunately, TTE/TEE alone is often insufficient to precisely define the characteristics of CM and can be limited further by poor acoustic windows, operator dependence and artifacts that can

sometimes be misinterpreted as CM, generating confusion.

In these cases, a stepwise approach with additional imaging tests including Cardiac Magnetic Resonance (CMR), cardiac-Computed Tomography (c-CT) and, eventually a positron emission tomography (PET) with 18F-fluorodexyglucose (18F-FDG), is needed[37,39]. The choice on the best imaging technique depends on initial imaging findings, availability of imaging modalities, institution expertise and clinical situation. Nevertheless, due to its availability, portability, low-cost imaging modality and repeatability, TTE/TEE remain the first-line imaging modality for the assessment of CM, that are usually incidentally found during routine cardiac imaging. However, its diagnostic accuracy has been tested only in small retrospective studies[10,11,48], leaving a gap in knowledge in the clinical utility of the different echocardiographic parameters and their combination in suggesting the histological nature of CM.

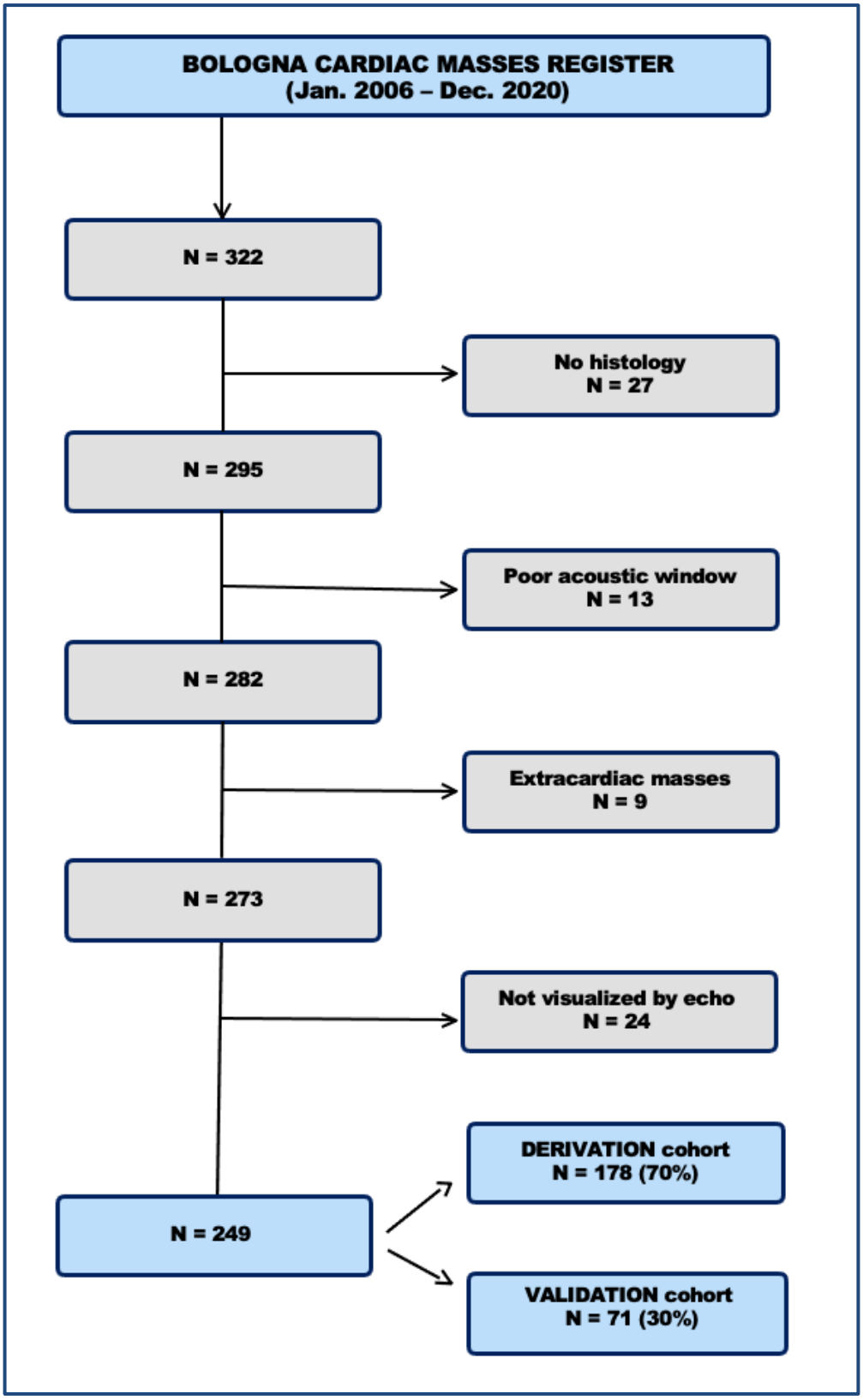
Therefore, to fill this gap, the purposes of this study were i) to evaluate the echocardiographic characteristics of CM and assess diagnostic accuracy of echocardiogram, ii) to determine the combination of parameters that best predicts CM nature and incorporate them into a multiparametric appropriate scoring system to guide physicians in diagnostic and therapeutic pathway; iii) to validate the resulting model in a validation cohort of patients with a diagnosis of CM and iv) to identify the determinants of long-term event-free survival following the diagnosis.

MATERIALS AND METHODS

Study population

The study included all consecutive patients who underwent instrumental investigations for suspected CM at University Hospital Policlinico Sant'Orsola Malpighi, in Bologna, Italy, from January 2006 to December 2020. A total of 249 patients who had a complete 2D-echocardiographic evaluation, and a definitive histologic diagnosis, were considered for the final analysis and for development of the echocardiographic score. A definitive diagnosis was achieved by the histologic examination of bioptic/surgical samples or, in case of cardiac thrombi, by radiological evidence of thrombus resolution after adequate anticoagulant treatment. After the diagnostic work-up, CM were classified as benign or malignant and subsequently subdivided into 4 subtypes: pseudotumours, primary cardiac benign tumours, primary cardiac malignant tumours and secondary cardiac tumours. Pseudotumours were defined as lesions not originating from a neoplastic transformation of a specific cell type. Normal anatomical variants were excluded due to the impossibility of obtaining histological examination. We also excluded infective endocarditis because in its diagnostic pathway echocardiography could only support clinical and biological findings clinical and diagnosis is mainly driven by clinical presentation. We also excluded patients who had a poor acoustic window and those in which masses seemed to be intracardiac at TTE but were later confirmed to be extracardiac at a second level imaging approach. The study flow chart is shown in **Figure 1**.

Figure 1. Study Flow-chart.



Pathology

Cardiac tissue masses were evaluated following surgical resection, biopsies, autopsy or analysis of pericardial fluid. All cases were classified according to the World Health Organization 2015 Classification of Tumors of the Heart and Pericardium[9]; Sarcomas were graded according the Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC) system[49,50]. A fourth, extremely heterogenous subgroup, is represented by pseudo-tumours, which are non-neoplastic lesions - such as thrombi or valvular nodules - not included in the current World Health Organization classification of cardiac tumours[51]. As regarding pseudotumours, thrombi are the most common intracardiac masses and their diagnosis is confirmed by the evidence of imaging resolution after appropriate anticoagulant treatment (systemic anticoagulation therapy with either infusion of unfractionated heparin or a therapeutic dose (1 mg/kg) of subcutaneous low–molecular weight heparin and then after three months or more with warfarin therapy (international normalized ratio [INR], between 2 and 3).

Data collection and outcomes

For each patient, demographic and clinical data were collected, including age, sex, anthropometric data, cardiovascular risk factors, history of comorbidities, and first admission diagnosis. All patients underwent a complete diagnostic work-up including clinical evaluation and laboratory testing (with specific examinations according to the clinical scenario). The echocardiographic protocol is reported in the Echocardiography section. In case of uncertain nature and/or localization, second level instrumental investigations were performed. When a second-level imaging technique was required, the choice between C-CT, MR, 18F-FDG PET/CT varied according to each specific case. All patients were followed after the index presentation and clinical follow-up data were obtained from clinical visits or telephone interviews.

All patients were managed in accordance with the Declaration of Helsinki and provided informed consent for anonymous publication of scientific data. All authors have read and approved the final version of the manuscript and have no conflict of interest to declare in relation to the present work.
The study protocol was approved by the local ethics committee (Comitato Etico Indipendente dell'Azienda Ospedaliero-Universitaria di Bologna, Policlinico S. Orsola-Malpighi, registration number102/2017/0/0ss).

Echocardiography

All CM were evaluated by 2D-echocardiogram using a high-quality ultrasound machine (Philips iE33 or EPIQ) with a TTE probe (S5-1). Echocardiographic evaluation was performed in accordance with the recommendations of the American Society of Echocardiography and the European Association of Cardiovascular Imaging with the subjects in the left lateral recumbent position with the use of standard parasternal and apical views[52,53,54]. At least 3 consecutive beats were recorded for each view and all images were stored for offline analysis (Philips software, Intellispace). The analysis of the images recorded was performed off-line by two expert echocardiography cardiologists, with more than 10-years' experience in cardiac imaging, blinded to clinical information and CM histology, using the Philips IntelliSpace calculation software package. Disagreements in imaging evaluation were solved by a third echocardiography cardiologist. To assess the echocardiographic sensitivity, we compared CM echocardiography diagnosis with definitive histological diagnosis.
The presence of the mass, the location (left/right atrium/ventricle/pericardium, great vessels), the site of attachment (interatrial/interventricular septum or roof/side wall of the atrium, ventricular free-wall), the largest dimension, shape (regular/irregular), margins (well defined/irregular - if more than 50% of the border is not clearly demarcated), mass characteristics (sessile - attached directly by the base and not raised upon a stalk or peduncle, pedunculated - raised upon a stalk, polylobate - having two or more lobes), the mobility, the presence of infiltration (defined as disruption of neighboring tissue and extension of the mass across the pericardium into myocardium, with interruption of

epicardial and endocardial contours or, alternatively, by the presence of at least one of the following echocardiographic features i) evidence of a different echogenicity compared to the normal myocardium - infiltrating masses could have a peculiar, granular echocardiographic texture; ii) increased thickness in comparison with the adjacent myocardial segments; iii) hypo/akinesia of a focal myocardial area compared to closest cardiac segments in absence of coronary distribution that could lead to the suspicion of ischemic etiology)[55], the presence of pericardial effusion (defined as a fluid accumulation between the two pericardial layers), the echogenicity patter (hypo-, iso- or hyperechogenic as compared with normal myocardium) and associated valvular abnormalities were assessed.

Statistical analyses

Data are reported as mean and SD or median and interquartile range. Pearson χ^2 test was used to compare categorical variables among groups. The normality of the distribution of continuous variables was assessed using Shapiro-Wilks test and equality of variance was tested between groups using Levene's test. In the case of departure from normality, non-parametric tests were used (Mann-Whitney or Kruskal-Wallis test), while Welch test was used when variances were unequal between groups. To assess diagnostic accuracy, the diagnostic endpoint was the presence of a confirmed CM. Accuracy indicators (sensitivity and PPV) were calculated by standard formulas. Lastly, we analyzed the predictive validity of an echocardiographic score using Kaplan-Meier survival estimates. Statistical analyses were performed using IBM SPSS, version 25.

Model creation

The study population was randomly split into a derivation sample, including about 70% of cases (N = 178) and a validation sample, including the remaining 71 cases. Echocardiography variables which were potentially predictive of the presence of a malignant mass in the derivation sample were included in univariable logistic regression analyses. There were 7 dichotomous variables: irregular margins,

moderate/severe pericardial effusion, inhomogeneity, immobility, polylobate, infiltration, non-left localization and one continuous variable, i.e., diameter. For the variables significantly associated with malignancy in simple logistic regression analyses, we calculated the AUC to determine their accuracy to diagnose malignant masses. Variables showing statistical significance at the 5% level in univariable logistic regression were selected for multivariable logistic regression analysis with a stepwise procedure and robust standard errors, avoiding combinations of variables that would lead to collinearity. The model with the minimum AIC value and the highest Nagelkerke R^2 was selected as the one best fitting the data. Brier's score was used to determine the calibration of the model. It ranges from 0 to 1: lower scores denote better calibration of the predictions. Variables predicting independently malignancy in the multivariable logistic regression analysis were used to build a predictive score. Specifically, the regression coefficient of each of these variables was divided by the smallest coefficient in the model and allocated a weight based on rounding off to the nearest integer. The overall risk score for the sample was obtained by summing the weights thereby obtained from all coefficients. Bar charts were drawn to show the frequency distribution of patients for increasing values of the score. Cut-offs for all points of the scores were created. For each cutoff, accuracy indicators of malignancy were calculated. Youden's index, computed as sensitivity + specificity -1, was used to identify the optimal cut-off to detect malignancy.

Model validation

Bootstrap validation was used to determine the performance of the prediction model set up in the derivation sample on hypothetical sets of new patients[56]. In particular, 5000 bootstrap datasets were created by sampling "with replacement" from the original dataset. The median regression coefficients obtained from the bootstrap procedure were compared with those of the original model to determine whether the weights assigned to the variables were accurate. The performance of the score was also tested in the validation sample (including 30% of patients) using ROC analysis. The ability of the score to predict patient survival was estimated using Kaplan-Meier curves in the overall sample.

Statistical analyses were carried out using JASP, version 0.14.1, Copyright 2013-2020, University of Amsterdam and IBM SPSS, version 25.0.

RESULTS

Sample overview

A total of 322 patients, included in the Bologna Cardiac Masses Registry, underwent complete recorded TTE and/or TEE echocardiographic evaluation from January 2006 to December 2020 in our Cardiovascular Department at University of Bologna, Italy. We had to exclude 27 CM from the original sample because of the lack of a definitive histological diagnosis and 13 CM because of a poor acoustic window. Finally, 282 CM with a definitive diagnosis obtained with histological examination or, in case of cardiac thrombi, with radiological evidence of thrombus resolution after an appropriate anticoagulant treatment were considered for the analysis. The final study sample consisted of 249 patients, in fact 24 CM were excluded because not visualized by echocardiogram but detected at CT, MRI or 18-FD PET and 9 CM echocardiographically diagnosed as intracardiac were later confirmed extracardiac with a second level imaging approach (**Figure 1**). Therefore, the diagnostic sensitivity of TTE in detecting a CM was 91%, with a positive predictive value (PPV) of 96% and a diagnostic accuracy of 88%. Among the 24 masses not visualized by TTE, 7 were localized in the pericardium and 7 involved the great vessels (6 pulmonary artery sarcoma and 1 pulmonary artery choriocarcinoma) and 8 had a maximum diameter of less than 30 mm. The remaining 2 CM were small myxomas incidentally found during valve surgery.

Histological diagnosis was obtained by endomyocardial biopsy in 29 patients, by cytologic analysis of pericardial effusion in 26 patients, by surgical samples in 166 patients and by autopsy in 5 patients. 27 patients had radiological evidence of thrombus resolution after an adequate anticoagulant regimen. 4 patients who had a first histological diagnosis with cytological analysis of pericardial fluid or with endomyocardial biopsy, subsequently underwent to surgical excision of the mass and had a second histological confirmation. Based on the histopathologic examination, we identified 181 (72%) patients with benign CM [123 (49%) primary cardiac benign tumours – mainly constituted by

myxomas, followed by papillary fibroelastomas, and 58 (23%) pseudo-tumours, in particular thrombi]. Malignant CM were 68 (28%), mainly represented by secondary lesions **(Table 2).**

Table 2. Histological characterization of benign and malignant masses.

CARDIAC MASSES (N = 249)			
Benign masses N = 181		**Malignant masses N = 68**	
Primitive benign tumours 49% (n = 123)		*Primitive malignant tumours 9% (n = 21)*	
Myxoma	77 (95)	Sarcoma,	81 (17)
Fibroelastoma	17 (20)	Lymphoma	14 (3)
Lipoma	3 (4)	Mesotelioma	5 (1)
Fibroma	2 (3)		
Paraganglioma	1 (1)		
Pseudo-tumours 23% (n = 58)		*Metastasis 19% (n = 47)*	
Thrombus	48 (28)	Lymphoma	41 (19)
Cyst	14 (8)	Sarcoma	13 (6)
Valvular nodule	14 (8)	Melanoma	11 (5)
Lipomatosis	10 (6)	Hepatocellular carcinoma	11 (5)
Reactive inflammatory process	9 (5)	Colon carcinoma	6 (3)
Calcification	3 (2)	Renal and urological tumor	6 (3)
Cystic atrioventricular node tumor	2 (1)	Lung carcinoma	6 (3)
		Gynecological tumor	4 (2)
		Plasmacytoma	2 (1)

Every patient enrolled completed the follow-up, with the median follow-up time of 28 months.

Derivation vs Validation Cohort

To predict the benign versus malignant nature of CM according to echocardiographic characteristic, from the study population we randomly create a **derivation cohort**, including 70% of cases (N = 178) on which the Diagnostic Echocardiographic Mass (DEM) Score was derivate and a second

sample, including the remaining 71 cases, on which the score was validated (**validation cohort**). The mean age of our population was 60.5 ±15.8 years (range 22-91), and 135 were women (54.2%). As shown in **Table 3**, clinical and demographic criteria did not differ between the derivation and the validation cohort, except for a slightly more frequent accidental diagnosis in the validation cohort (p = 0.048). Regarding echocardiographic parameters, the two cohort only differed for the presence of more sessile masses in the validation cohort and more pedunculated mass in the validation cohort (p = 0.024 and p = 0.04, respectively). All patients' characteristics of each cohort are summarized in **Table 3.**

Table 3. Comparison of demographic, anamnestic, clinical and laboratory features between Derivation and Validation cohorts.

	Total population	**Derivation cohort**	**Validation cohort**	**P value**
	N = 249	**N = 178**	**N = 71**	
Male gender, n (%)	114 (44.8)	87 (48.9)	27 (38.0)	ns
Age in years, mean ± SD	60.5 ± 15.8	60.6 ±15.8	60.4±15.8	ns
BMI in kg/m^{2,} mean ± SD	25.3 ± 4.2	25.3 ± 4.2	25.4 ± 4.4	ns
Cardiovascular risk factors				
Smoking habit, n (%)	126 (51.2)	92 (52.3)	34 (48.6)	ns
Hypertension, n (%)	143 (58.1)	105 (59.7)	38 (54.3)	ns
Dyslipidemia, n (%)	113 (46.1)	75 (42.6)	38 (55.1)	ns
DM, n (%)	39 (15.9)	27 (15.3)	12 (17.1)	ns
Medical History				
Congestive Heart failure, n (%)	33 (13.7)	24 (14.0)	9 (13.0)	ns
Prior stroke, n (%)	60 (24.5)	43 (24.7)	17 (23.9)	ns
History of neoplasia, n (%)	77 (31.3)	55 (31.4)	22 (31.0)	ns
CHA2DS2-VASc, mean ± SD	2.8 ± 1.9	2.8 ± 1.9	2.9 ± 1.9	ns
Histology and location				
Malignant mass, n (%)	68 (27.3)	51 (28.7)	17 (23.9)	ns
Pseudotumor	58 (22.3)	45 (25.3)	13 (18.3)	ns
Primitive Benign	123 (49.4)	82 (46.1)	41 (57.7)	ns

Primitive Malignant	21 (8.4)	16 (9.0)	5 (7.7)	ns
Metastasis	47 (18.9)	35 (19.7)	12 (16.9)	ns
Right cardiac chambers	73 (29.3)	50 (28.1)	23 (32.4)	ns
Left cardiac chambers	145 (58.2)	103 (57.9)	42 (59.2)	ns
Pericardium	22 (8.8)	17 (9.6)	5 (7.0)	ns
Great vessels	9 (3.6)	8 (4.5)	4 (1.4)	ns
Clinical features				
Accidental diagnosis, n (%)	96 (39.2)	61 (34.9)	35 (49.3)	0.028
Dyspnea, n (%)	103 (42.2)	79 (45.1)	24 (34.8)	ns
NYHA classes, n (%)				
I- II	176 (73.6)	124 (72.9)	52 (75.4)	ns
III-IV	70 (26.5)	46 (27.1)	17 (24.6)	ns
Chest pain, n (%)	37 (15.2)	27 (15.4)	10 (14.5)	ns
Peripheral embolism, n (%)	37 (15.2)	28 (16.0)	9 (13.0)	ns
Pulmonary embolism, n (%)	23 (9.4)	17 (19.7)	6 (8.7)	ns
Laboratory parameters				
Creatinine in mg/dL, median [IQR]	0.88 [1.04-0.76]	0.9 [1.07-0.76]	0.87 [1.0-0.77]	ns
GFR mL/min, median [IQR]	82.5 [97.7-62.4]	82.4 [98.2-61.0]	83.3 [97.6-64.4]	ns
Hb in g/dL, median [IQR]	12.8 [13.9-11.4]	12.8 [14.0-11.8]	12.4 [13.8-11.0]	ns
WBC in n/mmc, median [IQR]	7.565 [10.000-6.170]	7.630 [10.240-6.110]	7.490 [9.125-6.375]	ns
CRP in mg/dL, median [IQR]	1 [4.0-0.32]	1.15 [4.18 – 0.35]	0.69 [3.4 – 0.17]	ns
Echocardiographic features				
EF, mean ± SD	60.2 ±9.5	59.5 ± 10.2	62 ± 7.4	ns
Pericardial effusion, n (%)				
Mild, n (%)	32 (55.2)	28 (58.3)	4 (40.0)	ns
Moderate/severe, n (%)	26 (44.8)	20 (41.7)	6 (60.0)	ns
Infiltration, n (%)	51 (20.6)	40 (22.6)	11 (15.5)	ns
Implant				
Lat/sup. atrial wall, n (%)	49 (19.7)	32 (18.0)	17 (23.9)	
IAS, n (%)	79 (31.7)	51 (28.7)	28 (39.4)	
Max. diam. mm, mean ± SD	35.8 ± 20.1	36.9 ±21.2	33.1 ±16.9	ns
Diameter > 30mm, n (%)	129 (51.8)	95 (53.4)	34 (47.9)	ns
Inhomogeneity, n (%)	63 (25.3)	48 (27.0)	15 (21.1)	ns
Irregular margins, n (%)	64 (25.8)	48 (27.0)	16 (22.9)	ns
Mobility, n (%)	123 (49.4)	84 (47.2)	39 (54.9)	ns
Sessile mass, n (%)	106 (42.7)	84 (47.2)	22 (31.4)	0.024
Polylobate mass, n (%)	69 (27.8)	47 (26.4)	22 (31.4)	ns

Continuous variables are presented as mean (SD) or median (IQR), when appropriate; categorical ones as n (%). Abbreviations: BMI: body mass index; DM: Diabetes Mellitus; NYHA: New York Heart Association; GFR: glomerular filtration rate; Hb: hemoglobin; WBC: white blood cells; CPR: C-reactive protein; EF: ejection fraction.

Derivation cohort: benign vs malignant masses

Over the 178 patients with CM pathologically confirmed, benign CM were detected in 127 (71.3%), while malignant CM were observed in 51 patients. No significant differences were observed for most of the demographic characteristics, cardiovascular risk factors and comorbidities between benign and malignant masses. However, the male gender was more frequently represented in malignant masses than in the benignant ones ($p = 0.03$). Benign formations were often located in the left heart chambers while malignancies were usually detected on the right side, in the pericardium or the pulmonary arteries ($p < 0.005$). Clinical presentation was different because malignant masses presented significantly more dyspnea ($p < 0.005$), mostly NYHA Class III/IV ($p < 0.005$), and a lower rate of incidental diagnosis than benign ones ($p = 0.001$). On the other hand, patients with benign masses exhibited a greater occurrence of incidental diagnosis and peripheral embolization compared to the malignant ones ($p = 0.001$ for both). Laboratory findings were similar between the two groups, except for C-Reactive Protein (CRP) values, which were significantly higher in patients with malignant CM than in those with benignant ones ($p = 0.009$) **(Table 4)**.

Table 4. Comparison of clinical and laboratory parameters between cardiac benign and malignant masses in the Derivation Cohort.

Variables	**Benign cardiac Masses N = 127**	**Malignant cardiac Masses N = 51**	**P-value**
Male gender, n (%)	53 (41.7)	34 (66.7)	0.003
Age in years, mean ± SD	61.0 ± 15.3	59.3 ± 17.2	ns
BMI in kg/m^2, mean ± SD	24.8 ± 3.7	26.5± 5.0	0.02
Cardiovascular risk factors			

Smoking Habit, n (%)	66 (52.4)	26 (52.0)	ns
Hypertension, n (%)	80 (63.5)	25 (50.0)	ns
Dyslipidemia, n (%)	56 (44.4)	19 (38.0)	ns
DM, n (%)	20 (15.9)	7 (14.0)	ns
Medical History			
Congestive Heart Failure, n (%)	17 (13.9)	7 (14.0)	ns
Prior stroke, n (%)	33 (26.6)	10 (20.0)	ns
History of cancer, n (%)	38 (30.2)	17 (34.7)	ns
CHA2D2-VASc, mean ± SD	2.9± 1.9	2.4 ±1.9	ns
Location			
Right cardiac chambers, n (%)	21 (16.5)	29 (56.9)	<0.001
Left cardiac chambers, n (%)	96 (75.6)	7 (13.7)	<0.001
Pericardium, n (%)	9 (7.1)	8 (15.7)	ns
Great Vessels, n (%)	1 (0.8)	7 (13.7)	<0.001
Clinical Presentation			
Incidental diagnosis, n (%)	53 (42.4)	8 (16.0)	0.001
Dyspnea, n (%)	46 (36.8)	33 (66.0)	<0.001
NHYA Class, n (%)			<0.001
I-II	100 (81.3)	24 (51.)	
III-IV	23 (18.7)	23 (48.9)	
Chest pain, n (%)	18 (14.4)	9 (18.0)	ns
Peripheral embolism, n (%)	24 (19,2)	4 (8.0)	0.001
Pulmonary embolism, n (%)	6 (4.8)	11 (22.0)	0.001
Laboratory parameters			
Creatinine levels in mg/dL, median [IQR]	0.89 [1.04-0.76]	0.94 [1.15-0.75]	ns
GFR in mL/min/1.73 m2, median [IQR]	82.3 [97.8-62.3]	84.9 [100.6-59.9]	ns
Hb in g/dL, median [IQR]	13.0 [14.0-12.05]	12.05 [14.3-10.7]	ns
WBC in n/mmc, median [IQR]	7.370 [9.490 – 6.000]	9.085 [10.810-6.400]	ns
CRP in mg/dL, median [IQR]	0.8 [2.55-0.31]	3.9 [6.9-0.7]	0.009

Continuous variables are presented as mean (SD) or median (IQR), when appropriate; categorical ones as n (%). Abbreviations: BMI: body mass index; DM: Diabetes Mellitus; NYHA: New York Heart Association; GFR: glomerular filtration rate; Hb: hemoglobin; WBC: white blood cells; CPR: C-reactive protein.

Moreover, the vast majority of echocardiographic parameters differ significantly between benign and malignant masses and their evaluation could help in orienting the diagnosis. Benign cardiac masses were localized predominantly in left heart chambers and were more frequently pedunculated ($p < 0.001$), mobile ($p < 0.005$) and adhered to interatrial septum ($p < 0.001$). On the other side, malignant masses showed a greater diameter, in particular a diameter > 30 mm was statistically significantly associated with malignancies ($p < 0.001$) and exhibited higher frequency of irregular margins ($p < 0.001$), an inhomogeneous appearance ($p < 0.001$), sessile implantation ($p < 0.005$) and polylobate shape ($p < 0.001$). Finally, compared to benign ones, malignant masses presented more frequently pericardial effusion ($p < 0.001$); besides, when pericardial effusion present in benign tumours, it is usually of milder degree ($p = 0.001$) (**Table 5)**.

Table 5. Comparison of echocardiographic features between Benign or Malignant Masses in the Derivation Cohort.

Variables	**Benign cardiac Masses N = 127**	**Malignant cardiac Masses N = 51**	**P-value**
EF, mean ± SD	59.0 ± 11.4	60.8 ± 6.1	ns
Pericardial effusion, n (%)			
Mild	14 (93.3)	14 (42.4)	0.001
Moderate/ Severe	1 (6.7)	19 (57.6)	<0.001
Infiltration, n (%)	6 (4.7)	34 (68.0)	<0.001
Implant			
Lat./sup. atrial wall, n (%)	13 (10.2)	19 (37.3)	<0.001
Left IAS, n (%)	11 (8.7)	3 (5.9)	ns
Max. diameter mm, mean ± DS	30.9 ±16.9	52.1 ±23.3	<0.001
Diameter > 30mm, n (%)	51 (40.2)	44 (86.3)	<0.001
Inhomogeneity, n (%)	17 (13.4)	31 (60.8)	<0.001
Irregular margins, n (%)	17 (13.4)	31 (60.8)	<0.001
Mobility, n (%)	77 (60.6)	7 (13.7)	<0.001
Sessile mass, n (%)	47 (37.0)	37 (72.5)	<0.001
Polylobate mass, n (%)	14 (11.0)	33 (64.7)	<0.001

Continuous variables are presented as mean (SD), while categorical ones as n (%). Abbreviations: EF: Ejection Fraction, IAS: Inter-Atrial Septum.

Validation cohort: benign vs malignant masses

The validation cohort included 71 consecutive patients (54 with benign cardiac masses and 17 with malignat cardiac masses). As shown in **table 6,** patients with malignant masses were more frequently male (p=0.043); with dyspnea (p =0.02), mostly NYHA Class III/IV (p = 0.025).

Table 6. Comparison of clinical and laboratory parameters between cardiac benign and malignant masses in the Validation Cohort.

Variables	**Benign cardiac Masses N = 54**	**Malignant cardiac Masses N = 17**	**P-value**
Age in years, mean ± SD	59.6 ± 16.0	62.6 ± 15.2	ns
Male gender, n (%)	17 (31.5)	10 (58.8)	0.043
BMI in kg/m^2, mean ± SD	25.4 ± 4.5	25.4 ± 4.3	ns
Cardiovascular risk factors			
Smoking Habit, n (%)	25 (47.2)	9 (52.9)	ns
Hypertension, n (%)	27 (50.9)	11 (64.7)	ns
Hypercholesterolemia, n (%)	31 (59.6)	7 (41.2)	ns
Diabetes mellitus, n (%)	9 (17.0)	3 (17.6)	ns
Medical History			
Congestive heart failure, n (%)	7 (13.5)	2 (11.8)	ns
Prior stroke, n (%)	14 (25.9)	3 (17.6)	ns
History of cancer, n (%)	15 (27.8)	7 (41.2)	ns
CHA2D2-VASc, mean ± SD	3 ± 1.8	2.6 ± 2.1	ns
Location			
Right cardiac chambers, n (%)	13 (24.1)	10 (58.8)	0.008
Left cardiac chambers, n (%)	38 (70.4)	4 (23.5)	0.001
Pericardium, n (%)	3 (5.6)	2 (11.8)	ns
Great vessels, n (%)	0 (%)	1 (5.9)	ns

Clinical Presentation			
Incidental diagnosis, n (%)	28 (51.9)	7 (43.8)	ns
Dyspnea, n (%)	15 (27.8)	9 (60.0)	0.02
NHYA Class, n (%)			0.025
I-II	44 (81.5)	8 (53.3)	
III-IV	10 (18.5)	7 (46.7)	
Chest pain, n (%)	7 (13.0)	3 (20.0)	ns
Peripheral embolism, n (%)	8 (14.8)	1 (6.7)	ns
Pulmonary embolism, n (%)	3 (5.6)	3 (20.0)	ns

Laboratory parameters			
Creatinine levels in mg/dL, median [IQR]	0.87 [1.0-0.78]	0.86 [0.97-0.72]	ns
GFR in mL/min/1.73 m2, median [IQR]	80.3 [94.4-63.9]	86.6 [100.8-72.7]	ns
Hemoglobin in g/dL, median [IQR]	12.75 [13.9 -11.4]	11.2 [13.1-10.3]	0.048
WBC in n/mmc, median [IQR]	7.270 [8.560 – 6.300]	8.870 [10.500-6.960]	0.023
CRP levels in mg/dL, median [IQR]	0.43 [1.67-0.13]	4.0 [5.95-0.88]	0.027

Continuous variables are presented as mean (SD) or median (IQR), when appropriate; categorical ones as n (%). Abbreviations: BMI: body mass index; DM: Diabetes Mellitus; NYHA: New York Heart Association; GFR: glomerular filtration rate; Hb: hemoglobin; WBC: white blood cells; CPR: C-reactive protein.

Echocardiographic parameters **(Table 7)** differ significantly between benign and malignant masses. Benign cardiac masses were localized predominantly in left heart chambers and were more frequently mobile ($p < 0.001$). On the other hand, malignant masses showed a greater diameter, in particular a diameter > 30 mm was statistically significantly associated with malignancies ($p < 0.001$) and exhibited higher frequency of irregular margins ($p < 0.001$), an inhomogeneous appearance ($p < 0.001$) and polylobate shape ($p < 0.001$).

Table 7. Comparison of echocardiographic features between Benign or Malignant Masses in the Validation Cohort.

Variables	**Benign cardiac Masses N = 54**	**Malignant cardiac Masses N = 17**	**P-value**
EF, mean ± SD	62.3 ± 8.05	61.1 ± 4.9	ns

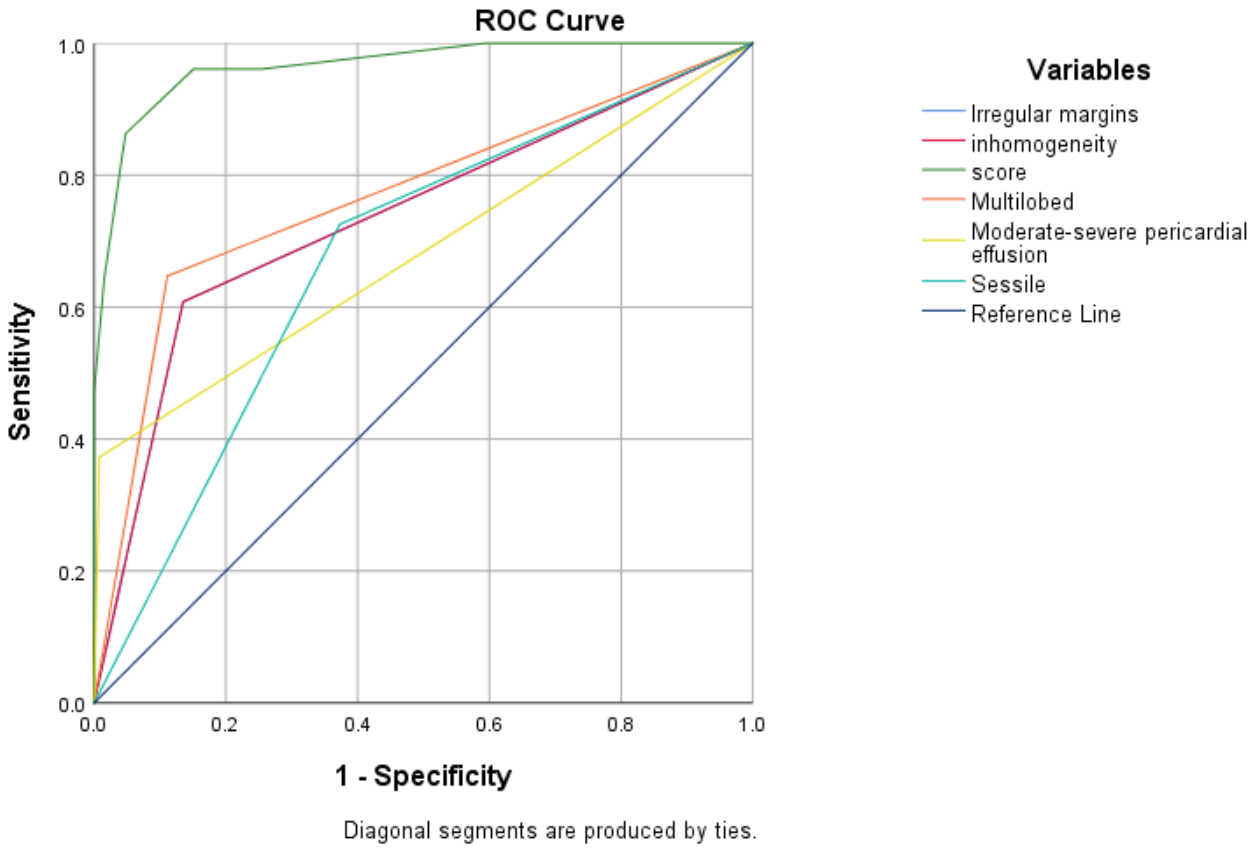
Pericardial effusion, n (%)			
Mild	0 (0.0)	4 (40.0)	ns
Moderate/Severe	0 (0.0)	6 (60.0)	ns
Infiltration, n (%)	1 (1.9)	10 (58.8)	
Implant			
Lat./sup. atrial wall, n (%)	10 (18.5)	7 (41.2)	ns
Left IAS, n (%)	5 (9.3)	1 (5.9)	ns
Max. diameter mm, mean ± DS	29.07 ± 13.07	45.9 ± 21.3	<0.001
Diameter > 30mm, n (%)	20 (37.0)	14 (82.4)	0.001
Inhomogeneity, n (%)	6 (11.1)	9 (52.9)	<0.001
Irregular margins, n (%)	7 (13.0)	9 (56.3)	<0.001
Mobility, n (%)	36 (66.7)	3 (17.6)	<0.001
Sessile mass, n (%)	14 (25.9)	8 (50.0)	ns
Polylobate mass, n (%)	9 (16.7)	13 (81.3)	<0.001

Continuous variables are presented as mean (SD), while categorical ones as n (%). Abbreviations: EF: Ejection Fraction, IAS: Inter-Atrial Septum.

Score development

Six variables were identified as independent predictors of malignancy in univariate logistic regression models: infiltration (β=3.4 [OR =32.35]), moderate-severe pericardial effusion (β=2.9 [OR=18.06]), polylobate shape (β=2.4 [OR=11.07]), sessile (β=2.03 [OR=7.61]), inhomogeneity (β=1.77 [OR=5.87], non-left mass localization (β=1.4 [OR=4.24]) (Table 5). The model including these variables had an overall AUC=0.969, a sensitivity = 0.840, a specificity = 0.960 and an accuracy = 0.894. Brier's score was 0.057, denoting good calibration. The ROC curves and the corresponding AUC of echography dichotomous variables significantly associated with malignancy at $p < 0.05$ in the univariate logistic regression models are shown in **Figure 2.**

Figure 2. ROC curves for the echography predicting malignant masses in univariate analyses and for the DEM score.



In order to identify the set of independent predictors of malignant masses, the six variables were entered into a multivariable logistic regression model (**Table 8**).

Table 8. Multivariable logistic regression model showing the variables independently associated with malignancy.

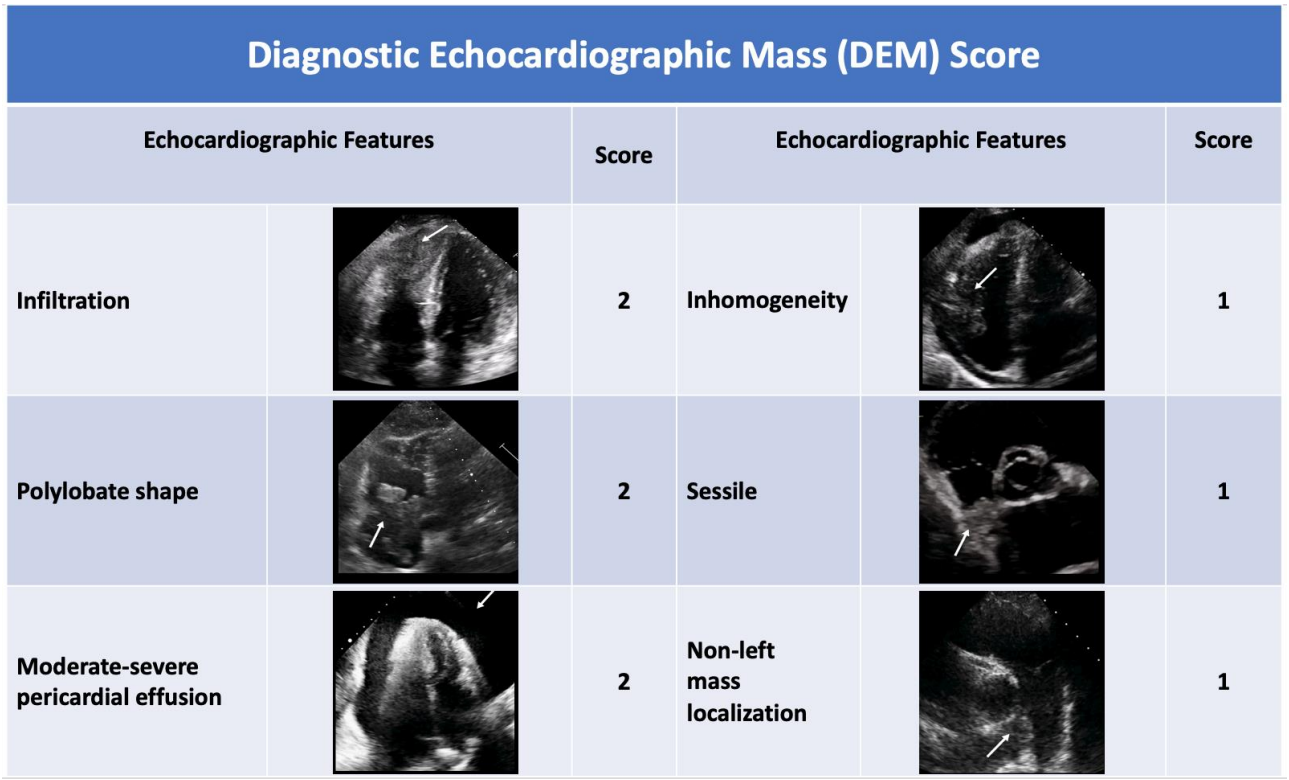
	β-Estimate	**Robust Standard Error**	**Odds Ratio**	**Z value**	**Wald Statistic**	**Weight**	**Score**
(Intercept)	5.693	1.042	0.003	5.466	30.179		
Infiltration	3.477	0.679	32.348	5.121	17.996	2.40	**2**
Polylobate mass	2.404	0.656	11.068	3.665	11.782	2	**2**

Pericardial effusion (*)	2.894	1.459	18.062	1.983	5.589	1.66	**2**
Sessile	2.03	0.639	7.616	3.178	7.702	1.40	**1**
Inhomogeneous	1,77	0.643	5.869	2.753	7.284	1.22	**1**
Non-left mass localization	1.445	0.656	4.242	2.201	4.667	1	**1**

*Moderate-severe;

Based on the weight assigned to regression coefficients, a DEM score ranging from 0 to 9 was obtained from these 6 variables: infiltration, polylobate shape and moderate-severe pericardial effusion, 2 points; inhomogeneity, sessile, non-left mass localization, 1 point each (**Figure 3**).

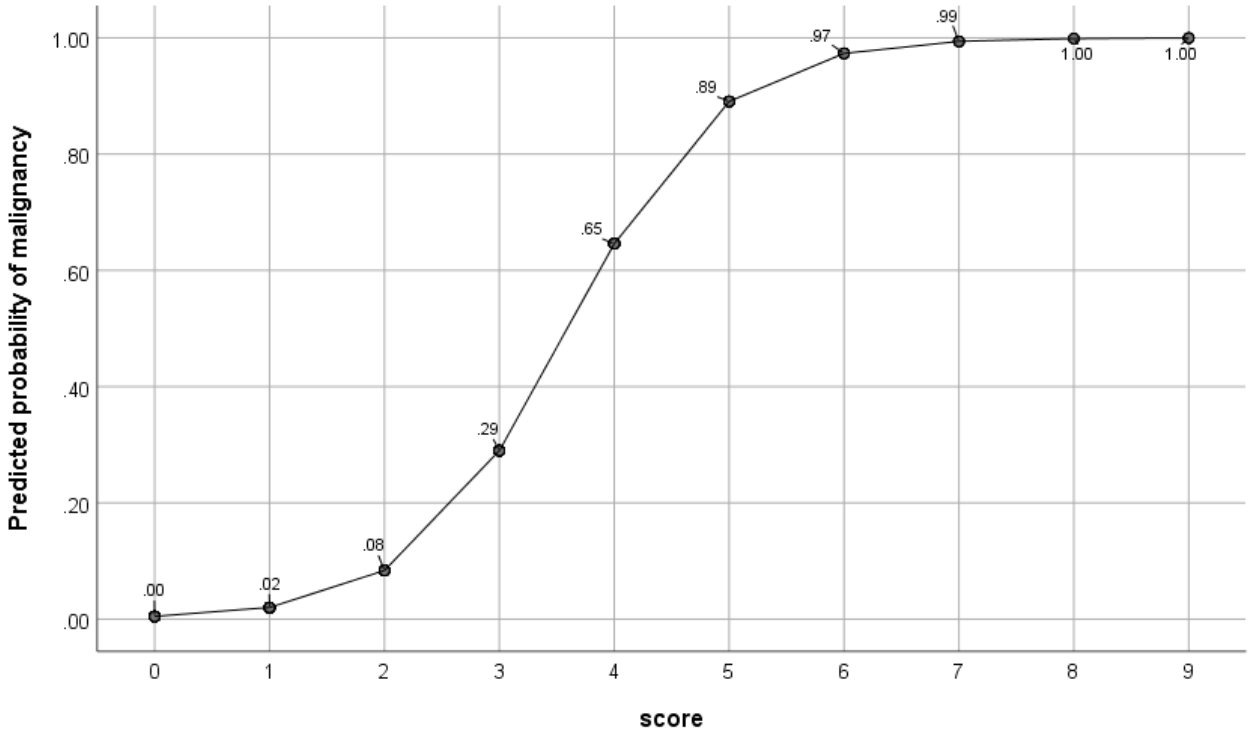
Figure 3. Diagnostic Echocardiographic Mass Score



The AUC for the score was 0.965 (95% CI [0.938-0.993]). We then carried out a bootstrap analysis on the derivation sample to determine the accuracy of the DEM score. Inspection of the median bootstrap coefficients revealed that they were slightly higher than those obtained in the original

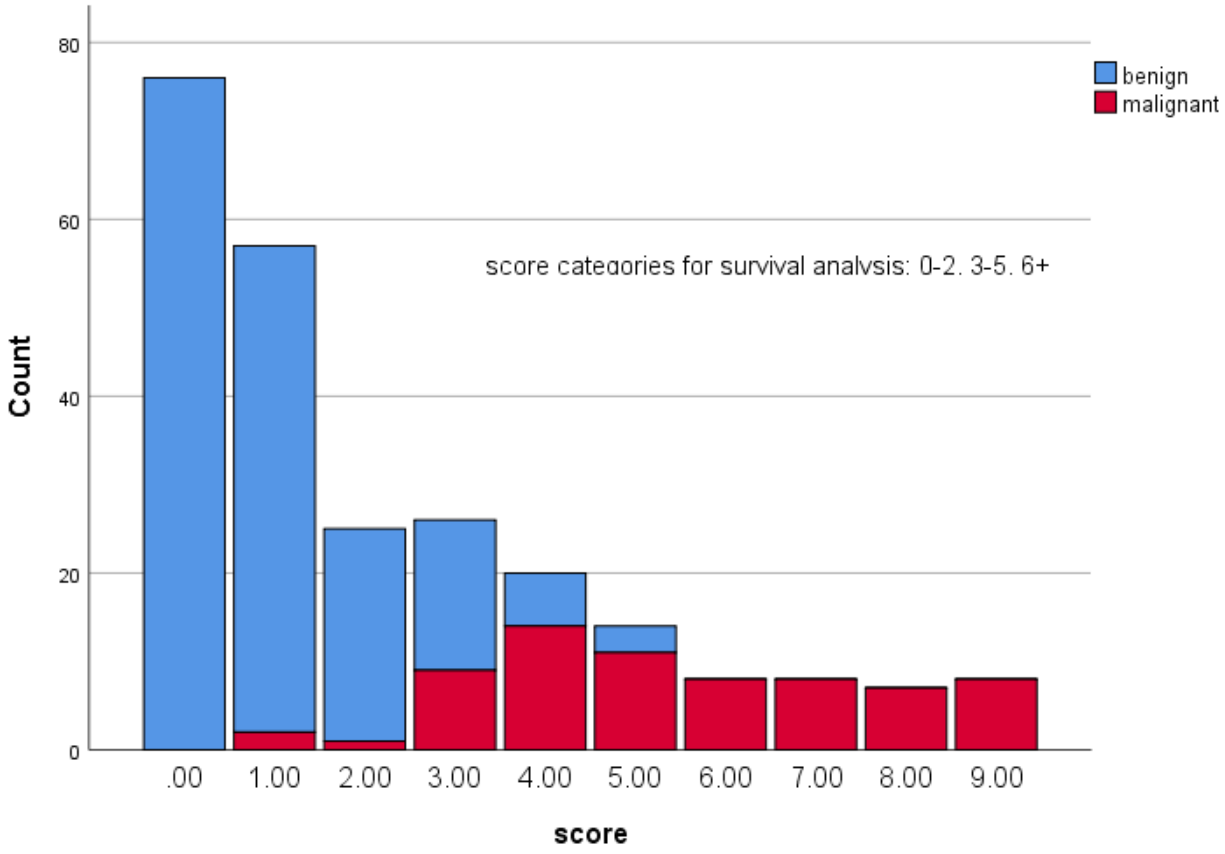
model, but still their order of magnitude was the same as those used to build the risk score, confirming its accuracy. In a logistic regression analysis using the DEM score as a predictor, the likelihood of malignant CM increased more than 4 times for a 1-unit increase in the score (OR=4.468; 95% CI 2.733-7.304). Patients with a score < 3 had an 8% probability of malignancy, while patients with a score > 5 had a 97% probability of malignancy (**figure 4**).

Figure 4. Cumulative estimated probability of malignancy as a function of the score derived from logistic regression.



Based on these findings, we split the DEM scores into 3 categories, with a score < 3 denoting a high probability of a benign diagnosis, and a score > 4 a high probability of malignant diagnosis. Conversely, an intermediate score between 3 and 4, identifies a "gray zone". The stacked bar chart showing the frequency of patients with and without malignancy as a function of the DEM score is shown in **Figure 5**.

Figure 5. Stacked bars showing the frequency distribution of patients with benign or malignant masses according to the DEM score



The accuracy indicators for each cut-off of the score are shown in **Table 6**. The best cut-off of DEM score to detect malignancy is a score ≥ 3.

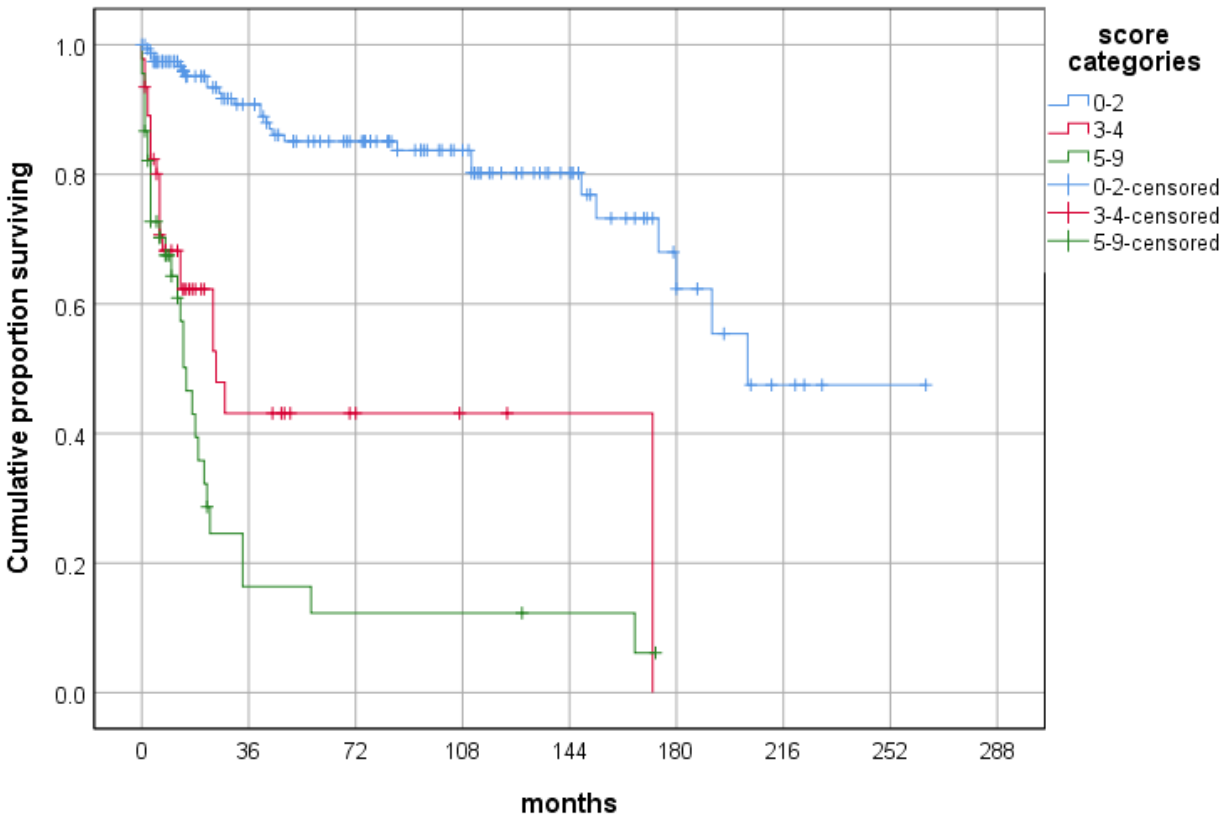
Table 9. Diagnostic accuracy of malignancy probability according to each cut-off of the score.

Cut-off	Sens	Spec	PPV	NPV	Youden's J
1+	1.00	0.42	0.39	1.00	0.42
2+	0.97	0.72	0.57	0.98	0.69
3+	0.96	0.86	0.71	0.98	0.82
4+	0.82	0.95	0.86	0.93	0.77
5+	0.62	0.98	0.93	0.87	0.60
6+	0.46	1.00	1.00	0.83	0.46
7+	0.34	1.00	1.00	0.80	0.34
8+	0.22	1.00	1.00	0.77	0.22
9	0.12	1.00	1.00	0.75	0.12

Predictive validity of the DEM score

Of the 249 patients followed for a median of 25 months, 78 (31.3%) died. The predictive validity of the score was determined as its ability to predict survival during the follow-up in the three subgroups of patients with a DEM score of 0-2, 3-4, 5-9, respectively. Kaplan-Meier survival curves were different among patient subgroups (Log-rank test = 102.4, $p<0.001$, all significant pairwise comparisons), with a median survival of 15 months (95% CI 2.4-10.2) among patients scoring 5 to 9, a median of 25 months (95% CI 7.3-10.7) among patients with a score of 3 to 4 and a median survival of 104 months (95% CI 59.6-168.0) among those scoring < 3 **(Figure 6)**.

Figure 6. Kaplan-Meier survival curves in patients with different categories of the DEM score.



DISCUSSION

Summary of findings

The aim of our study was to offer a simple tool to estimate the to refer correctly patients to a second level imaging test. Throughout our Bologna Cardiac Masses Registry analysis, we investigated the diagnostic performance of echocardiography in 249 patients with histologically confirmed CM. Integrating the echocardiographic tools, we derived a simple multiparametric score to detect benign CM and to rapidly identify patients who require mandatory second level imaging exams. The main novelties of our study were that for the first time we assessed the diagnostic accuracy of integrating

multiple echocardiographic parameters in one of the largest cohort of patients published, stratified into 4 sub-types - primary cardiac benign tumours, primary malignant tumours, secondary malignant tumours and PT - according to the histological or radiological (in cases of thrombi) confirmation of all lesions. Importantly, all patients had a second-level imaging technique and surgery/biopsy confirming the nature and the exact location of the CM and they were followed over time so that we were able to assess long-term outcome according to the lesions' nature and score.

Echocardiographic assessment of cardiac mass

Nowadays, most of the knowledge regarding cardiac tumours is still mainly based on postmortem studies, and the neoplastic nature and specific type of CM can only be established with certainty by histology[1,5]. Intracardiac masses are more and more frequently detected by chance during routine imaging examinations. Most benign tumors are curable with surgery and many malignant tumors also have a good prognosis in case of early diagnoses and treatment, therefore, early tumor detection and characterization are critical and play a pivotal role in patients' outcomes[57,58,59]. Currently, echocardiography is the cornerstone in the evaluation of patients with CM and provides accurate information on the localization, size, shape, surface characteristics, as well as their relationship with adjacent structures, without subjecting patients to radiation exposure[31,60]. Nevertheless, in this setting there are few data on echocardiography diagnostic accuracy, and all these derive from retrospective studies with low simple size, in which only one histotype was often included[10,11,48]. Thus, it is essential for the echocardiographer to be prepared to gather and properly interpret the full range of data derived by cardiac ultrasound. The present study confirms that some echocardiographic characteristics relate to the histologic nature. In fact, right chamber location, a diameter > 30 mm, pericardial effusion, inhomogeneous echogenicity, polylobate shape and irregular margins can predict malignancy. Unfortunately, transthoracic echocardiography has some intrinsic limitations that may lead to misdiagnosed lesions or to a delayed diagnosis, reducing the diagnostic accuracy by up to 88%. Furthermore, the diagnostic accuracy can vary in relation to the experience and expertise of

the operator, to the acoustic window but also, as we have seen from our case histories, according to the localization and histology of the mass. In our Registry there are 6 patients with pulmonary artery angiosarcomas, in which echocardiographic diagnosis is strongly limited by the localization in the pulmonary artery. According to these limitations, the initial echocardiographic evaluation per se is often inconclusive and second-level imaging techniques are usually required. In fact, more and more the multimodality approach with cardiac MR, CT and 18F-FDG PET becomes an important part of non-invasive evaluation, although not all centers have the necessary expertise to routinely assess and interpret CT or CMR images[2,61].

Diagnostic Echocardiographic Mass Score Model

Our findings may improve the current clinical practice and the diagnostic work-up of CM. In the present study, we assessed the diagnostic value of 6 pre-specified echocardiographic parameters, combined together into the DEM Score, to discriminate between benign and malignant CM. Notably, the presence of infiltration, moderate-severe pericardial effusion, polylobate shape, sessile, with inhomogeneity and non-left localization were found to be associated with malignancies. The most challenging issue in the management of patients with CM is identifying those who quickly and mandatory need of a second-level investigation. Our analyses confirm that these echocardiographic items on their own are associated with a variable degree of diagnostic accuracy, but the combination of them into a score has the potential to increase the diagnostic accuracy of echocardiography in the challenging clinical scenario examined. This model had a good predictive performance in the training cohort, with an AUC of 0.969. To add further support of the value of our score, it was tested in a validating cohort of 71 patients with CM with a similar performance. The score ranges from 0 to 9. In particular, a DEM score < 3 most likely indicates a diagnosis of benign mass, conversely, a score > 5 suggests an almost certain diagnosis of malignancy. Presence of infiltration, moderate-severe pericardial effusion and polylobed shape greatly increases the likelihood of malignancy, suggesting the need of second level imaging. It should be stressed that the dimensions were not selected in our

model, because even benign masses, as myxomas, can spread large dimensions, remaining asymptomatic for a long time. The infiltration was found to have the best diagnostic accuracy of malignancy. Although this result is predictable, as associated with most malignant masses, it is not easy to identify by TTE and/or TEE, especially for non-expert operators; thus, we tried to define this parameter as objective and precise as possible[55]. On the other hand, identifying only one or two of the parameters with a score of 1 (inhomogeneity, sessile, non-left mass localization) excludes with a high likelihood a diagnosis of benignity. A "diagnostic gray zone" was observed, namely patients exhibiting an intermediate score of 3 and 4 points. In this group of patients, a second-level imaging technique (MRI, CT and/or 18F-FDG PET) is mandatory to better identify the nature of the mass.

Practical clinical implication

The algorithm proposed in the present study is associated with a significantly higher diagnostic accuracy and would have immediate implications in terms of treatment strategies. The major usefulness of this score would be to help clinicians to identify patients who require second level imaging exams for a better mass characterization or directly for staging in case of malignant masses. Undoubtedly, it is essential to avoid misdiagnosis of CM, but on the other hand, with the need of optimizing resources it is not possible to perform a second level imaging in all patients with a suspected CM. For example, CMR is a time-consuming and expensive method with limited availability in some European regions. Therefore, the real-life choice of the appropriate technique is based on expert knowledge, cost–benefit ratio and, most importantly, its availability[62]. Thus, primary aim of the cut-off provided is to use second-level tests in the most efficient way. We calculated that in the years between 2010 and 2016 (before that in our Cardiology Department there was a systematic study of patients with CM and so that the decision on which imaging examination to perform was "only" based on the clinical cardiologist indication), the application of our echocardiographic score would have saved about 49.3% (33/67) of CMR performed in patients with score 0-2 and therefore with almost certainty of a benign mass. This means both economic savings for the Hospital, but

mostly, a better management of CMR available slots for the Cardiology Department. At the same time, this would allow a reduction in the average diagnosis time and, in patients with a low DEM score, a rapid therapeutic and surgical management, reducing the time of exposure to possible embolization of the mass. In fact, in patients with CM the prognosis does not exactly correspond to the histology of the lesion, because even benign masses can embolize systemically and/or neurologically producing severe disability. In patients with a CM, we strongly believe that the application of a score-based approach will prove to be a valuable tool for sonographers and clinicians, serving to support earlier clinical suspicion of benign cardiac mass, both in hospital and prehospital settings.

Prognostic significance of the DEM Score

An increase in the cumulative score was generally associated with a larger percentage of patients with malignant cardiac masses, indicating that patients with a higher score were at a progressively higher risk of death. A score of 3 points was the pivot point, as described previously. Event-free survival curves showed that patients with 3-4 points had a moderate risk of death, patients with > 5 points were in the highest risk category. Therefore, prognosis was related to the cumulative score, and the event rate increased as the score increased.

Study Limitations

Despite providing the largest series on CMs with histological documentation, our study has some limitations. First, data were collected both retrospectively and prospectively, therefore the protocol was not uniform. In addition, the study was conducted in a single Institution. Moreover, surgical techniques and diagnostic procedures evolved in the 15 years of patient recruitment, so it is possible that the identification and survival of CMs changed over time. In our cohort, the prevalence of malignant cardiac tumors might be underestimated; in fact, patients with advanced neoplasia often do not undergo further diagnostic investigations thus precluding a histological confirmation.

CONCLUSIONS

Nowadays, echocardiography still plays a pivotal role in the diagnostic of cardiac masses, providing a high diagnostic accuracy. However, echocardiography is unable to allow a precise evaluation of every cardiac and extracardiac structures, such as great vessels or mediastinum and has some intrinsic limitations in patients with a poor acoustic window. As we showed in this study, a comprehensive evaluation throughout a multiparametric assessment, more than focusing on specific anatomical characteristic, could be useful in suggesting the histological nature of a cardiac mass. As we demonstrated, the application of a score-based approach is a valuable tool for sonographers and clinicians to support the clinical suspicion of benign cardiac mass and to identify those patients who need to be addressed to second level imaging techniques, such as Cardiac MRI and PET.

REFERENCES

1. Burke A, Jeudy J, Virmani R. Cardiac tumours: an update. Heart. 2008;94(1):117-123. doi:10.1136/hrt.2005.078576

2. Wu PW, Chen S-J, Lin W-C, et al. Imaging of Cardiac and Pericardial Masses. Cardiovasc Imaging Asia. 2017;1(1):23. doi:10.22468/cvia.2016.00059

3. Basso C, Rizzo S, Valente M, Thiene G. Cardiac masses and tumours. Heart. 2016;102(15):1230-1245. doi:10.1136/heartjnl-2014-306364

4. Kassop D, Donovan MS, Cheezum MK, et al. Cardiac Masses on Cardiac CT: A Review. Curr Cardiovasc Imaging Rep. 2014;7(8):9281. doi:10.1007/s12410-014-9281-1

5. Butany J, Nair V, Naseemuddin A, Nair GM, Catton C, Yau T. Cardiac tumours: diagnosis and management. Heart 2011;97:151-160. http://dx.doi.org/10.1136/hrt.2009.186320

6. Gaziano TA, Gaziano JM. Global Burden of Cardiovascular Disease. In: Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine. Elsevier; 2012:1-20. doi:10.1016/B978-1-4377-0398-6.00001-9

7. Miller DV, Tazelaar HD. Cardiovascular Pseudoneoplasms. Arch Pathol Lab Med. 2010;134:7.

8. Amano J, Nakayama J, Yoshimura Y, Ikeda U. Clinical classification of cardiovascular tumors and tumor-like lesions, and its incidences. Gen Thorac Cardiovasc Surg. 2013;61(8):435-447. doi:10.1007/s11748-013-0214-8

9. Burke A, Tavora F. The 2015 WHO Classification of Tumors of the Heart and Pericardium. J Thorac Oncol. 2016;11(4):441-452. doi:10.1016/j.jtho.2015.11.009

10. Xia H, Gan L, Jiang Y, et al. Use of transesophageal echocardiography and contrast echocardiography in the evaluation of cardiac masses. Int J Cardiol. 2017;236:466-472. doi:10.1016/j.ijcard.2017.01.073

11. Sun JP, Asher CR, Yang XS, et al. Clinical and Echocardiographic Characteristics of Papillary Fibroelastomas. Circulation. 2001;103:2687–2693

12. Burke A, Virmani R. Pediatric heart tumors. Cardiovasc Pathol. 2008;17(4):193-198. doi:10.1016/j.carpath.2007.08.008

13. Motwani M, Kidambi A, Herzog BA, Uddin A, Greenwood JP, Plein S. MR Imaging of Cardiac Tumors and Masses: A Review of Methods and Clinical Applications. Radiology. 2013;268(1):26-43. doi:10.1148/radiol.13121239

14. Bianco F, Bucciarelli V, Todiere G, et al. Tumori cardiaci: il ruolo della risonanza magnetica. G Ital Cardiol. 2017;18:9.

15. Loukas M. Primary cardiac angiosarcoma – a review. Med Sci Monit. 2014;20:103-109. doi:10.12659/MSM.889875

16. Gowda RM, Khan IA. Clinical Perspectives of Primary Cardiac Lymphoma. Angiology. 2003;54(5):599-604. doi:10.1177/000331970305400510

17. Bussani R, De-Giorgio F, Abbate A, Silvestri F. Cardiac metastases. J Clin Pathol. 2007;60(1):27-34. doi:10.1136/jcp.2005.035105

18. Burazor I, Aviel-Ronen S, Imazio M, et al. Metastatic cardiac tumors: from clinical presentation through diagnosis to treatment. BMC Cancer. 2018;18(1):202. doi:10.1186/s12885-018-4070-x

19. Al-Mamgani A, Baartman L, Baaijens M, de Pree I, Incrocci L, Levendag PC. Cardiac metastases. Int J Clin Oncol. 2008;13(4):369-372. doi:10.1007/s10147-007-0749-8

20. Goldberg AD, Blankstein R, Padera RF. Tumors Metastatic to the Heart. Circulation. 2013;128(16):1790-1794. doi:10.1161/CIRCULATIONAHA.112.000790

21. Malik SB, Chen N, Parker RA, Hsu JY. Transthoracic Echocardiography: Pitfalls and Limitations as Delineated at Cardiac CT and MR Imaging. RadioGraphics. 2017;37(2):383-406. doi:10.1148/rg.2017160105

22. Thiene G, Basso C. Pathology and pathogenesis of infective endocarditis in native heart valves. Cardiovasc Pathol. 2006;15(5):256-263. doi:10.1016/j.carpath.2006.05.009

23. Nonbacterial thrombotic endocarditis - UpToDate. Accessed May 4, 2020. https://www-uptodate-com.ezproxy.unibo.it/contents/nonbacterial-thrombotic-endocarditis

24. V. Kumar, A.K. Abbas, J.C Aster. Robbins & Cotran Le Basi Patologiche Delle Malattie. 9th ed. Edra; 2015.

25. Auger D, Pressacco J, Marcotte F, Tremblay A, Dore A, Ducharme A. Cardiac masses: an integrative approach using echocardiography and other imaging modalities. Heart. 2011;97(13):1101-1109. doi:10.1136/hrt.2010.196006

26. Ragland MM, Tak T. The Role of Echocardiography in Diagnosing Space-Occupying Lesions of the Heart. Clin Med Res. 2006;4(1):22-32. doi:10.3121/cmr.4.1.22

27. Thyagarajan B, Kumar MP, Patel S, Agrawal A. Extracardiac manifestations of atrial myxomas. J Saudi Heart Assoc. 2017;29(1):37-43. doi:10.1016/j.jsha.2016.07.003

28. Palaskas N, Thompson K, Gladish G, et al. Evaluation and Management of Cardiac Tumors. Curr Treat Options Cardiovasc Med. 2018;20(4):29. doi:10.1007/s11936-018-0625-z

29. Bruce CJ. Cardiac tumours: diagnosis and management. Heart. 2011;97(2):151-160. doi:10.1136/hrt.2009.186320

30. Catherine M. Otto. Textbook of Clinical Echicardiography. VI edizione. Elsevier; 2018.

31. Mankad R, Herrmann J. Cardiac tumors: echo assessment. Echo Res Pract. 2016;3(4):R65-R77. doi:10.1530/ERP-16-0035

32. Lobo A, Lewis JF, Conti CR. Intracardiac masses detected by echocardiography: Case presentations and review of the literature. Clin Cardiol. 2000;23(9):702-708. doi:10.1002/clc.4960230914

33. Acar J, Cormier B, Grimberg D, et al. Diagnosis of left atrial thrombi in mitral stenosis--usefulness of ultrasound techniques compared with other methods. Eur Heart J. 1991;12 Suppl B:70-76. doi:10.1093/eurheartj/12.suppl_b.70

34. Aschenberg W, Schlüter M, Kremer P, Schröder E, Siglow V, Bleifeld W. Transesophageal two-dimensional echocardiography for the detection of left atrial appendage thrombus. J Am Coll Cardiol. 1986;7(1):163-166. doi:10.1016/S0735-1097(86)80275-3

35. Meng Q, Lai H, Lima J, Tong W, Qian Y, Lai S. Echocardiographic and pathologic characteristics of primary cardiac tumors: a study of 149 cases. Int J Cardiol. 2002;84(1):69-75. doi:10.1016/S0167-5273(02)00136-5

36. Esposito A, De Cobelli F, Ironi G, et al. CMR in the Assessment of Cardiac Masses. JACC Cardiovasc Imaging. 2014;7(10):1057-1061. doi:10.1016/j.jcmg.2014.08.002

37. Fussen S, De Boeck BWL, Zellweger MJ, et al. Cardiovascular magnetic resonance imaging for diagnosis and clinical management of suspected cardiac masses and tumours. Eur Heart J. 2011;32(12):1551-1560. doi:10.1093/eurheartj/ehr104

38. Tumma R, Dong W, Wang J, Litt H, Han Y. Evaluation of cardiac masses by CMR—strengths and pitfalls: a tertiary center experience. Int J Cardiovasc Imaging. 2016;32(6):913-920. doi:10.1007/s10554-016-0845-9

39. D'Angelo E.C., Paolisso P., Pizzi C., N. Galiè. Diagnostic Accuracy of Cardiac Computed Tomography and 18F-Fluorodeoxyglucose With Positron EmissionTomography/Computed Tomography in Cardiac Masses. JACC Cardiovasc Imaging 2020;13:2400–2411.

40. Hori Y, Funabashi N, Miyauchi H, et al. Angiosarcoma in the right atria demonstrated by fusion images of multislice computed tomography and positron emission tomography using F-18 Fluoro-Deoxyglucose. Int J Cardiol. 2007;123(1):e15-e17. doi:10.1016/j.ijcard.2006.11.093

41. Nensa F, Tezgah E, Poeppel TD, et al. Integrated 18F-FDG PET/MR Imaging in the Assessment of Cardiac Masses: A Pilot Study. J Nucl Med. 2015;56(2):255-260. doi:10.2967/jnumed.114.147744

42. Rahbar K, Seifarth H, Schafers M, et al. Differentiation of Malignant and Benign Cardiac Tumors Using 18F-FDG PET/CT. J Nucl Med. 2012;53(6):856-863. doi:10.2967/jnumed.111.095364

43. Leone O, Veinot JP, Angelini A, et al. 2011 Consensus statement on endomyocardial biopsy from the Association for European Cardiovascular Pathology and the Society for Cardiovascular Pathology. Cardiovasc Pathol. 2012;21(4):245-274. doi:10.1016/j.carpath.2011.10.001

44. Amano J, Nakayama J, Yoshimura Y, Ikeda U. Clinical classification of cardiovascular tumors and tumor-like lesions, and its incidences. Gen Thorac Cardiovasc Surg 2013;61:435–447.

45. Rahouma M, Arisha MJ, Elmously A, El-Sayed Ahmed MM, Spadaccio C, Mehta K, Baudo M, Kamel M, Mansor E, Ruan Y, Morsi M, Shmushkevich S, Eldessouki I, Rahouma M, Mohamed A, Gambardella I, Girardi L, Gaudino M. Cardiac tumors prevalence and mortality: A systematic review and meta-analysis. Int J Surg 2020;76:178–189.

46. Sultan I, Bianco V, Habertheuer A, Kilic A, Gleason TG, Aranda-Michel E, Harinstein ME, Martinez-Meehan D, Arnaoutakis G, Okusanya O. Long-Term Outcomes of Primary Cardiac Malignancies. J Am Coll Cardiol 2020;75:2338–2347.

47. Tyebally S, Chen D, Bhattacharyya S, Mughrabi A, Hussain Z, Manisty C, Westwood M, Ghosh AK, Guha A. Cardiac Tumors. JACC CardioOncology 2020;2:293–311.

48. Patel R, Lim RP, Saric M, Nayar A, Babb J, Ettel M, Axel L, Srichai MB. Diagnostic Performance of Cardiac Magnetic Resonance Imaging and Echocardiography in Evaluation of Cardiac and Paracardiac Masses. Am J Cardiol 2016;117:135–140.

49. Trojani M, Contesso G, Coindre JM, Rouesse J, Bui NB, De Mascarel A, Goussot JF, David M, Bonichon F, Lagarde C. Soft-tissue sarcomas of adults; study of pathological prognostic variables and definition of a histopathological grading system. Int J Cancer 1984;33:37–42.

50. Coindre JM, Trojani M, Contesso G, Rouesse J, Mascarel AD, Goussot J-F. Reproducibility of a histopathologic grading system for adult soft tissue sarcoma. Cancer. 1986 Jul 15;58(2):306-9.

51. Miller DV, Tazelaar HD. Cardiovascular pseudoneoplasms. Arch Pathol Lab Med 2010;134:362–368.

52. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W, Voigt J-U. Recommendations for Cardiac Chamber Quantification by Echocardiography in Adults: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J – Cardiovasc Imaging 2015;16:233–271.

53. Pepi M, Evangelista A, Nihoyannopoulos P, Flachskampf FA, Athanassopoulos G, Colonna P, Habib G, Ringelstein EB, Sicari R, Zamorano JL, on behalf of the European Association of Echocardiography, Document Reviewers:, Sitges M, Caso P. Recommendations for echocardiography use in the diagnosis and management of cardiac sources of embolism: European

Association of Echocardiography (EAE) (a registered branch of the ESC). Eur J Echocardiogr 2010;11:461–476.

54. Celeste F, Muratori M, Mapelli M, Pepi M. The evolving role and use of echocardiography in the evaluation of cardiac source of embolism. J Cardiovasc Echography 2017;27:33.

55. Lestuzzi C, Biasi S, Nicolosi GL, Lodeville D, Pavan D, Collazzo R, Guindani A, Zanuttini D. Secondary neoplastic infiltration of the myocardium diagnosed by two-dimensional echocardiography in seven cases with anatomic confirmation. J Am Coll Cardiol 1987;9:439–445.

56. Steyerberg EW, Jr FEH. Internal validation of predictive models: Efficiency of some procedures for logistic regression analysis. J Clin Epidemiol 2001;8.

57. Abu Saleh WK, Ramlawi B, Shapira OM, Al Jabbari O, Ravi V, Benjamin R, Durand J-B, Leja MJ, Blackmon SH, Bruckner BA, Reardon MJ. Improved Outcomes With the Evolution of a Neoadjuvant Chemotherapy Approach to Right Heart Sarcoma. Ann Thorac Surg 2017;104:90–96.

58. ElBardissi AW, Dearani JA, Daly RC, Mullany CJ, Orszulak TA, Puga FJ, Schaff HV. Survival After Resection of Primary Cardiac Tumors: A 48-Year Experience. Circulation 2008;118:S7–S15.

59. Foà A, Paolisso P, Bergamaschi L, Rucci P, Di Marco L, Pacini D, Leone O, Galié N, Pizzi C. Clues and pitfalls in the diagnostic approach to cardiac masses: are pseudo-tumours truly benign? Eur J Prev Cardiol 2021;zwab032.

60. Peters PJ, Reinhardt S. The Echocardiographic Evaluation of Intracardiac Masses: A Review. J Am Soc Echocardiogr 2006;19:230–240.

61. Palaskas N, Thompson K, Gladish G, Agha AM, Hassan S, Iliescu C, Kim P, Durand JB, Lopez-Mattei JC. Evaluation and Management of Cardiac Tumors. Curr Treat Options Cardiovasc Med 2018;20:29.

62. Mizia-Stec K, Charron P, Gimeno Blanes JR, Elliott P, Kaski JP, Maggioni AP, Tavazzi L, Tendera M, Felix SB, Dominguez F, Ojrzynska N, Losi M-A, Limongelli G, Barriales-Villa R, Seferovic PM, Biagini E, Wybraniec M, Laroche C, Caforio ALP, on behalf of the EORP Cardiomyopathy Registry Investigators. Current use of cardiac magnetic resonance in tertiary referral centres for the diagnosis of cardiomyopathy: the ESC EORP Cardiomyopathy/Myocarditis Registry. Eur Heart J - Cardiovasc Imaging 2021;jeaa329.