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PhD thesis

New trends in breast imaging for breast cancer and cardiovascular risk

Rubina Manuela TRIMBOLI

R11690

Advisor: Prof. Francesco SARDANELLI

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List of abbreviations

AI Artificial Intelligence

ANN Artificial Neural Networks

BAC Breast Arterial calcifications

BC Breast Cancer

CAD Coronary Artery Disease

CC cranio-caudal

CE-MRI Contrast-enhanced Magnetic Resonance Imaging

CHD Coronary Hearth Disease

CNN Convolutional Neural Network

CV Cardiovascular

DL Deep Learning

ER Estrogen Receptor

IQR Interquartile Range

LDA Linear Discriminant Analysis

ML Machine Learning

MLO Medio-Lateral Oblique

MRI Magnetic Resonance Imaging

PEP Peak Enhancement Percentage

PIEP Post-Initial Enhancement Percentage

PR Progesterone Receptor

RF Random Forest

ROI Region Of Interests

SD Standard Deviation

SIP Signal Intensity At Peak

SVM Support Vector Machines

VEGF Vascular Endothelial Growth Factor

Summary

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Background

Qualitative, subjective reading of medical images have been the backbone of image interpretation for the past century, providing useful information to the treating physician. During the past two decades, advances in medical imaging technology have offered the possibility to extract high-resolution anatomic, physiologic, functional, biochemical, and metabolic information from clinical images, all of which reflect the molecular composition of the healthy or diseased tissue of organs imaged in the human body. We are now entering the era of "quantitative imaging" recently formally defined as "the extraction of quantifiable features from medical images for the assessment of normality, or the severity, degree of change, or status of a disease, injury, or chronic condition relative to normal". With appropriate calibration, most of the current imaging technologies can provide quantitative information about specific properties of the tissues being imaged.

Purpose

This doctoral thesis aims at exploring the possible use of imaging methods such as mammography and breast magnetic resonance imaging (MRI) as imaging biomarkers, measuring functional, biochemical and metabolic characteristics of the breast through medical images.

Part I. Breast arterial calcifications for cardiovascular risk

Breast arterial calcifications (BAC) are easily recognizable on screening mammography and are associated with coronary artery disease. We tried to implement the estimation of BAC to be easily applicable in clinical prevention of cardiovascular disease. In particular, we evaluated the intra- and inter-observer reproducibility of i) a specifically developed semi-automatic tool and of ii) a semi-quantitative scale for BAC quantification on digital mammograms.

Part II. Multiparametric breast MRI for breast cancer management

Multiparametric breast MRI allows to simultaneously quantify and visualize multiple functional processes at the cellular and molecular levels to further elucidate the development and progression of breast cancer (BC) and the response to treatment. The purpose of our study was to verify the correlation between enhancement parameters derived from routine breast contrast-enhancement MRI and pathological prognostic factors in invasive BC as a condition for the use of MRI-derived imaging biomarkers in adjunct to traditional prognostic tools in clinical decision making.

Part III. Artificial intelligence in Breast MRI

Recent enthusiasm regarding the introduction of artificial intelligence (AI) into health care and, in particular, into radiology has increased clinicians' expectations and also fears regarding the possible impact of AI on their profession. The large datasets provided by and potentially extractable from breast MRI make it the right

stuff for fitting AI applications. This session focuses on a systematic mapping review of the literature on AI application in breast MRI published during the past decade, analysing the phenomenon in terms of spread, clinical aim, used approach, and achieved results.

Conclusions

Medical images represent imaging biomarkers of considerable interest in evidence- based clinical decision-making, for therapeutic development and treatment monitoring. Among imaging biomarkers, BAC represent the added value of an ongoing and consolidated cancer screening to act for preventing the main cause of death among women in which traditional CV risk scores do not adequately perform.

Breast MRI may act as a prognostic tool to improve BC management through the extraction of a plenty of functional cancer parameters.

AI might certainly implement the use of imaging data interacting with and integrating quantitative imaging for improving patient outcome and reducing several sources of bias and variance in the quantitative results obtained from clinical images. The intrinsic multiparametric nature of MRI has the greatest potential to incorporate AI applications into the so called *precision medicine*. Nevertheless, AI applications are still not ready to be incorporated into clinical practice nor to replace the trained and experienced observer with the ability to interpret and judge during image reading sessions.

Part I

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Breast arterial calcifications for cardiovascular risk

Note: The part I research yielded following publications:

1. Trimboli RM, Codari M, Bert A, Carbonaro LA, Maccagnoni S, Raciti D, Bernardi D, Clauser P, Losio C, Tagliafico A, Sardanelli F. *Breast arterial calcifications on mammography: intra- and inter-observer reproducibility of a semi-automatic quantification tool.* Radiol Med. 2018 Mar;123(3):168-173. doi: 10.1007/s11547-017-0827-6

2. Trimboli RM, Codari M, Guazzi M, Sardanelli F. *Screening mammography beyond breast cancer: breast arterial calcifications as a sex-specific biomarker of cardiovascular risk.* EJR 2019. https://doi.org/10.1016/j.ejrad.2019.08.005

3. A manuscript entitled *A reproducible semi-quantitative scale for the assessment of breast arterial calcifications,* authored by Trimboli RM, Codari M, Cozzi A, Monti C, Nenna C, Spinelli D and Sardanelli F is under review on European Radiology

Introduction

Cardiovascular (CV) disease represents a major public health issue and the first cause of death for men and women, accounting for more than 30% of cases worldwide [1]. Over the last fifty years, increasing attention has been paid to primary prevention, through the identification and control of risk factors and a progressive improvement in phenotyping CV risk. The complex biological pathway leading to CV events encompasses functional and structural changes of heart and vessels that develop over the years with a variable progression rate. Hence, there is a chance for these changes to be identified long before CV events occur and for a preventive strategy to be effective. In the last years, several attempts have been made for improving the performance of traditional CV risk scores with the help of improved algorithms including alternative blood-based risk markers and imaging biomarkers [2] such as the coronary artery calcium score in asymptomatic individuals at intermediate-risk [3].

Notably, a substantial sex-related difference in CV risk factors has been repeatedly emphasized and studied [4]. Based on population-based registries, the mortality rate for coronary heart disease (CHD) in young women (aged 55 years or less) did not fall as it did for male and in elderly populations [5]. Up to 20% of all coronary events occur in the absence of traditional CV risk factors [6], whereas many women with traditional risk factors do not experience coronary events [7]. One possible reason behind this fact is the occurrence of non-traditional risk factors unique to women. Indeed, pregnancy complications, contraceptive, fertility and menopausal hormonal therapies, and systemic autoimmune disorders [8] are not included in current CV risk algorithms for women, which are not tailored and are basically the same as 30 years ago.

Moreover, the awareness of CV risk among young women is poor, as they perceive hearth diseases as a "male problem". This reflects in the failure of basic preventive actions, such as lifestyle modifications or appropriate screening tests. Breast cancer campaigns have been building women awareness for more than 20 years, stressing on the importance and efficacy of early diagnosis. In Europe, half of organized mammographic screening programs achieves a participation rate higher than 70%, demonstrating that women education is the first step to call for action [9]. These different and somewhat paradoxical trends certainly reflect inadequate prevention strategies [5].

Breast arterial calcifications (BAC) have been recently described among "the top five women's health issues in preventive cardiology, at the forefront of recent and ongoing research", together with coronary microvascular dysfunction, hormone replacement therapy, calcium and vitamin D supplementation as well as metabolic considerations during pregnancy [4]. BAC are easily recognizable on routine mammograms that women periodically undergo spontaneously or through organized population-based programs for breast cancer screening from 40, 45 or 50 years of age, according to different national or local policies. Thus, there is a strong rationale for mammography to serve as a preventive test beyond breast cancer screening, spotlighting on the heart and more comprehensively on CV risk. The reported association of BAC with coronary artery disease (CAD) also in middle age [10] strongly suggests their potential as an additional risk factor when traditional CV risk assessment is somewhat inadequate and does not impact on CV mortality [5].

In this light, efforts should be made aiming at: i) improving the awareness of BAC by physicians providing

preventive care to women, including radiologists, cardiologists, and general practitioners; ii) implementing the estimation of BAC to be easily applicable in clinical prevention.

BAC as a biomarker for CV risk

BAC appear on mammograms [11] as linear, parallel opacities, typically showing a "tram-track" appearance [12,13] (Fig. 1).

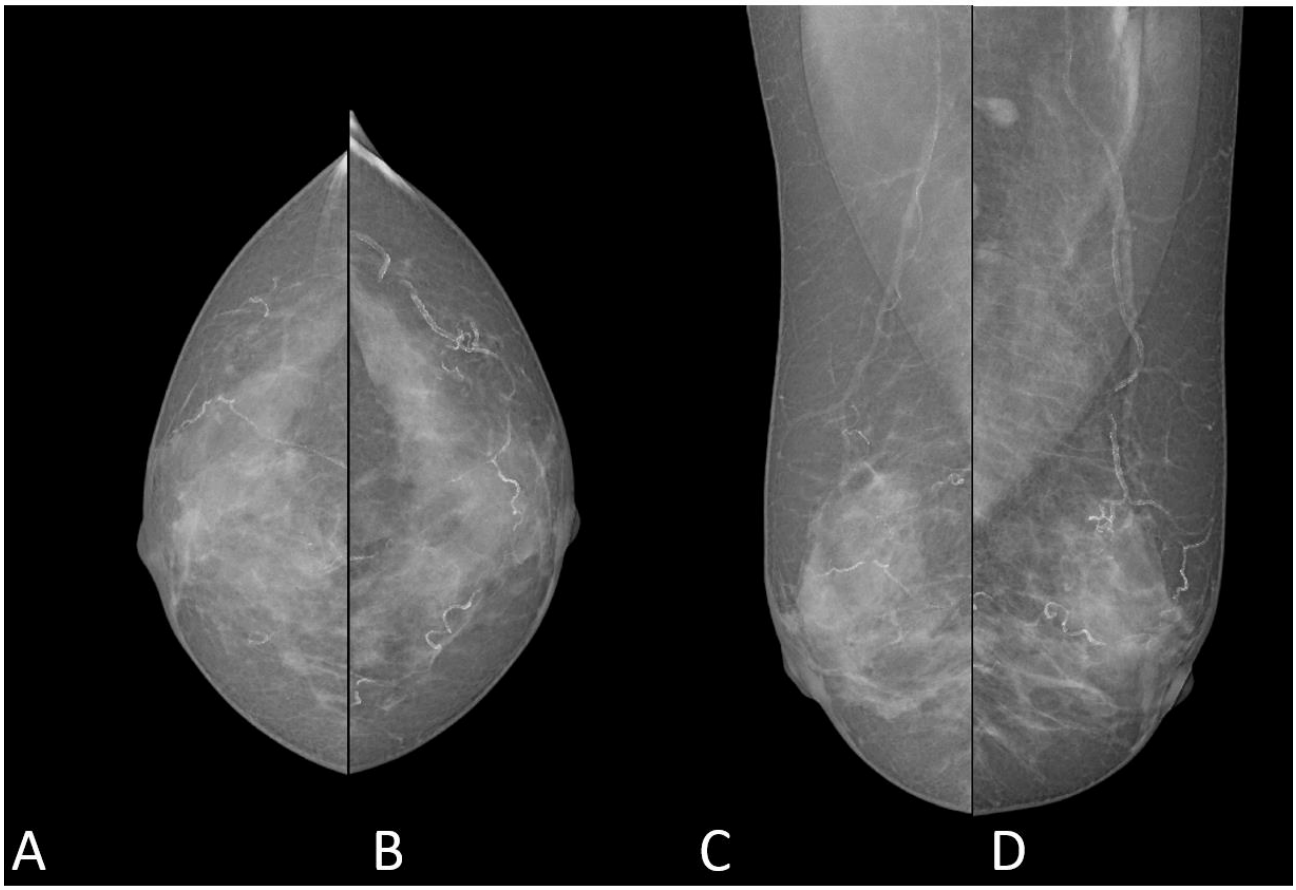

***Figure 1**. Screening mammography (A, B cranio-caudal and C, D mediolateral oblique views) of a 65-year old woman showing bilateral breast arterial calcifications (BAC), more prominent on the left side (B, D). Morphology of these calcifications can be appreciated in the magnifications (E, F) of the squared regions of the left breast.*

They express Monckeberg's calcification, a non-atheromatous vascular lesion developing in the internal elastic or in the medial layer of muscular arteries, different from atherosclerotic calcification, involving the intima layer of large and medium sized elastic arteries. Monckeberg's calcification contains hydroxyapatite crystal deposition in the plaques, while accumulation of calcium phosphate salts in the vascular tissue is seen in advanced atherosclerosis [14].

A systematic review and meta-analysis by Hendriks et al. [11] assessed the available evidence on the associations between BAC and CV risk factors (Table 1).

Table 1. *Odds ratios (OR), 95% confidence interval (CI) and heterogeneity (I^2) of the risk and reproductive factors as determinants of BAC*

Determinant	OR	95% CI	I^2 (%)
Risk factor			
Age*	2.98	2.31-3.85	87.02
Reproductive factors			
Parity	3.43	2.23-5.47	0
HRT	0.56	0.37-0.84	88.23
Cardiovascular risk factors			
Hypertension	1.08	0.98-1.19	0
Smokers	0.48	0.39-0.60	45.58
Hyperlipidemia	1.72	0.95-3.09	63.87
BMI	0.99	0.95-1.04	27.5
Diabetes	1.88	1.36-2.59	79.53

OR=odds ratio; 95% CI= 95% confidence interval; I2= heterogeneity; HRT= hormone replacement therapy; BMI=body mass index. *For every 10 years of increasing age. Data are adapted from Hendriks et al [11]

Pooled BAC prevalence resulted to be 12.7% among women attending screening programmes. A higher BAC prevalence was associated with increasing age, diabetes, and parity as opposed to nulliparity, while smoking was associated with lower BAC prevalence.

No associations were found with other well-known CV risk factors such as hypertension, obesity, or dyslipidemia. Although longitudinal studies (n = 3) were scarce, BAC appeared to be associated with an increased risk of CV disease events (adjusted hazard ratios for CHD ranging from 1.32 to 1.44).

The authors concluded that BAC appear to be associated with an increased risk of CV disease events, and with some of the known CV risk factors, illustrating that medial arterial calcification might contribute to CV disease through a pathway distinct from the intimal atherosclerotic process.

The association between BAC, merely reported as "present" at mammographic images, and CV risk was investigated in several studies [15–18], summarized in Table 2.

Table 2. *Risk of death and cardiovascular outcomes associated with BAC*

Variable	Risk	95% CI
a)		
Transient ischemic attack/stroke	1.4 (RR)	1.01-1.08
Thrombosis	1.5 (RR)	1.00-2.20
Myocardial infarction	1.8 (RR)	1.01-2.90
b)		
Death (all causes)	1.29 (HR)	1.06-1.58
With diabetes	1.74 (HR)	1.19-2.56
Cardiovascular deaths (total)	1.29 (HR)	1.01-1.66
With diabetes	1.71 (HR)	1.00-2.94
Death from coronary artery disease	1.44 (HR)	1.02-2.05
c)		
CHD	1.32 (HR)	1.08-1.60
Ischemic stroke	1.41 (HR)	1.11-1.78
Heart failure	1.52 (HR)	1.18-1.98
d)		
Any CHD	3.54 (OR)	2.28-5.50

BAC = breast arterial calcifications; CHD = coronary heart disease; 95% CI= 95% confidence interval; RR= relative risk; HR= hazard ratio; OR= odds ratio. Risks of death and cardiovascular outcomes were considered available evidence and then reported in the table only if the 95% CI did not include 1. a) Data adapted from van Noord et al [15]; b) Data adapted from Kemmeren et al [16]; c) Data adapted from Iribarren et al [17]; d) Data adapted from Schnatz et al [18].

It is well-known that the transition to menopause is associated with an increase in CV risk due to dysregulation of glucose and lipid metabolism and consequently of estrogens. Indeed early menopause and premature ovarian insufficiency increase CV risk (1.5-2 folds). According to the literature, hormonal therapy has a positive impact on CV risk factors, with beneficial effects on both CV morbidity and mortality in women at early menopausal age [19]. In this light, the association between BAC and hormonal therapy was investigated by [18]. Their study demonstrated that BAC prevalence was higher (eight times) in menopausal women than in pre-menopausal ones, thus highlighting the role of estrogenic regulation in BAC development. Moreover, even when adjusting for age, past hormonal therapy was significantly associated to a lower prevalence of BAC. This study highlights the role of BAC as a potential biomarker of sex-specific CV risk due to the close link between CV risk factor and hormonal balance in women during and after transition to menopause.

When evaluating the interaction between BAC and CV disease, woman's age plays as a major cconfounder. To investigate the potential role of BAC as a biomarker of CV risk beyond the ageing progress, Moshyedi et al. [10]investigated the association between BAC, CAD and diabetes mellitus, adjusting for patient age. Their results showed that BAC may still indicate an additional risk factor for CAD in women with less than 59 years of age (positive predictive value [PPV] of BAC for CAD was 0.88, negative predictive value was 0.65), particularly in diabetic patients (PPV of diabetes mellitus for CAD increased from 0.62 when BAC was absent to 1.00 when BAC was present) [10]

Later on, also Schnatz et al [20] investigated the association between BAC and hormonal therapy in 1,919 women undergoing screening mammography. As expected, the higher was the age, the higher the prevalence of BAC. Nevertheless, the prevalence of atherosclerotic cardiovascular disease and CAD remained higher in women with BAC stratified for age. Indeed, CAD prevalence was always greater in women with BAC than in women without BAC, in women under 55 (10.4% versus 3.8%), in women from 55 to 64 (6.7% versus 1.1%), and in women over 64 (18.9% versus 10.1%), confirming that BAC correlated con CV risk factors even in women aged less than 55 years, when it is especially important to detect CV risk factors [20].

The same research group investigated on the same cohort [18] whether mammography could predict the development of CAD. Among women who did not have CAD at baseline, women with BAC were significantly more likely to develop a heart disease or a stroke than those without BAC (6.3% versus 2.3%, $p = 0.003$; 58.3% versus 13.3%, $p < 0.001$), respectively. These results remained significant even when adjusting for age. BAC together with hypertension, hypercholesterolemia, and family history contributed to the 5-year incidence of CAD and BAC had the highest odds ratio for predicting CHD after 5 years.

Thus, identifying and consistently reporting BAC presence and severity on mammography is paramount at all ages, in particular in women under 65, where traditional risk factors may not be so prevalent due to the later onset of CV events in women and actual CV risk may be underestimated. BAC are not only an imaging biomarker for CV risk, but represent a predictive factor for CV events. This strengths the potential of their application in preventing but also in monitoring the progression of the disease over time and the impact of any preventive measures.

What is missing?

Although BAC can be easily detected on routine mammograms, their assessment represents a crucial challenge. Various appearance patterns (bright tubular, single or parallel linear structures, or sporadic bright spots), topological complexity, and vessels overlap on two-dimensional projections make both identification and quantification of BAC difficult to standardize [12].

Currently, screening mammography readers BAC aside since they are not suspect for an underlying cancer, i.e. they do not "alarm". While parenchymal calcifications, potentially associated with cancer, were extensively analyzed also using computer-aided detection tools [21], BAC, when detected, are generally just reported as "present" but not interpreted according a CV risk preventive perspective [22–25].

It is unlikely that all subjects with BAC may benefit from the same preventive intervention. To express BAC with a dichotomic assessment (i.e., as present or absent), allows only to classify women into two CV risk classes. However, even at an early research stage, the binary classification hinders the identification of women with intermediate CV risk, who may mostly benefit of a tailored and personalized CV disease prevention. Personalized medicine may be based on the identification of quantitative biomarkers, even blood-based or imaging-based, ideally expressed on a continuous scale. This issue opens the challenge of expressing BAC as a quantitative (or at least semi-quantitative) scale that will allow to stratify patients into multiple CV risk levels.

Recently, few attempts have been made for improving BAC assessment using semi-quantitative scales [26–29]. In dedicated studies, BAC grading ranges from four-level Likert scale [29] to complex scores based on number and maximum length of involved vessels and calcium density [27]. Nevertheless, the heterogeneity among grading scales reflects the lack of standardized criteria for BAC burden estimation. However, to the best of our knowledge, there are no studies that stratify CV risk by means of continuous BAC assessment. When quantified, BAC are manually identified by radiologists [30, 31], through a time consuming, operator-dependent process, far to be applied in a daily clinical workflow. Only a minority of studies tried to quantify BAC on a continuous scale [2,12, 30¬¬-32].

Operator-dependency in BAC quantification is crucial, representing the major source of bias during BAC estimation. Indeed, the few studies that focused on the development of automatic methods for BAC segmentation and quantification employed more than one reader to establish the reference standard for algorithm validation [12, 32]. Moreover, a recent original research highlighted this issue comparing the performance of two adequately trained observers in BAC segmentation on a multivendor image dataset of 212 mammographic views from routine practice. In this study, each reader placed rectangular ROIs on both CC and MLO views, separately, then BAC were automatically segmented using an adaptive thresholding algorithm. Reader performance were compared using Bland--Altman analysis, which proved the existing disagreement among manual delineations, with an intraobserver and interobserver reproducibility of only 55% and 3%, respectively [2].

A reliable and automated quantification of BAC is indispensable and could be the solution for contributing to the stratification of CV risk. To this aim, efforts have been put in the development of BAC quantification tools [12, 32]. Cheng et al. [10] proposed an automatic algorithm for the delineation of calcified vessels based on a tracking with uncertainty scheme and validated it on 63 mammograms by comparison with manual delineations from two experts. The overall detection performance of their algorithm in terms of sensitivity and specificity reached 92.6 ± 2.2% and 83.9 ± 3.6%, respectively when compared to the first expert and 91.3 ± 3.5% and 82.7 ± 4.1% when compared to the second one. These promising results demonstrated that manual segmentation may be replaced by automatic detection tools, however the need of stratifying algorithm parameters depending on breast density keeps the path open for further improvements. [12].

More recently, due to the promising performance of artificial intelligence systems in medical image analysis, a recent study [32] investigated the potential of deep learning for BAC detection on mammograms. In their study, Wang et al. proposed a deep convolutional neural network (CNN) that discriminates between BAC and non-BAC pixels [32]. The performance of the proposed CNN was compared with manual delineations performed on 210 cases (840 images) by three expert readers in a two-round reader study. The proposed solution reached detection ability similar to that of human experts at FROC analysis and good performance also in calcium mass quantification (determination coefficient 96.2%). These results proved the promising application of deep CNN for BAC detection. Nevertheless, further large scale studies are needed to improve and test model generalization across different experimental setup [32]. Table 3 shows different attempts of BAC assessment reported in the literature.

Future perspectives

BAC may become an important sex-specific biomarker for CV risk stratification, potentially guiding CV preventive programs in the female population. Women entering screening program for breast cancer and otherwise not considered for CV risk will benefit doubly from mammography, aiming at cancer secondary prevention and CV primary and/or secondary prevention. Although evidence supports a strong association between BAC prevalence and CV risk, this association, per se, is not enough for a clinical use. In fact, while in a low-risk population a preventive intervention is likely to be not cost-effective, in a population at increased risk, a preventive treatment could be cost-effective [3]. In the context of a consolidated breast cancer screening, BAC assessment may enable subjects at increased CV risk to be identified and to be offered with tailored preventive and possibly therapeutic interventions.

Recently, several papers pointed out the need to move from the evidence of the association between BAC and CV events to a medical action [33–35]. However, the lack of validated BAC quantification methods that overcome the intrinsic limitation of the dichotomous assessment is a strong factor limiting this action. Only through the stratification into multiple risk classes, BAC on mammography may exploit their potential. Breast radiologists have to support BAC reporting, although this is not recommended by guidelines and promote the awareness of their significance by women and general practitioners.

Of note, a recent study demonstrated an overwhelming preference of patients to be informed on their BAC status [36]. More than 95% of 397 responding women declared to prefer to have BAC reported; all 107 patients who were unaware of a personal history of CV disease wanted to have information about their BAC; interestingly, of those who chose one action option, 87% preferred coronary artery computed tomography for decision-making, of those who selected multiple options, 53% opted for coronary artery computed tomography for decision-making.

Table 3. *Methods of BAC assessment reported in original studies and retrieved for this review.*

Assessment scale	Authors	Year	Measure
Dichotomic scale	Moshyedi et al. [10]	1995	Present/absent
	Van Noord et al. [15]	1996	Present/absent
	Kemmeren al. [16]	1998	Present/absent
	Kataoka et al. [22]	2006	Present/absent
	Schnatz et al. [18]	2011	Present/absent
	Bae et al. [23]	2013	Present/absent
	Newallo et al. [24]	2015	Present/absent
	Chadashvili et al. [25]	2016	Present/absent
	Schnatz et al. [20]	202007	Present/absent
Semi-quantitative scale	Mostafavi et al. [26]	2015	4 levels visual scale+
	Margolies et al. [27]	2016	12 levels scale*
	Kelly et al. [28]	2018	4 levels visual scale+
	Ružičić et al. [29]	2018	4 levels visual scale+
Continuous scale	Molloi et al. [30]	2008	Manual segmentation
	Molloi et al. [31]	2009	Manual segmentation
	Cheng et al. [12]	2012	Automatic segmentation
	Wang et al. [32]	2017	Automatic segmentation
	Trimboli et al. [2]	2018	Semi-automatic segmentation

+Based on BAC severity; *Based on number of vessels, max length and calcium density

Conclusions

To summarize, mammography allows to identify the presence of BAC, turning on an alarm bell on woman's CV status. In Europe, about 64 million women aged 50-69 years access screening mammography every two or three years [37] and about 8 million of these women may have BAC identified. A similar rough estimation is for the United States [38, 39] where spontaneous screening starts at 40 years of age and about 45 million women yearly access screening mammography with 6 million having BAC identified. This enormous potential needs to be exploited and awareness campaigns have to be promoted. A preventive action could be initiated over a threshold defined by retrospective and prospective studies. BAC represent the added value of

an ongoing and consolidated cancer screening to act for preventing the main cause of death among women in which traditional CV risk scores do not adequately perform. We need high-quality research for this, the first step being to make reliable and user-friendly BAC quantification tools available.

Preventive campaigns usually require huge efforts to be implemented, both social and economic. In a historical phase of great attention to the healthcare expenditure, to work in favor of using BAC for CV prevention in women, using the infrastructure of an already existing screening, implies that important results could be obtained with relatively limited costs.

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Original investigation. Breast arterial calcifications on mammography: intra- and inter-observer reproducibility of a semi-automatic quantification tool

Methods

The purpose of the study was to evaluate the intra- and inter-observer reproducibility of a specifically developed semi-automatic tool for BAC quantification on digital mammograms.

Image selection

For the training phase, 42 bilateral mammograms from different vendors, each including bilateral cranio-caudal (CC) and medio-lateral oblique (MLO) projections, were selected in five centers. Each case had to show in at least one projection in one breast a finding diagnosed as per BAC by a radiologist with at least 5-year experience in mammography. Subsequently, for the testing phase, a second independent multivendor image dataset of 53 bilateral mammograms from the same centers was selected to investigate the system reproducibility.

Images were acquired using full-field digital mammography systems, including: Senographe 2000D (General Electric Medical Systems, Milwaukee, WI, USA); AMULET FDR MS-100 (Fujifilm, Tokyo, Japan), Mammomat Inspiration (Siemens, Erlangen, Germany) or Giotto Tomo or Giotto Image 3D (IMS, Bologna, Italy) or Selenia (Hologic, Bedford, MA, USA).

Image processing and training phase

Considering the software functionalities, an adaptive thresholding algorithm was implemented and trained by a breast radiologist with a 9-year experience in breast imaging that precisely manually drawn BAC on the selected views using ITK-Snap [9]. Such manual BAC segmentation represented the reference standard for the training of the semi-automatic system.

The algorithm segmented and quantified BAC, by providing an estimate of the image surface area occupied by BAC, starting from rectangular region of interests (ROIs) drawn by radiologists. The BAC surface area was expressed in mm^2, and, in order to help the study logistics, the system allowed radiologists to visualize the mammograms and draw the ROIs online, through a simple ad-hoc web-based interface. During the segmentation process, overlapping ROIs were joined in order to obtain a unique segmentation of the shared portion of rectangles. Inside the ROIs, the segmentation was fully automatic, so that the only possible source of variability was the ROIs' selection by the radiologist.

Reproducibility assessment (testing phase)

Two residents in Radiodiagnostics with more than 6-month experience in mammography independently positioned the ROIs to identify the image portions where they recognized BAC. To standardize the human component of the segmentation method, both operators were intensively trained (total training time 5 hours for each of the two residents) by a radiologist with a 9-year experience in mammography and by a

bioengineer with a 5-year experience in image segmentation. One of the two residents estimated the BAC burden twice in separate sessions at 2-week interval. The decision tree used during segmentation process is depicted in Figure 1.

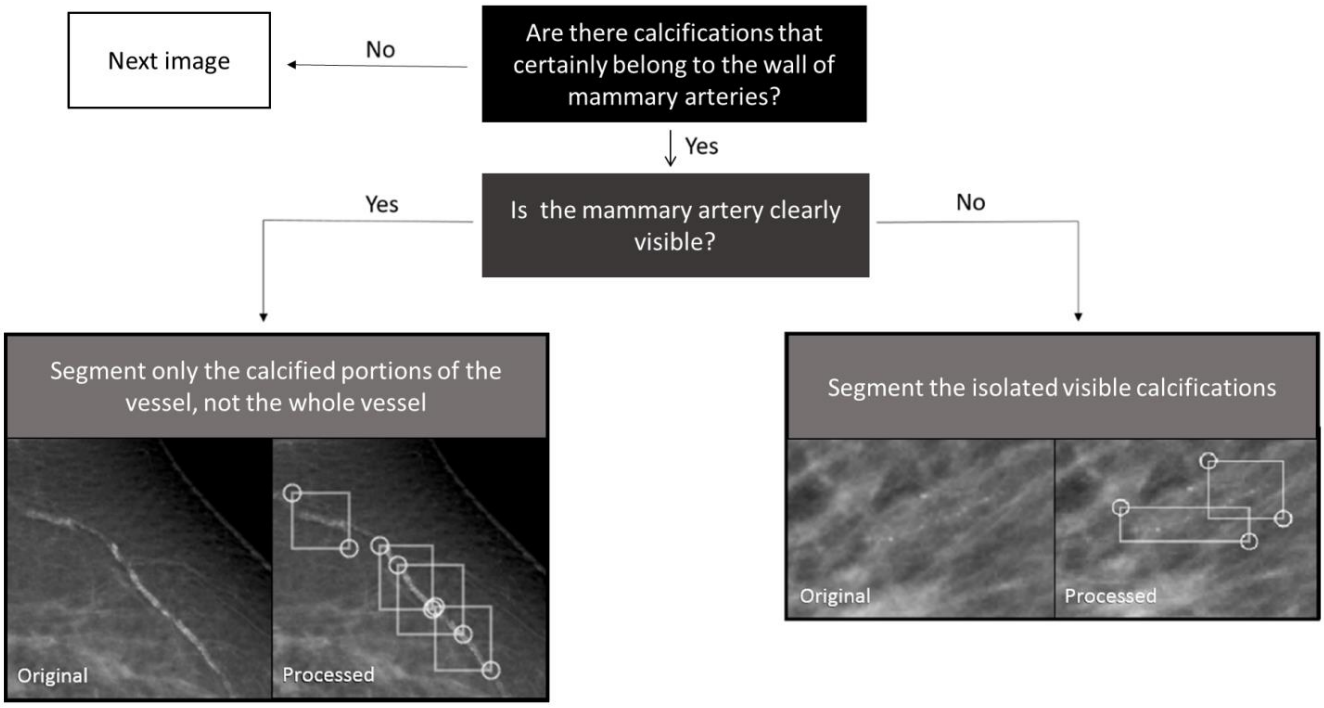

Figure 1. *Flowchart representing the decision tree adopted for breast arterial calcification (BAC) segmentation using a semi-automatic tool*

Considering the projective nature of mammography, the standard CC and MLO views were separately segmented for each breast (Figure 2). Finally, in order to find a unique index useful to represent the total BAC burden of each analyzed subject, the total BAC surface (BAC_{Tot}) was calculated as:

$$BAC_{Tot} = \left(\frac{BAC_{CC,l} + BAC_{MLO,l}}{2}\right) + \left(\frac{BAC_{CC,r} + BAC_{MLO,r}}{2}\right)$$

where $BAC_{CC,l}$ and $BAC_{CC,r}$ represent the respective segmented BAC surface on the CC view of the left (l) and right (r) breasts. In the same way, $BAC_{MLO,l}$ and $BAC_{MLO,r}$ represent the segmented BAC surface on the MLO view of the left (l) and right (r) breasts.

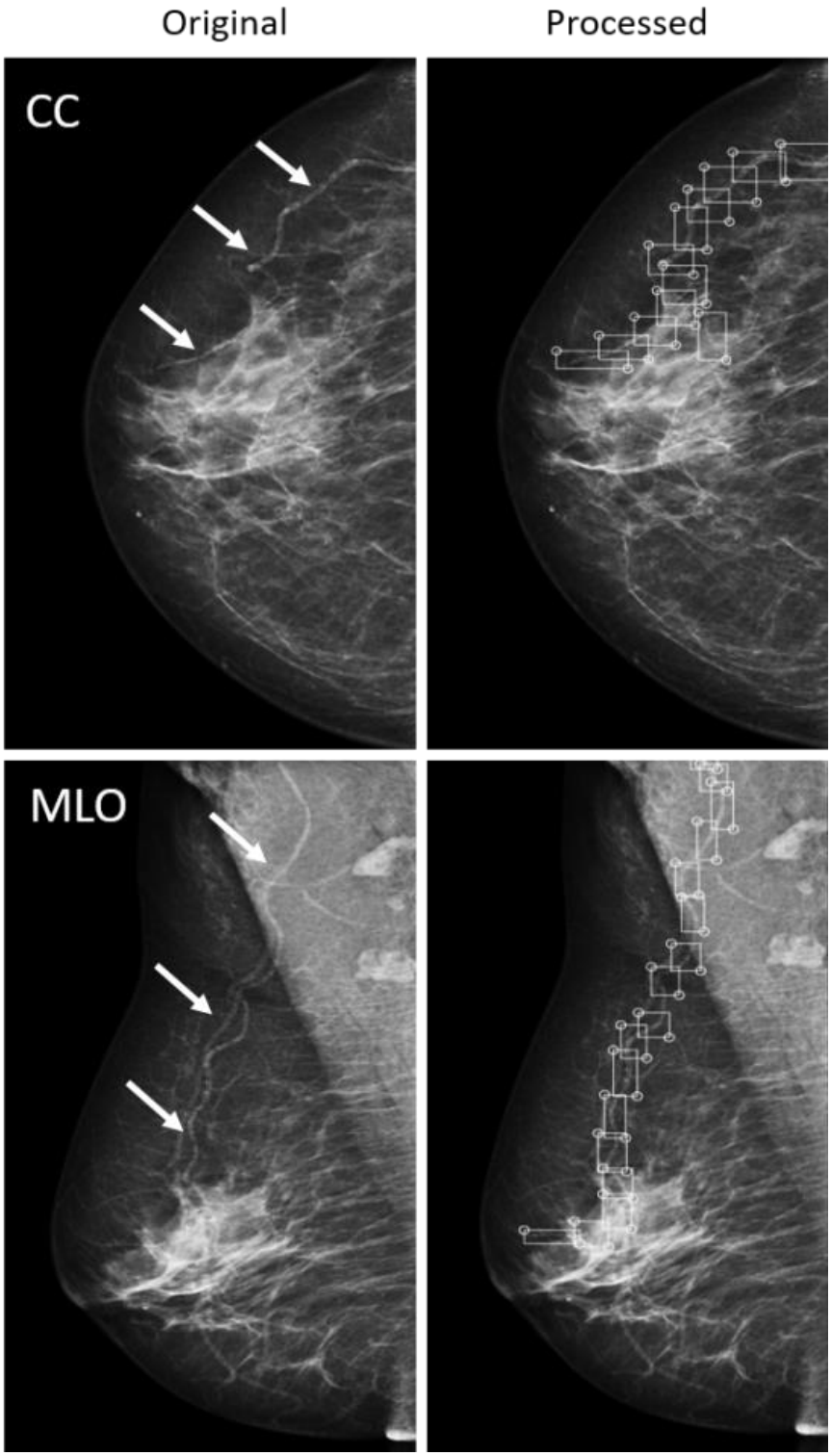

Figure 2. *Original CC and MLO mammographic views (left). Processed corresponding views with manually positioned rectangular ROIs containing breast arterial calcification (BAC) (right).*

Statistical analysis

Shapiro-Wilk test was used to assess the normal distribution of data. Due to the not normal distribution, descriptive statistics are reported as median and interquartile range (IQR). In order to assess intra- and inter-observer reproducibility, the Bland-Altman method was used.

Results

A total number of 212 images were segmented, obtaining 53 values of BAC_{Tot}. Table 1 shows the descriptive statistics related to the segmentation performed by both observers.

Table 1. *Descriptive statistics of the total breast arterial calcification amount (BAC_{Tot}) of each patient. Due to data distribution, descriptive statistics are reported as median and interquartile range (IQR) defined as Q_3-Q_1. Data are reported for the first measurements of Observer1 ($O_{1,1}$) and Observer2 ($O_{2,1}$) and for the second measurement of Observer1 ($O_{1,2}$).*

	BAC_{Tot} (mm^2)		
	$O_{1,1}$	**$O_{2,1}$**	**$O_{1,2}$**
Median	56.6	41.0	52.6
IQR	18.1 – 91.1	18.8 – 90.9	30.3 – 114.0
Min	5.1	1.1	9.4
Max	313.9	258.3	367.9

The intra-observer Bland Altman analysis showed a bias of 11.9 mm^2, a coefficient of repeatability equal to 32.7 mm^2 for an average BAC_{Tot} measurement equal to 72.8 mm^2 and a corresponding reproducibility value of 55%. On the other hand, the inter-observer analysis showed a bias of -7.0 mm^2, a coefficient of repeatability equal to 61.4 mm^2 for an average BAC_{Tot} measurement equal to 63.4 mm^2 and a corresponding reproducibility value of only 3%. Bland-Altman plots are depicted in Figure 3.

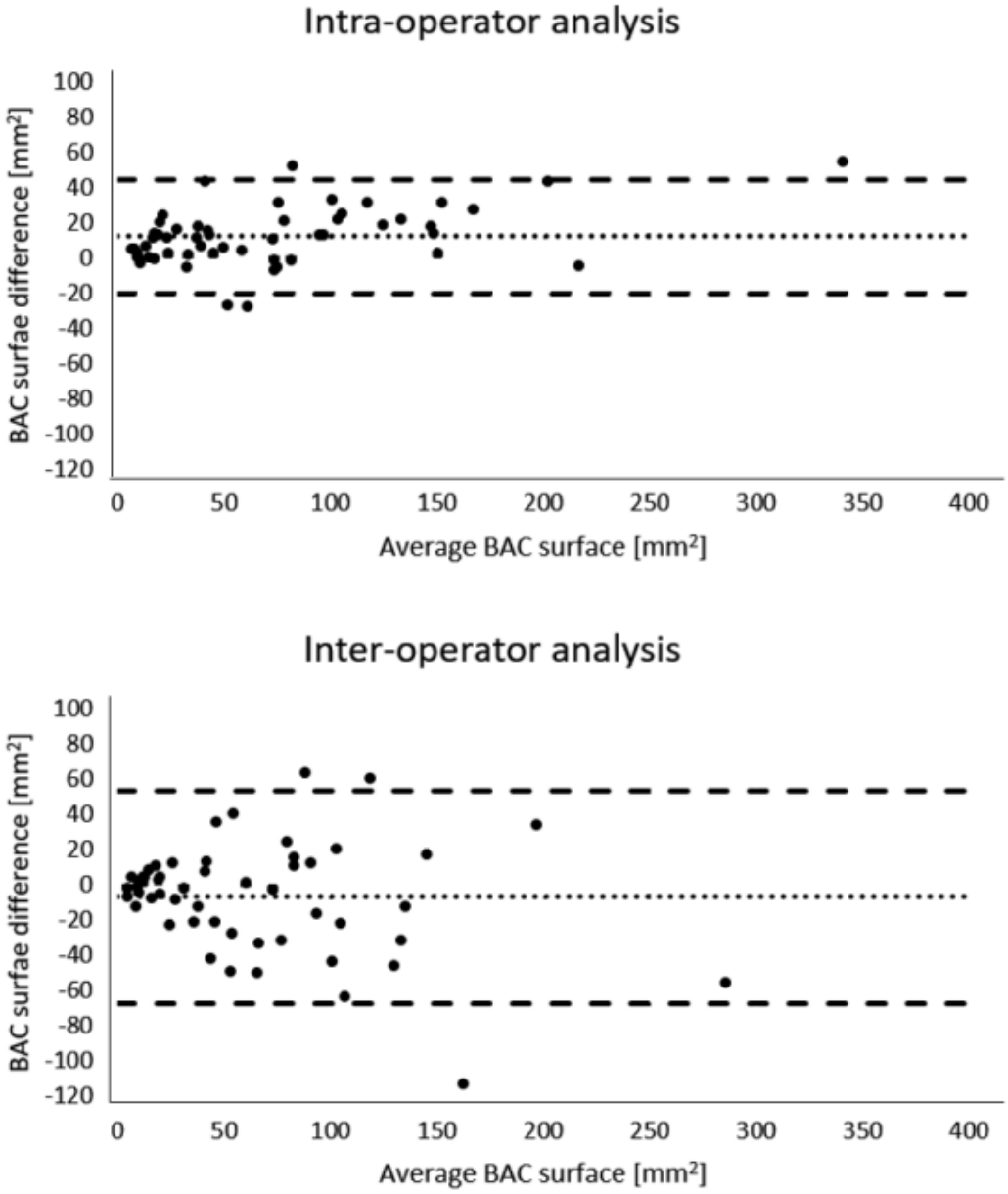

Figure 3. *Bland-Altman plots representing the intra and inter-observer variability in breast arterial calcification (BAC) surface measurement. The dotted line represents the bias that affects measurement process and the dashed lines represents the limits of agreements between different repetitions (intra-observer analysis) or readers (inter-observer analysis)*

Discussion

BACs are common findings on mammograms where they appear as linear, parallel opacities, typically described as a "tram-track" appearance [10]. Although an overall BAC prevalence up to 29% has been reported [7], they are not commonly described by radiologists in their reports being considered neither suggestive of nor a risk factor for breast cancer. In fact, BAC are an expression of arteriosclerosis belonging to Monckeberg's sclerosis, a sclerosing calcifying process involving the media tunica of breast arteries [11].

Up to now, BAC are only a research topic. Being considered only a secondary finding on mammograms, no big efforts have been made for standardize their quantitative evaluation similarly to mammographic density.

As previously mentioned, a strong association between BAC and CV disease has been demonstrated, related to a distinct pathophysiological pathway from the intimal atherosclerotic process [12]. A recent meta-analysis by Hendriks et al reported increased hazards from 1.32 to 1.44 for CV disease for women with BAC after adjusting for age and traditional CV risk factors [6]. Jiang et al [7] analyzed 10 cross-sectional studies for a total of 3,952 women and found a 3.86 odds ratio (OR) for CAD in those with BAC versus those without BAC. Thus, there is a potential for BAC to estimate CV risk in asymptomatic women. Considering the established role of screening mammography as a method to reduce breast cancer mortality by over 40% in women who attend a screening program [13], a reliable quantification of BAC used for CV risk estimation could be an important additional value of screening mammography. To date, this perspective is only an investigational issue. Only results from analyses using a dichotomic (present/absent BAC) scale were used because quantification methods adopted were largely heterogeneous and not comparable [14-18]. In most cases BAC were visually detected on mammograms by radiologists [19]. Molloi et al [20] developed a technique for quantification of BAC using standard full field digital mammography, demonstrating the feasibility of quantifying vascular calcium mass using densitometry upon calcium calibration on phantom, with an excellent inter-observer agreement.

In this study, BAC were detected by human readers who selected encompassing ROIs whithin mammographic images. Being the segmentation within the ROIs fully automatic, the only possible source of variability of this process was the ROIs selection and positioning, entirely depending on the reader. Surprisingly, our experiment resulted only in a moderate intra-observer reproducibility (55%) and in a very poor inter-observer reproducibility (3%). These results highlight that detection and estimation of BAC extent is not a trivial task. As highlighted by Cheng et al [21], BAC analysis is complicated by relevant geometrical issues. The appearance patterns of vessel calcifications vary not only due to different amounts of calcium deposition but also due to projection effects. There is a topological complexity of calcified vessels that may also cross or overlap each other in the two-dimensional projections.

The current study shows that, in the absence of fully automatic tools for BAC detection and quantification, the estimation of BAC largely depends on the reader and that, 2) a mixed approach such as reader-detection and automatic thresholding results in a too low reproducibility. We can speculate that BAC recognition is not a mere matter of higher density findings on the background of breast parenchyma and/or fat. Indeed, anatomical recognition of a calcified vessel could be as important as high density area recognition. A key role should be played by a complex combination of these two factors: (i) density differences between BAC and background; and (ii) morphology of BAC along with background). As a consequence, developing a computed algorithm for BAC detection and quantitative estimation is far from easy.

To standardize and reduce operator-dependency, two strongly different strategies are possible. On one hand, fully automatic detection and segmentation methods can be developed. Recent advances from artificial intelligence, such as deep learning [19], could play a role. However, large datasets of images are needed for

algorithm training and validation while establishing the ground truth for BAC engage expert radiologists in time-consuming procedures. On the other hand, radiologists may define semi-quantitative ordinal scales for severity of BAC, similar to the four ACR classes for breast density [10]. The second way seems to be easier and of more rapid application in clinical practice. Future research could integrate these two apparently opposite approaches, trying to define a visual BAC severity scale compared to thresholds obtained with automated methods.

This study has limitations. Apart from the intrinsic characteristics of the software utilized, we should consider that the human readers were two residents in Radiodiagnostics with a limited experience in breast imaging. However, in this work, the clinical experience in cancer detection and characterization was not relevant. Moreover, preliminary first attempts for testing this method through long-experienced breast radiologists as observers were made, and a reproducibility even lower (unpublished data) resulted. In addition, for the specific aim of the experience here described, the two residents underwent an intensive training under a double supervision (a breast radiologist and a bioengineer, as described in Methods), with the specific aim of optimizing their reproducibility.

In conclusion, our experiment showed a poor reproducibility of a semi-automatic operator-dependent tool for BAC quantification. These results pointed out that the observer represents the main source of variability in BAC severity assessment and give the basis for further studies.

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Original investigation. Reproducibility of breast arterial calcifications assessment on a semi-quantitative scale.

Methods

The aim of this work was to explore intra- and inter-reader reproducibility of a semi-quantitative scale for BAC assessment.

Study population and image selection

The local Ethics Committee approved this retrospective, monocentric study. Due to the retrospective nature of this study, no specific informed consent was necessary.

Mammograms of asymptomatic women who consecutively underwent screening for breast cancer from January 1st to January 31st, 2018 were retrieved. Women in which BAC were recognized at least in one projection were selected for the study. In these women, among mammographic views, bilateral medio-lateral oblique (MLO) were considered for BAC assessment. Women's age was consequently retrieved.

Image acquisition

Images were acquired using full-field digital mammography systems (Giotto Tomo or Giotto Image 3D, IMS, Bologna, Italy). The breast was held in place during the exposure by a compression plate and by the image receptor to avoid artifacts. For each breast a compression, up to 40 seconds was applied. All examinations included a cranio-caudal (CC) and MLO projections for each breast.

Image assessment

Images were reviewed by a resident in Radiology with a 3-year experience in reading mammography (R1) and by a medical student (R2) adequately trained by a breast imager with a 15-year experience. At first, both R1 and R2 reviewed a subgroup of 10 randomly selected exams as training examples; subsequently, each reader independently evaluated all included mammograms. Finally, to estimate intra-reader agreement, R1 re-evaluated all selected mammograms in a separate session at a 2-week interval.

Images were reviewed on standard 5-megapixel mammography monitors with admitted access to all standard software tools including magnification and gray-scale inversion.

The semi-quantitative scale adopted for assessing BAC was defined as follows: 1. Number of calcified vessels; 2. Calcium burden; 3. Overall length of calcified vessels. The number of calcified vessels corresponded to the relative score (*i.e.*: 3 calcified vessels yielded a score of 3). Calcium burden was defined as "present" when the lumen appeared obliterated in the 2D plane with a corresponding score of 1, or "absent" when the lumen was clearly or partially visible with a corresponding score of 0. The overall length of calcified vessels, expressed in millimeters, was obtained by adding together the single lengths of each calcified segment; afterwards, four categories were defined based on overall lengths distribution by R1 and

corresponding scores established according to the relative quartiles (category 0, category 1 from 1% to < 25%, category 2 from 25% to < 50%, category 3 from 50% to < 75%, category 4 from 75% to 100%). The median length of calcified vessels was 33 mm with an interquartile range (IQR) of 12–84 mm; five categories were defined: category 0 in absence of BAC, category 1 from 1 mm to 11 mm, category 2 from 12 mm to 32 mm, category 3 from 33 mm to 83 mm, category 4 for ≥ 84 mm. Category scores varied from 0 to 4, accordingly (Table 1).

Table 1: *Variables and possible scores of the semi-quantitative scale for breast arterial calcifications (BAC) assessment.*

Variable	Score
Number of calcified vessels	Number of vessels
Calcium burden	0/1
Overall length of calcified vessels[a]	0/4[a]
Final score	0/*n*[b]

[a]Categories were defined by quartiles of lengths distribution by Reader 1.
[b]*n* = sum of the scores related to calcified vessels, overall length of calcified vessels, and calcium burden

An example of BAC assessment is shown in Figure 1. Grading time for each MLO image was recorded for both readers on a subgroup of 10 subjects.

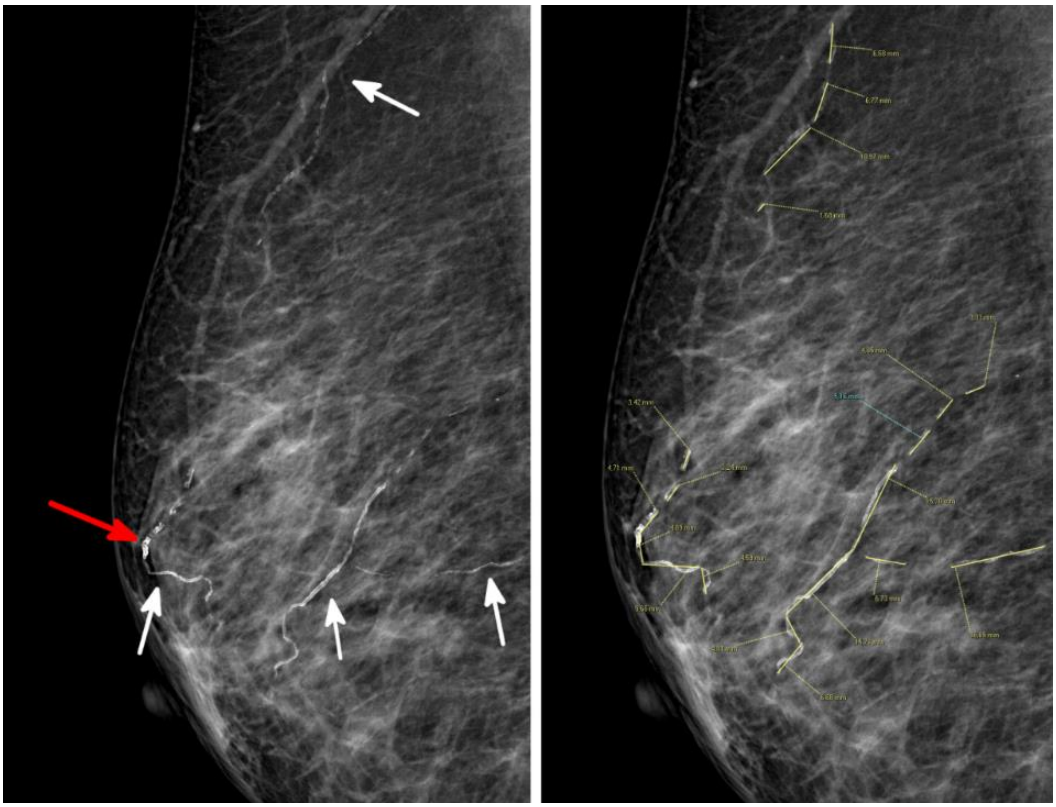

Figure 1*. Image features used to estimate: number of calcified vessels (white arrows in panel A; score = 4), calcium burden (red arrow in panel A; score = 1), overall length of calcified vessels (panel B; overall length = 153 mm; score = 4). Final score = 9*

Statistical analysis

Shapiro-Wilk test was performed to ascertain data normality. If at least one distribution was non-normal, all data were treated with non-parametric statistics. Descriptive statistics of continuous variables were expressed as mean ± standard deviation (SD) or median and IQR according to data distribution. T-test or Mann-Whitney U test were used to compare: age of women with BAC with age of women without BAC; median BAC score between the two readers; median BAC score in two age-groups (50–69 years, ≥ 70); median grading time between the two readers.

To assess intra and inter-reader agreement the Bland–Altman method was used in case of discrete variables while Cohen κ statistics and raw concordance (RC) were used categorical variables. Results of Bland–Altman analysis were reported as bias, coefficient of repeatability (CoR), and reproducibility (R) defined as the complement to one of the ratios between CoR and overall mean differences. Cohen κ with linear weighting for multiple categories was used with resulting values characterized according to the Landis and Koch scale [32]: < 0 no agreement; 0–0.20 slight agreement; 0.21–0.40 fair agreement; 0.41–0.60 moderate agreement; 0.61–0.80 substantial agreement; 0.81–1 almost perfect agreement. The level of statistical significance was set at $p < 0.050$.

Results

A total of 408 asymptomatic women underwent mammography during the study period. Among them, 57/408 (14%) presented BAC. Women without BAC, with a mean age of 59 ± 8 years, were younger than women with BAC, aged 67 ± 9 years ($p < 0.001$), as shown in Figure 2.

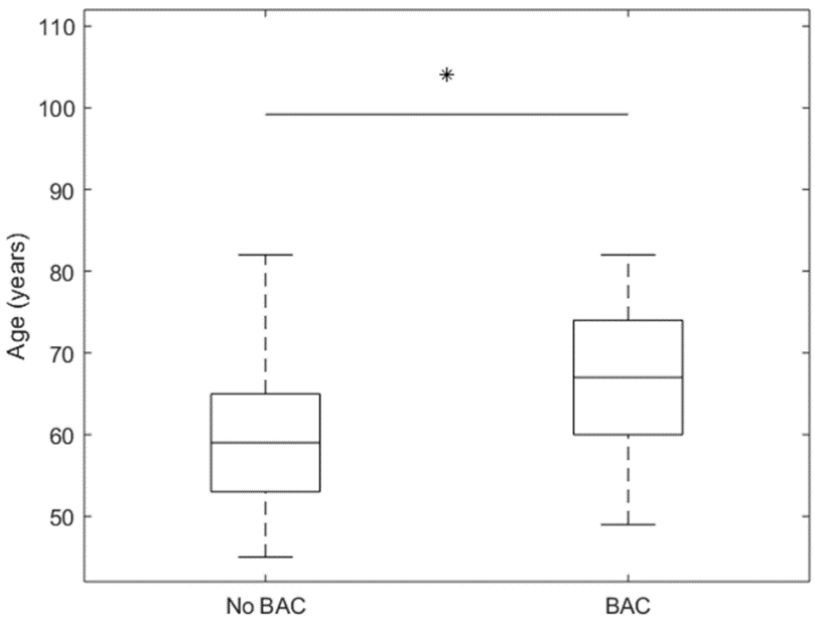

Figure 2. *Boxplot of age distributions in women without and with breast arterial calcifications (BAC)*

Image analysis was feasible in all 57 women and 114 MLO views were evaluated (Fig. 3). BAC presence was reported in 96/114 and 95/114 views respectively in the first and second assessment by R1 ($\kappa = 0.968$, $p < 0.001$, RC 99%) and in 94/114 views by R2 ($\kappa = 0.937$, $p < 0.001$, RC 98%). According to R1, BAC were bilateral in 39/57 and 38/57 women during the first and second assessment, respectively ($\kappa = 0.846$, $p < 0.001$, RC 95%), and in 37/57 women by R2 ($\kappa = 0.921$, $p < 0.001$, RC 96%).

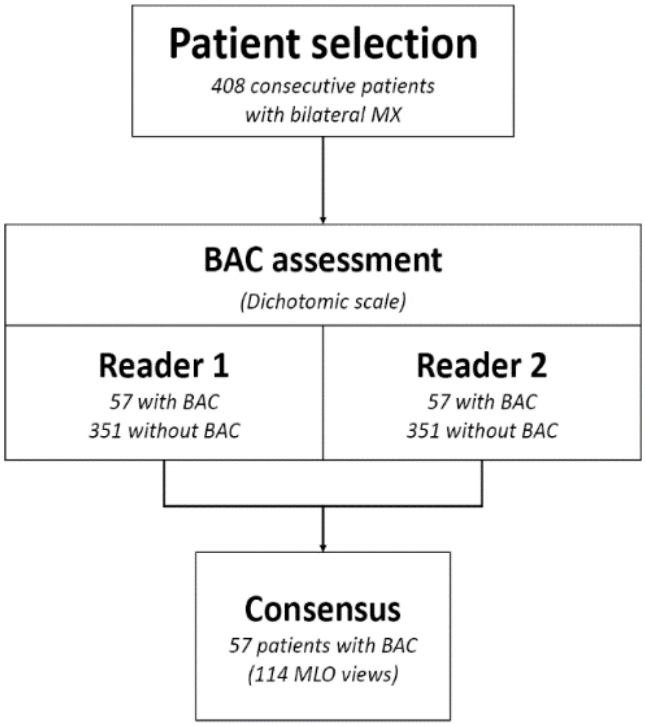

Figure 3. *Flowchart of the study population selection.*

After the application of the semi-quantitative scale, a median final score of 4 (IQR 3–4) and 4 (IQR 2–4) resulted for R1 and R2, respectively ($p = 0.417$); Bland–Altman plots of the intra- and inter-reader reproducibility are shown in Figure 4 and Figure 5.

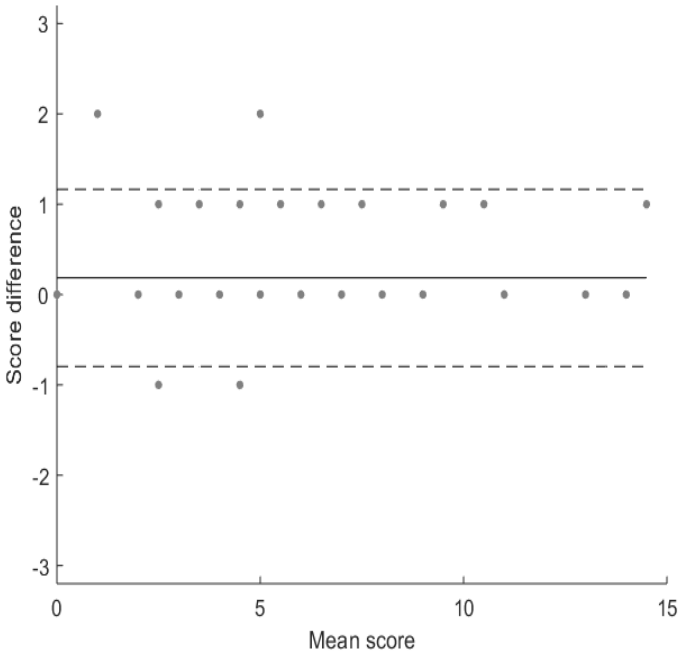

Figure 4. *Bland–Altman plot for intra-reader reproducibility of the final score of the semi-quantitative scale for breast arterial calcifications (BAC) assessment*

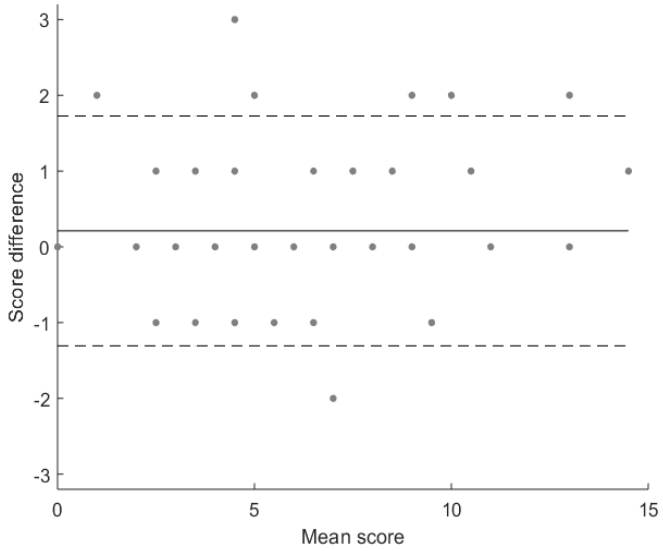

Figure 5. *Bland–Altman plot for inter-reader reproducibility of the final score of the semi-quantitative scale for breast arterial calcifications (BAC) assessment*

In women aged 50–69, median final score was 4 (IQR 3–5), while in women aged 70 and older it was significantly higher (5, IQR 3–8, $p = 0.018$) as depicted in Figure 6.

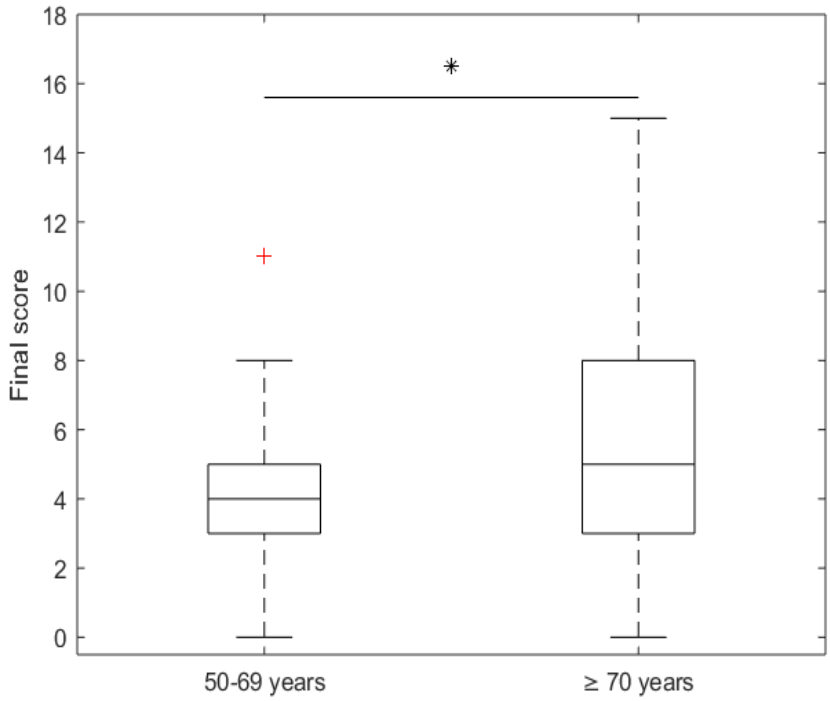

Figure 6. *Boxplot of final score of the semi-quantitative scale in patients aged 50–60 and 70 and older.*

Table 2 and Table 3 detail the results of intra- and inter-reader agreement for dichotomic and categorical variables, and of intra- and inter-reader reproducibility for the assessment of discrete variables.

Median grading time was 156 seconds (IQR 99–314 seconds) for R1 and 191 (IQR 137–292 seconds) for R2 (p = 0.743).

Table 2. *Intra-reader reproducibility of the semi-quantitative scale.*

Dichotomic and categorical variables	**Linear weighted κ**	***p***	**Raw concordance**
BAC presence/absence	0.968	< 0.001	99%
BAC bilaterality	0.846	< 0.001	95%
Calcium burden	0.961	< 0.001	99%
Overall length of calcified vessels[a]	0.912	< 0.001	87%

Discrete variables	**Bias**	**CoR**	**R**
Number of calcified vessels	0.079	0.604	66%
Final score	0.193	0.955	77%

Note—Dichotomic and categorical variables were analyzed with Cohen κ statistics, while discrete variables with the Bland–Altman method. BAC = breast arterial calcifications; CoR = coefficient of repeatability; R = reproducibility [a] Categories were defined by quartiles of lengths distribution by Reader 1.

Table 3. *Inter-reader reproducibility of the semi-quantitative scale.*

Dichotomic and categorical variables	Linear weighted κ	*p*	Raw concordance
BAC presence/absence	0.937	< 0.001	98%
BAC bilaterality	0.921	< 0.001	96%
Calcium burden	0.837	< 0.001	97%
Overall length of calcified vessels[a]	0.875	< 0.001	82%

Discrete variables	Bias	CoR	R
Number of calcified vessels	0.070	1.120	38%
Final score	0.211	1.516	64%

Note—Dichotomic and categorical variables were analyzed with Cohen κ statistics, while discrete variables with the Bland–Altman method. BAC = breast arterial calcifications; CoR = coefficient of repeatability; R = reproducibility.

[a]Categories were defined by quartiles of lengths distribution by Reader 1.

Discussion

CV disease represents a major public health issue, and is the first cause of death accounting for more than 30% of cases worldwide [1, 2, 33]. Over the last fifty years increasing attention has been paid to primary prevention, through the identification and control of risk factors and a progressive improvement in phenotyping CV risk; moreover, in recent times various efforts have been undertaken to improve the performance of traditional CV risk scores with the help of algorithms and also of imaging biomarkers [28].

In this framework, which implies also an attention to gender-specific risk assessment, BAC have been recently described among *"the top five women's health issues in preventive cardiology, at the forefront of recent and ongoing research"*, together with coronary microvascular dysfunction, hormone replacement therapy, calcium and vitamin D supplementation, and metabolic adaptations during pregnancy [34].

BAC are a common finding on mammograms where they appear as linear, parallel opacities, typically described as having a "tram-track" appearance [11, 12, 14, 15]. They are the expression of Mönckeberg's calcification, a non-atheromatous vascular lesion developing in the internal elastic lamina or in the tunica media of muscular arteries and have to be distinguished from atherosclerotic calcifications, which involve the intima of large and medium sized elastic arteries [35]. Mönckeberg's calcifications contain hydroxyapatite crystal deposition in the plaques, while accumulation of calcium phosphate salts in the vascular tissue is seen in advanced atherosclerosis [36].

BAC are easily recognizable on routine mammograms that women periodically undergo for breast cancer screening that – according to different local policies – starts from 40, 45 or 50 years of age. The reported association between BAC and CV disease in woman advocates the use of mammography as a preventive test

beyond breast cancer screening, spotlighting the heart and more comprehensively CV risk [15]. A systematic review and meta-analysis by Hendriks et al. [12]displayed evidence on the association between BAC and CV risk factors: high pooled BAC prevalence was found to be related with increasing age, diabetes, and parity as opposed to nulliparity, while smoking was linked with lower BAC prevalence. Thus, since BAC appear to be associated with an increased risk of CV disease events and with some known CV risk factors, their assessment represents a fundamental challenge [12].

Several attempts have been made to improve BAC estimation using fully automatic methods or semi-quantitative grading scales, such as the one proposed by Margolies et al. [25], in which both qualitative and quantitative evaluations were introduced [24, 25, 37, 38]. In all experiments performed, operator-dependency in BAC quantification remained critical and represented the major source of bias [30, 31].

Moreover, reproducibility of semi-quantitative grading scales for BAC assessment has never been explored. In our limited experience, preliminary tests on the reproducibility of such scales, – in particular the one proposed by Margolies et al. [25] – invariably resulted in low intra- and inter-reader agreement: this indeed prompted the development of our semi-quantitative scale, as a critical rethinking of existing ones.

The application of our newly built semi-quantitative scale started with a preliminary assessment of BAC prevalence in a population of 408 consecutive patients referring to our hospital for breast cancer screening in January 2018. As expected from literature reports that indicated an odds ratio of 2.98 linking age to BAC [15], we found a statistically significant difference (Mann-Whitney test with $p < 0.001$) in terms of age between the 57 women with BAC – which were aged 67±9 years on average – and the 351 women without BAC, which were aged an average 59±8 years. These data confirm that BAC prevalence increases significantly with age, like CV risk, considering that women in menopausal status loose the protective role of estrogenic hormones.

The final score of semi-quantitative scale showed good intra-observer (R=77%) and inter-observer (R = 64%) reproducibility. The number of calcified vessels was the most difficult variable to be assessed, showing lower reproducibility both in intra- and inter-reader comparison. On the contrary, calcium burden as well as overall length of calcified vessels showed low intra- and inter-operator variability.

Intra-reader reproducibility of bilaterality resulted to be lower than the inter-reader one. This apparently counterintuitive result stems from a minimal difference in raw agreement. In fact, RC values confirm the high level of agreement between assessments.

We also observed that the grading time for both readers was around 3 minutes, therefore suitable for integration in routine clinical practice; of note, the automatization of basic but time-consuming aspects such as the overall calculation of BAC length, which took an average 1 minute for both readers, could allow for an even smoother integration in standard mammography interpretation.

BAC may therefore become an important sex-specific biomarker for CV risk stratification, potentially guiding CV preventive programs in the female population. Women entering the screening program for breast cancer and not otherwise considered for CV risk would benefit from mammography in a double way, aiming at cancer secondary prevention and CV primary or secondary prevention. While such a preventive

intervention towards CV disease is likely not to be cost-effective in a low-risk population, it could be so in a population at increased risk [39]. BAC assessment in the context of breast cancer screening may enable subjects at increased risk to be identified and to be offered with tailored preventive and possibly therapeutic interventions, especially if this assessment could be easily integrated in the mammography interpretation workflow without substantial increase in time requirements. However, this approach has been indeed strongly limited by a number of factors, one of the strongest being the lack of validated BAC quantification methods. To exploit BAC potential on mammography, our semi-quantitative scale could be integrated with other approaches, such as fully automatic detection and segmentation systems. In the wake of artificial intelligence systems' promising performances in medical image analysis, a recent study investigated the potential of deep learning for BAC detection on mammograms: a deep convolutional neural network was used to discriminate between BAC and non-BAC pixels [31], reaching a detection ability similar to that of human experts, with false positives of 0.4762 cm^2, a true positive rate of 60%, and good performance also in calcium mass quantification (determination coefficient 96.2%). While these results once more confirmed the beneficial potential of deep learning in medical image processing and, in particular, for BAC detection, further large scale studies are needed to improve and validate these algorithms [31].

BAC represent an added value – swiftly recognized by patients [40]– in an ongoing and consolidated cancer screening strategy, shedding light on CV risk factors and prompting detection and prevention for the main cause of death among women, in which traditional CV risk scores do not adequately perform. High quality research is paramount to reach this aim, the first step being to make a reliable and user-friendly BAC quantification tool available.

Our study has limitations. First, it is a single-center study on a retrospectively retrieved relatively small number of subjects, that seems however statistically adequate given the narrow IC for BAC prevalence. Second, the two human readers were a Radiology resident and a medical student that – although adequately trained – still had limited experience in breast imaging. Yet, while clinical experience in cancer detection and characterization were not relevant in this study, it should also be noted how this factor represents indeed a strong point of this *ad hoc* semi-quantitative scale: the high intra- and inter-reader reproducibility show in fact the relative ease of its application, even in the hands of not-experienced readers. Third, a "ground truth" for BAC was not applied and it is unlikely that we will ever have large prospective studies that will ascertain the real burden of calcium from surgical specimens. Therefore, a higher intra- and inter-reader reproducibility is the most reliable method for a robust and objective quantification. Fourth, although the observer itself represents the main source of variability when assessing BAC, our reproducibility was high and intra- and inter-reader agreement rates all fell into the highest category according to the established classification by Landis and Koch [32].

In conclusion, this study showed that BAC can be semi-quantitatively assessed on mammography with high reproducibility and within an acceptable time, allowing for immediate clinical translation. Future prospective trials are needed to prove the ability of this score to stratify CV risk in women, guiding sex-specific preventive interventions.

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Part II

–

Multiparametric breast MRI for breast cancer management

Note. Part II research yielded following publications:

1. Trimboli RM, Codari M, Khouri Chalouhi K, Ioan I, Lo Bue G, Ottini A, Casolino D, Carbonaro LA, Sardanelli F. *Correlation between voxel-wise enhancement parameters on DCE-MRI and pathological prognostic factors in invasive breast cancers.* Radiol Med. 2018 Feb;123(2):91-97. doi: 10.1007/s11547-017-0809-8

2. Trimboli RM, Lo Bue G, Carbonaro LA, Sardanelli F. *BPE e altro: la RM "prognostica"*. Il Giornale Italiano di Radiologia Medica. 2016

Introduction

Breast cancer (BC) is the most common female cancer in the western world and represents the leading cause of cancer death in women aged 20 to 59 years [1]. A variety of entities with distinct morphological features and clinical behaviors are encompassed [2] and several chances exist for local and regional treatment [3]. Thus, a great effort has been made for the development of tailored therapies allowing for reducing BC mortality and treatment-related morbidity. Current decision making is based on traditional prognostic factors such as tumor size, histologic type, grading, and nodal status. All these parameters are derived from image-guided percutaneous biopsy or surgical intervention, which still play a crucial role in the diagnostic and prognostic process.

BC is an angiogenesis-dependent tumor since angiogenesis is necessary for tumor growth, invasion, and metastatic spread and takes on a prognostic value [4, 5]. Angiogenesis is the process by which, as the tumor grows, hypoxic stress on tumor cells, caused by the increasing gap between demand and supply of oxygen and nutrients through the normal vessels, leads to the formation of new vessels and/or the sprouting of existing capillaries in the peritumoral stroma through the release of growth factors, particularly the vascular endothelial growth factor (VEGF). The large endothelial fenestrations of the new capillary system, no longer controlled by regular physiologic mechanisms, give rise to increased capillary leakage of contrast material that can be appreciated on magnetic resonance imaging (MRI). One of the main advantages of MRI is the ability to go beyond morphological toward functional information providing insights of the hallmarks of a neoplasm. In particular, given the sensitivity to blood volume and vascular permeability, it can be used to measure the properties of tissue microvascularization that are associated with tumor neoangiogenesis [6,7]. The latter is essential for tumor growth and metastatic diffusion and is the physiopathological basis of contrast enhancement which is why in most cases we can distinguish a benign from a malignant lesion in breast MRI [6]. Breast magnetic resonance imaging (MRI) is the most accurate non-invasive method in the diagnosis of breast cancer with a sensitivity of 93% and a specificity of 71% as reported in a meta-analysis of 14 studies [8]. Significant technological advances and ever-increasing scientific evidence led to a widespread use of the method in the clinical field over the last ten years and allowed its introduction in different aspects of breast cancer diagnosis and management. Screening of high-risk women, preoperative staging, "problem solving" and monitoring of neoadjuvant therapy represent the main indications for the use of contrast-enhanced breast MRI and are currently recommended by the major scientific societies, such as the American Cancer Society, the European Society of Breast Imaging, the American College of Radiology, the European Society of Breast Cancer Specialists. Several perfusion parameters variably derived from breast MRI were initially correlated with traditional histological prognostic factors (grading, tumor size, HER2 expression and hormone receptors, Ki67 proliferation index), later with local recurrences, distant metastases and survival, opening a new scenario in the treatment of breast cancer where MRI becomes an imaging biomarker, a prognostic method able to predict the progression of the disease. Contrast-enhanced MRI allows to extract local perfusion parameters that permit to quantify the angiogenetic activity of breast lesions. So far,

perfusion parameters have been correlated with pathological prognostic factors such as grading, tumor size, human epidermal growth factor receptor 2 overexpression, hormonal receptors expression, and Ki67 positive cells percentage, with local recurrences, metastatic spread, and overall survival as well as response to neoadjuvant therapy [9, 10].

Original investigation. Correlation between voxel-wise enhancement parameters on DCE-MRI and pathological prognostic factors in invasive breast cancers

Methods

The purpose of our study was to verify the correlation between enhancement parameters derived from routine breast DCE-MRI and pathological prognostic factors in invasive BCs as a condition for the use of MRI-derived imaging biomarkers in adjunct to traditional prognostic tools in clinical decision making.

Patients

This retrospective study was approved by the local ethical committee. We retrospectively reviewed clinical and imaging records of newly diagnosed BC cases surgically treated at our Institution from January 2011 to December 2013, who also had preoperative breast MRI performed at our Department of Radiology. Women with unilateral unifocal, mass invasive BC were included in the analysis while those with multifocal, multicentric, or bilateral BCs and with in situ or non-mass enhancement carcinomas were excluded.

MRI technique

The MRI examinations were performed using a 1.5-T unit (Magnetom Sonata Maestro Class, Siemens Medical Solution, Erlangen, Germany). Patients were imaged in prone position with a dedicated bilateral breast surface coil, on days 7-14 of the menstrual cycle in premenopausal women and without scheduling limitations in postmenopausal women. After a three-plane scout view, the imaging protocol started with a bilateral axial T2-weighted short time inversion recovery sequence and an axial diffusion-weighted echo-planar sequence, both of them not considered for the current study. The DCE-MRI protocol consisted of a repetitive axial three-dimensional T1-weighted spoiled gradient-echo sequence: after an unenhanced scan, an intravenous bolus of 0.1 mmol/kg of gadobenate dimeglumine (MultiHance®, Bracco, Italy), at a rate of 2 ml/s, followed by a 20 ml saline flush, was administered and four contrast-enhanced dynamic scans were acquired (TR 11 ms, TE 4.9 ms, slice thickness 1,3 mm, matrix 512×512, acquisition time 1 min and 43 sec × 5, flip angle: 25°, voxel resolution 0.8×0.8×1.3 mm^3).

Image analysis

Two independent radiology residents, with a 3-year experience in breast MRI, retrospectively reviewed the images and segmented the entire lesion volume of each tumor. Both operators were trained for the segmentation protocol. Intra- and inter-observer reproducibility was tested on ten randomly selected patients in a double-blinded process (≥2-week interval). Segmentation was performed on the images obtained subtracting the pre-contrast frame from the second contrast-enhanced frame. At first, spatial resolution was doubled using super sampling tool in order to minimize partial volume effect; secondarily, the volume was outlined through constrains on consecutive slices. Segmentation was obtained by selecting a single seed that

propagates through slices, using an isointensity algorithm. Manual correction was done if necessary, as for removal of vessels (Figure 1).

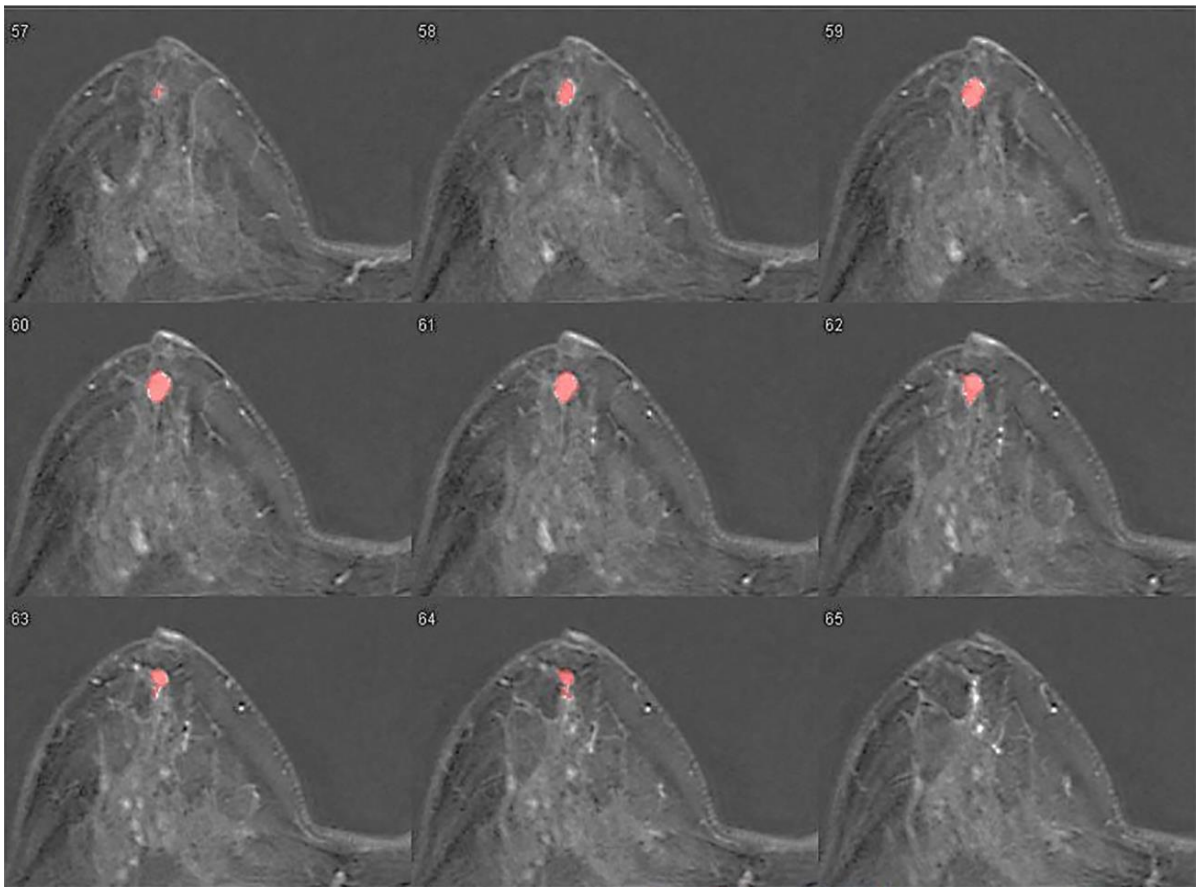

Figure 1. *Volume segmentation. Axial T1-weighted subtracted images show the application of the semi-automatic three-dimensional volume segmentation (Olea Medical, La Ciotat, France) of an invasive ductal carcinoma on the right breast. Segmentation was obtained by selecting a single seed that propagates through slices, using an isointensity algorithm.*

Enhancement parameters

The segmented volume was used as mask for the extraction of all voxel values from the computed DCE-MRI maps. Perfusion maps were extracted using a post-processing platform with dedicated DCE-MRI (Olea Sphere, Olea Medical, La Ciotat, France). The following voxel-wise semi-quantitative enhancement parameters were extracted: 1) time to peak enhancement; 2) signal intensity at peak (SIP); 3) peak enhancement percentage (PEP); and 4) post-initial enhancement percentage (PIEP).

PEP and PIEP were computed on three time points: the baseline point (t_0), the end of wash-in phase (t_1), and the post-bolus point (t_2). The PEP represents the percentage of initial signal increase of the concentration time curve:

$$PEP = 100 \times \frac{S_{t1} - S_{t0}}{S_{t0}}$$

The PIEP describes in percentage the post-initial behavior of the concentration time curve:

$$PIEP = 100 \times \frac{S_{t2} - S_{t1}}{S_{t1}}$$

Based on the PEP value, the initial signal increase of the pixel intensity curve has been classified between three wash-in types: slow (less than 50% increase in signal intensity compared with pre-contrast signal intensity), intermediate (between 50% and 100% increase in signal intensity compared with pre-contrast signal intensity), and fast (over than 100% increase in signal intensity compared with pre-contrast signal intensity). Similarly, based on the PIEP value, the post- initial signal course of the pixel intensity curve has been classified in: persistent (signal increase over 10% peak signal intensity), plateau (constant signal intensity +/- 10%) and washout (signal decrease over 10% peak signal intensity). As time to peak enhancement and corresponding peak are independently reached by each voxel also PEP and PIEP were computed taking this into account. Furthermore, time needed for lesion segmentation was recorded.

Histopathological assessment

Pathology was obtained on definitive surgical specimens in all patients. Histological features, including grading, estrogen receptor (ER) and progesterone receptor (PR) status, HER2 expression, Ki-67 proliferation, vascular and neural invasion, tumor and axillary nodal stage were obtained from the pathology reports. Among these, ER, PR status, HER2 expression, vascular and neural invasion were considered as binary variables (positive vs negative). Grading (G1,G2,G3) and Ki-67 proliferation (<15% vs. ≥ 15%, ≤30% vs. >30%) were scored on a three-level scale, while pathological tumor (pT1, pT2, pT3) and axillary nodal stages (pN0, pN1, pN2, pN3) were scored using breast tumor-node-metastasis (TNM) staging system [11].

Statistical analysis

Volume values and patients age were reported as mean ± standard deviation (SD) due to their normal distribution. Intra- and inter-observer reproducibility during volume segmentation was evaluated with the Bland-Altman analysis using segmented volume values. Correlations among enhancement parameters and pathological prognostic factors were evaluated using respectively Spearman (ρ) correlation coefficient for pT, pN, histologic grade and Ki67 proliferation or Phi (ϕ) correlation coefficients in case of vascular/neural invasion, ER expression, PR expression, HER2 expression (positive vs negative). Statistical significance level was set at $p<0.05$.

Results

Overall, 76 consecutive women were identified in the database; 56 women were excluded from the analysis for having ductal carcinoma in situ (1), multifocal (20), multicentric (15), non-mass enhancement lesions (8) or bilateral cancers (8). Moreover, 4 patients had incomplete MRI examinations and were also excluded. Thus, 25 women (age 64.5 ± 9.94, mean ± SD) with 25 BCs were included in the study: 22 (88%) invasive ductal, 2 (8%) invasive lobular and 1 (4%) invasive mucinous carcinomas.

Time for post-processing was 14.6 ±1.3 min (mean ± SD). The mean tumor volume was 2.78 ± 1.97 cm^3 (mean ± SD). Intra-observer bias ± 2 SD was 0.22 ± 0.53 cm^3 with a resulting reproducibility value equal to 60.2%. Inter-observer bias ± 2 SD was 0.15 ± 0.82 cm^3, with a resulting reproducibility value equal to 55.8%.

Significant correlations were found among MRI enhancement parameters and pathological prognostic factors. In particular, mean SIP correlated with pT (ρ = 0.424, p = 0.035) while mean PEP correlated with HER2 overexpression (ϕ = 0.471, p = 0.017) and pT (ρ = 0.449, p = 0.024). The percentage of voxels with a fast PEP directly correlated with pT (ρ = 0.482, p = 0.015) and pN (ρ = 0.446, p = 0.026) while the percentage of voxels with a slow PEP inversely correlated with pT (ρ = -0.421, p = 0.039) and pN (ρ = -0.481, p = 0.015). The percentage of voxels with an intermediate PEP also inversely correlated with pT (ρ = -0.415, p = 0.042) (Table 1).

Table 1. *Correlation coefficients and corresponding p-values among HER2, pT, pN and DCE-MRI enhancement parameters*

		Mean SIP	**Mean PEP**	**% PEP_{Slow}**	**% PEP_{Medium}**	**%PEP_{Fast}**
HER2	ϕ	-0.022	**0.471**	-0.240	-0.315	0.314
	p-value	0.916	**0.017**	0.247	0.125	0.127
pT	***ρ***	**0.424**	**0.449**	**-0.421**	**-0.415**	**0.482**
	p-value	**0.035**	**0.024**	**0.039**	**0.042**	**0.015**
pN	***ρ***	0.013	0.301	**-0.481**	-0.342	**0.446**
	p-value	0.952	0.144	**0.015**	0.094	**0.026**

ρ = Spearman correlation coefficient; ϕ = Phi correlation coefficient; SIP = signal intensity at peak; PEP = peak enhancement percentage; Statistical significant correlations are highlighted in bold.

Discussion

Our study confirmed that there is a correlation between enhancement parameters of invasive breast cancers as derived from breast MRI and pathological prognostic factors. In particular, SIP and PEP, that mainly reflect the increased permeability of vascular space in invasive cancers, correlated with histological unfavorable prognostic factors including HER2, pT and pN.

Yi et al. obtained model-based and model-free perfusion parameters of 102 invasive carcinomas and correlated them with histological prognostic factors. They found a significant correlation between model-based and model-free parameters and concluded that general information about tumor vascularization and pathologic prognostic factors may be obtained by routine acquisitions analyzing time-signal intensity curve [12]. However, dedicated MRI protocols aiming at deriving model-based perfusions parameters require T1 mapping and arterial input function favoring high temporal resolution with the sacrifice of high spatial resolution, the latter being indeed necessary for lesion morphology characterization. Accordingly, our study demonstrated that model-free enhancement parameters obtained *from a routine acquisition protocol* of breast MRI correlate with histological prognostic factors.

Important to note, *HER2* gene product is a trans-membrane receptor protein that plays an important role in regulating cell growth and differentiation. Amplification or overexpression of this oncogene occurs in approximately 15-30% of BCs and is relevant for the development and progression of certain aggressive BCs, being strongly associated with increased disease recurrence and a poor prognosis [13]. BC cells transfected with *HER2* acquire a more malignant phenotype, with increased cell invasion, angiogenesis and metastasis [14]. Previous studies showed that the *VEGF* expression, related to angiogenesis and microvessel density of BC, is positively correlated with *HER2* expression in human breast carcinomas [15]. Thus, the increased vascularization revealed by high perfusions indices on MRI well addresses the poor prognosis of HER2 positive BCs.

Tumor stage at diagnosis still influences BC overall survival significantly in the current era of effective systemic therapy [16], representing a strong predictor of a poor prognosis [17]. We found that SIP and PEP, which are indices of high vascularization, correlated with pT (Figures 2 and 3), and may potentially serve as predictive imaging-biomarkers [17]. In fact, the tumor neovascularization grade correlates with biologic aggressiveness and potential to metastasize [5,18].

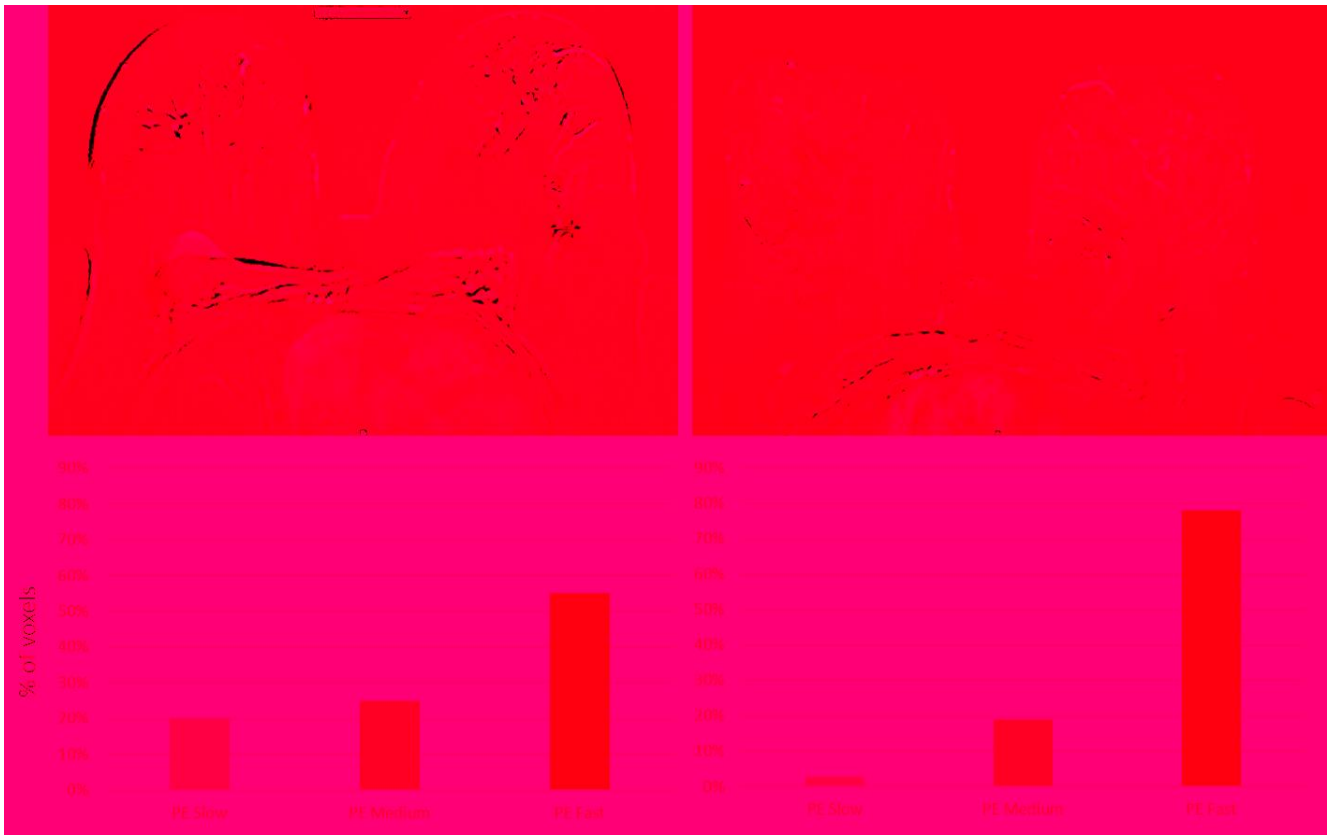

Figure 2. *Correlation between tumor size and peak enhancement percentage (PEP). Axial T1-weighted subtracted images (above) and corresponding PEP distribution (below) of a pT1 (left) and a pT2 (right) invasive ductal carcinoma. Histograms show that the larger tumor has higher percentage of voxels with fast PEP and lower percentage of voxels with slow PEP compared to the smaller tumor.*

Our results are in line with previous studies reporting an association between increased vascularization and higher histological grading with larger tumor size [10, 19].

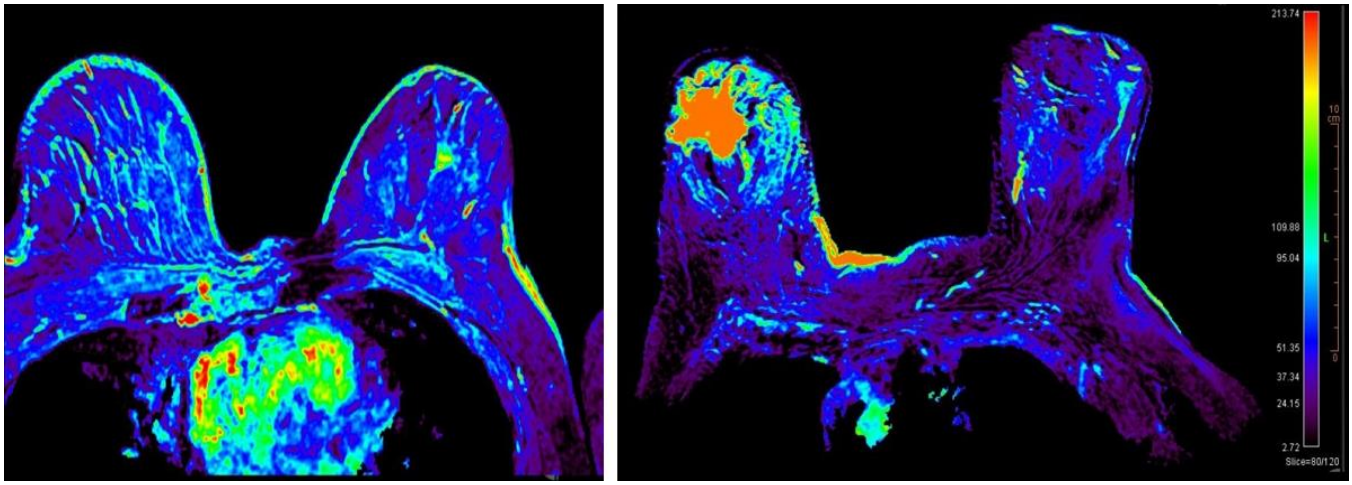

Figure 3. *Correlation between tumor size and signal intensity at peak (SIP). Representative parametric color-coded maps of SIP showing lower values in a pT1 invasive ductal carcinoma compared with a pT4 invasive ductal carcinoma (right).*

Lymph node metastases are well-recognized prognostic indicators. We found that high perfusion indices on MRI correlate with nodal status. This is in accordance with previous reports from Bonè et al [6, 20] suggesting that DCE-MRI may be influenced by factors that have prognostic value and may become a valuable prognostic tool for BC pretreatment evaluation.

As expected, the intra- and inter-reproducibility of volume segmentation resulted to be suboptimal. In fact, as it derives from the Euclidean geometry, greater the number of considered dimensions, greater the error and lower the reproducibility of the measurement [21]. Automatic segmentation systems are advocated to solve this geometrical difficulty.

A growing interest is in the use of MRI as a prognostic tool helping to define prognosis but also for a better planning of therapies. This is particularly true in patients candidates to neoadjuvant therapies where MRI could help to optimize the treatment in non-responders and in patients not suitable for surgery, such as elderly patients, where breast MRI could help understand hallmarks of cancers in a non-invasive way. . The strength of the present study is that it applies a semi-quantitative analysis using data deriving from routine clinical acquisitions of breast MRI, differently from what has been done in previous perfusion studies using dedicated acquisitions [10,22]. Perfusion indices can be obtained from normal workflow and may add prognostic information to diagnostics supporting the decision making on BC care.

This study has some limitations. First of all, it is a retrospective study on a small sample of patients. Thus, the sample size may be insufficient to reveal subtle differences in the various enhancement parameters and prevents from performing subgroup analyses. We strictly selected the study population, including only unifocal, unilateral, invasive mass cancers in order to avoid any confounding variable possibly diluting investigated correlations. Notably, 73% of identified patients was excluded for multifocal, multicenter, bilateral, or non-mass lesions, as however expected in a population of women newly diagnosed with breast cancer requested with MRI. Thus, in order to definitively ascertain the relation between enhancement parameters and pathological prognostic factors of BC, larger prospective studies are needed to figure out the applicability of routine MRI acquisitions in a prognostic potential for a predictive, personalized, preventive, participatory (P4) medicine [23].

In conclusion, our study showed that voxel-wise enhancement parameters of invasive BCs derived from a routine clinical DCE-MRI protocol correlated with HER2, pT and pN. This supports thinking breast MRI as a promising tool to improve BC patient management.

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Part III

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Artificial intelligence in breast MRI

Note. Part III research yielded following publications:

1. Codari M, Schiaffino S, Sardanelli F, Trimboli RM. *Artificial Intelligence for Breast MRI in 2008-2018: A Systematic Mapping Review.* AJR Am J Roentgenol. 2019 Feb;212(2):280-292. doi: 10.2214/AJR.18.20389

Introduction

Recent enthusiasm regarding the introduction of artificial intelligence (AI) into health care and, in particular, into radiology has increased clinicians' expectations regarding the possible impact of AI on their profession [1, 2]. Indeed, in 2017 AI was included as one of the three top trends in the Gartner hype cycle for emerging technologies [3]. However, this technology has not yet reached the stage of stable and massive adoption, and it is indeed currently evolving.

AI refers to a subfield of computer science focused on allowing computers to mimic human cognitive functions [4]. The recent hype regarding AI applications in health care is mainly attributable to the use of deep learning (DL) to address diagnostic tasks [5]. DL is a subset of machine learning(ML), which, in turn, is a domain of AI that enables computers to learn and detect patterns in data without being explicitly programmed [6]. ML was first introduced in 1959 [7] and has been used for daily tasks such as filtering spam e-mails. In the past decade, thanks to recent technologic advancements that bring graphic processing units and other highly performing computational resources within the reach of all individuals, ML and DL algorithms have been applied to diagnostic tasks with encouraging performance [8].

ML includes a large variety of methods that can be classified according to the training approach, as follows: supervised learning algorithms, which use labeled data to predict or classify data according to a known output; unsupervised learning algorithms, which do not use labeled data but aim to find naturally occurring patterns within data; and reinforcement learning algorithms, which aim to determine the best behavior on the basis of simple reward feedback [9]. Among the supervised learning approaches, artificial neural networks (ANNs), support vector machines (SVMs), random forest (RF), linear discriminant analysis (LDA), and logistic regression classifiers are the most frequently used [10, 11].

ANN architecture, which is inspired by biologic neural networks of the brain, comprises interconnected nodes, which perform the weighted sums of several input data (features) and then pass them to an activation function to produce the target output. Nodes are structured in layers: the input layer, which represents input features; a variable number of hidden layers, which represent the network depth; and the output layer, which represents the target output. During the training phase, all weights are dynamically optimized to maximize model accuracy. The output layer is then connected to a softmask function that converted the raw data generated by output nodes into a target class probability [5].

SVMs are supervised learning models that allow classification of input data by calculating the widest hyperplane, the support vector, between two classes. Created as binary classifiers, SVMs are now used also for multiclass classification and are widely used both for classification and regression purposes because of their ability to model nonlinear relationship between input features and output target [6].

Another popular branch of the ML is represented by decision trees, which are one of the most popular ML algorithms because of their ease of interpretation compared with other black-box techniques like ANNs and SVMs [6]. Decision trees make predictions or classifications by bifurcating the feature space at each decision node. Among decision trees, RF classifiers aggregate votes of a set of decision trees generated by a randomly created subset of the training dataset to improve classification accuracy. On the other hand, among

unsupervised learning methods, clustering is the most frequently used subset of unsupervised learning methods [12], with the fuzzy C-means clustering algorithm being one of the methods most often used [9]. Clustering algorithms classify data into a defined number of clusters (groups) by iteratively calculating the cluster configurations that minimize intragroup variability and maximize the intergroup variability. In the fuzzy C-means algorithm, each datum, instead of being assigned to a specific cluster (hard clustering methods), can belong to several clusters with a certain degree of membership that ranges between zero and one [9].

One of the first fields of medical imaging that benefited from the introduction of ML techniques is breast imaging. The pioneer applications of ML to breast imaging date back to the 1990s and, predictably, were focused on the detection of microcalcifications and breast lesions on mammograms to overcome the limitations of conventional computer-assisted diagnosis systems [13–15]. These efforts were justified by the combination of high-volume workflow in mass screening and the intrinsic limitation of mammography, which remains the standard method for breast cancer screening but which clearly shows its imperfections in terms of both sensitivity and positive predictive value.

MRI represents the most sophisticated method for breast imaging. When, in 1986 [16], the introduction of a gadolinium chelate as a contrast material opened the door to contrast-enhanced (CE) MRI, and highly spatially and temporally resolved images were further obtained over the years, it was immediately evident that this functional method would have preserved a great potential for diagnosis and care of breast cancer. Today, selected clinical settings are recommended for CE breast MRI [17], which reaches a sensitivity close to 100% [18]. In addition, unenhanced sequences (in particular, T2-weighted imaging, proton spectroscopy, and especially DWI) have been applied in clinical practice, ushering in the era of multiparametric breast MRI [19]. The large datasets provided by and potentially extractable from breast MRI make it the right stuff for fitting AI applications. Moreover, AI interacts with and integrates radiomics, which is now the other emerging topic in radiology. Radiologic images and especially MR images encompass hidden information that is not always perceivable from human interpretation but can be extracted using ML methods and analyzed for a better understanding of the disease in vivo [20]. Patient care may hence benefit from a faster, more accurate, and tailored diagnosis and prognosis.

Original investigation. Artificial Intelligence for breast MRI in 2008-2018: A systematic mapping review

Methods

Search Strategy and Eligibility Criteria

In June 2018, with the use of PubMed (MEDLINE, U.S. National Library of Medicine and National Institutes of Health) and EMBASE (Elsevier), a systematic search of the literature was performed to identify articles that evaluated the application of ML to breast MRI. A controlled vocabulary (using medical subject headings in PubMed and the thesaurus in EMBASE) was used. Search syntax was built combining search terms related to three main domains: "artificial intelligence," "breast disease," and "MRI." The exact search query was ('breast disease'/exp OR 'breast disease' OR 'breast' OR 'breast'/exp OR breast) AND ('nuclear MRI' OR 'nuclear MRI'/exp OR 'mri') AND ('artificial intelligence' OR 'artificial intelligence'/exp OR 'machine learning' OR 'machine learning'/exp OR 'deep learning' OR 'deep learning'/exp). The search was limited to original articles on in vivo studies of humans published since 2008 in peer-reviewed journals, all of which were written in English and featured an available abstract. The initial screening for eligibility was performed by two independent readers with 10 and 6 years of experience in medical image analysis. Articles considered to address the application of AI to breast MRI on the basis of the title and abstract were considered eligible for inclusion. Eligible articles were retrieved and read in full. To be included in our systematic review, an article had to discuss any attempt to apply any method of ML, DL, or AI to breast MRI for any clinical or technical aim. No specific limitations were applied regarding the aim of the study, including image processing, diagnosis, prognosis, or outcome prediction. Finally, references of analyzed articles were searched manually to determine further eligibility for inclusion.

Data Extraction

Data extraction was performed independently by the same two readers. Agreement was achieved by consensus involving two other readers. For each article analyzed, the first author's surname; year of publication; journal of publication; Web of Science Core Collection journal category; first author's country of affiliation; study design; dataset; study aim; ML, DL, or AI methods used; and corresponding performance were recorded. Among the MRI characteristics, static magnetic field strength and adopted sequences were noted. When multiple AI, DL, and ML approaches were compared, only the outperforming approach was included in this review. A quantitative general overview of study characteristics was reported using descriptive statistics and median and interquartile range (IQR) values. However, because of the heterogeneity of aims, the dataset used, applied techniques, and evaluation metrics specified in the selected publications, we decided to stratify results by pursued clinical aim. Moreover, to summarize the results accomplished in studies that addressed the same aim, the descriptive statistics (minimum, median, IQR, and maximum values) were reported for the most frequently used performance metric.

Results

Literature Search and Study Characteristics A flowchart illustrating the literature search is presented in Figure 1. From the initial search and after removal of duplicate studies, 258 articles were identified. In addition, one more article was included after a manual search. So, 259 articles were selected for further screening. Of these, 112 articles met the exclusion criteria, whereas 147 were selected for title and abstract screening. A total of 67 studies were ultimately included in this systematic mapping review.

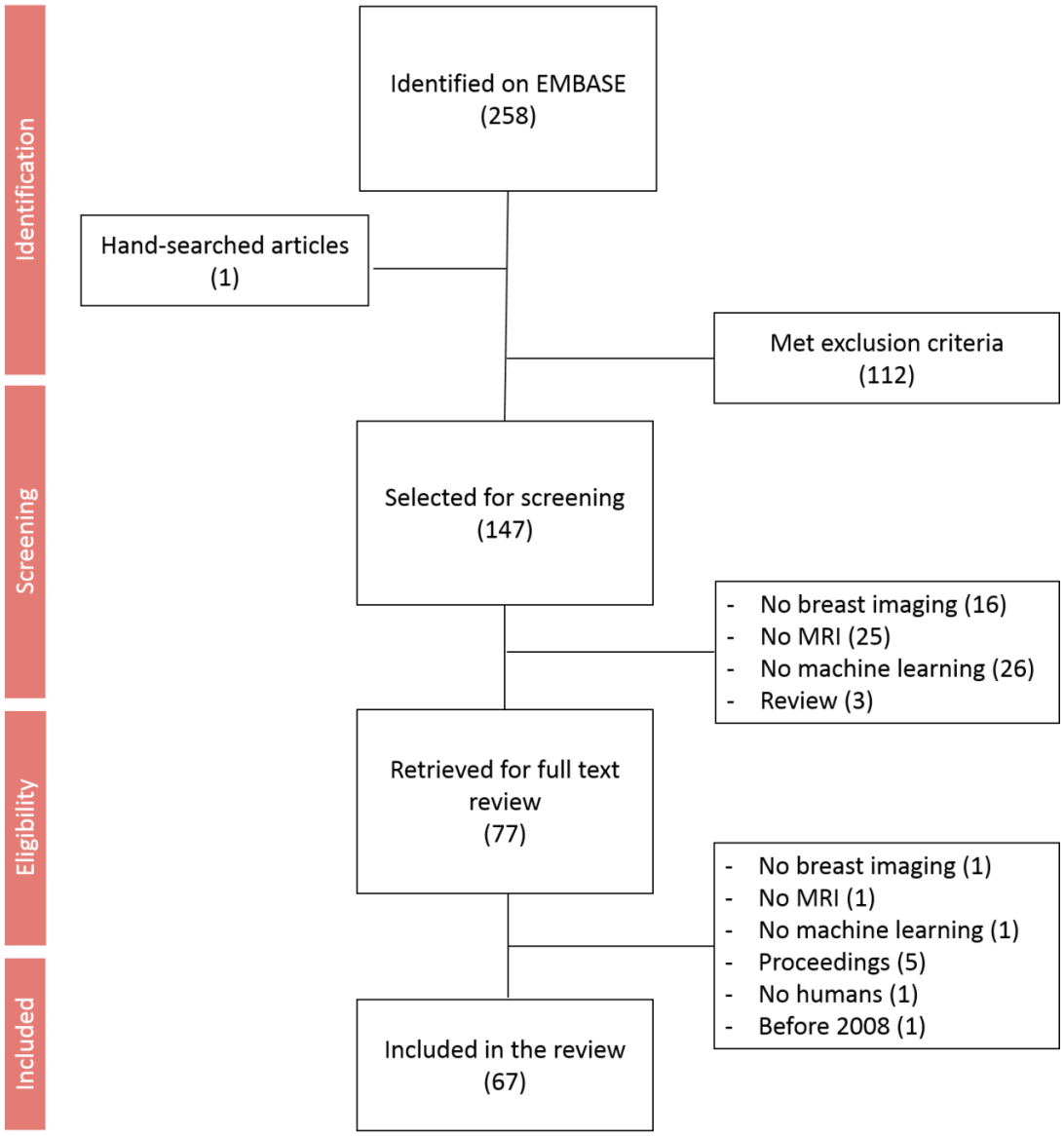

Figure 1. *PRISMA (preferred reporting items for systematic reviews and meta-analyses) flowchart of systematic identification, screening, eligibility, and inclusion information from retrieved studies in this analysis.*

Of the full texts that were reviewed, 58 studies (87%) had a retrospective design, whereas the remaining nine studies (13%) had a prospective prospective design. Included articles were published between January 2008 and June 2018. Figure 2 shows an increase in the number of published original articles on the topic of AI.

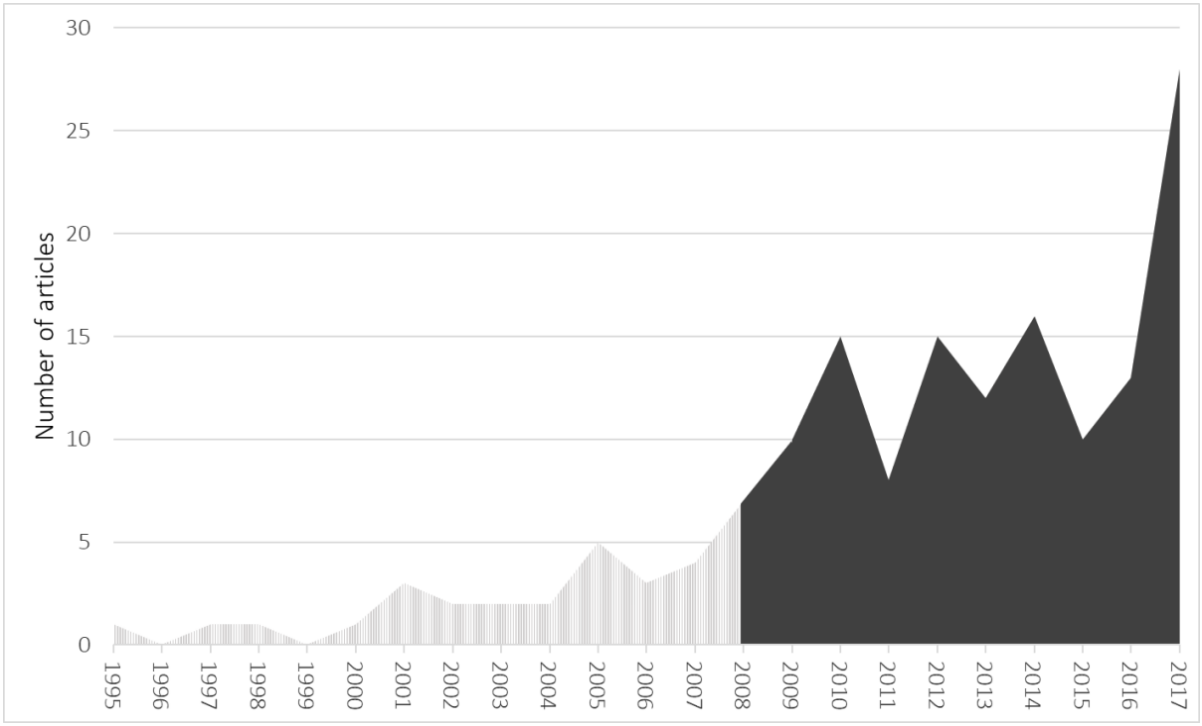

Figure 2. *Graph of number of original articles on application of artificial intelligence to breast MRI published annually, as indexed in EMBASE and PubMed.*

Figure 3 shows the distribution of articles according to the Web of Science Core Collection journal category. When journal categories were categorized into two main groups (medical journals versus engineering or computer science journals), 45% of selected articles were published in medical journals, whereas 55% were published in engineering or computer science journals. Of note, approximately one-third of the reviewed articles (36%) were included in the radiology, nuclear medicine, and medical imaging article category.

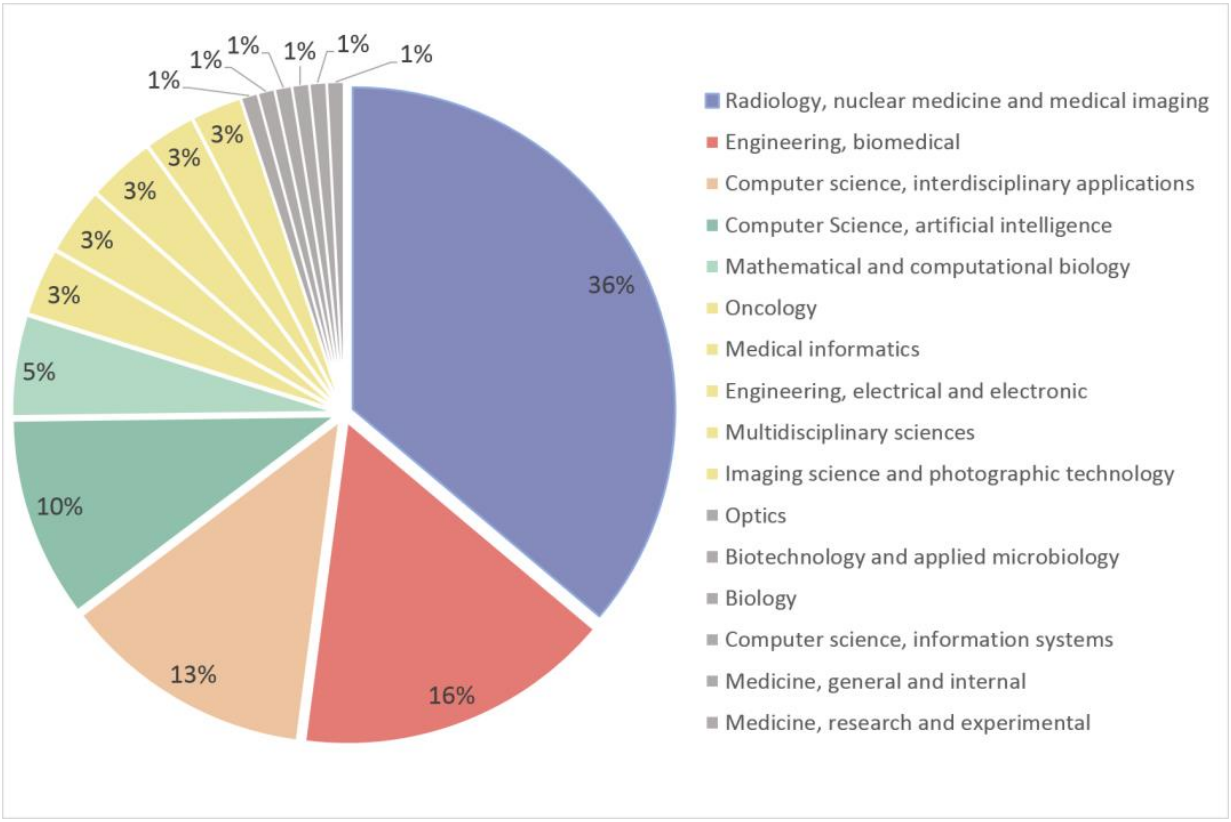

Figure 3. *Graph of number of original articles on application of artificial intelligence to breast MRI published annually, as indexed in EMBASE and PubMed.*

Regarding geographic distribution of the studies, 29 studies (43%) came from North America, 21 (31%) from Europe, 16 (24%) from Asia, and one (2%) from Australia. Among European countries, The Netherlands accounted for 24% of published articles; the United Kingdom, 19%; Germany, 14%; Italy and Slovenia, 9% each; and Belgium, Norway, Portugal, France, and Turkey, 5% each. The United States alone accounts for 90% of publications from North America. Among publications from Asia, 75% are from China, 13% from Taiwan, 6% from India, and 6% from South Korea. Figure 4 shows the geographic distribution of published works.

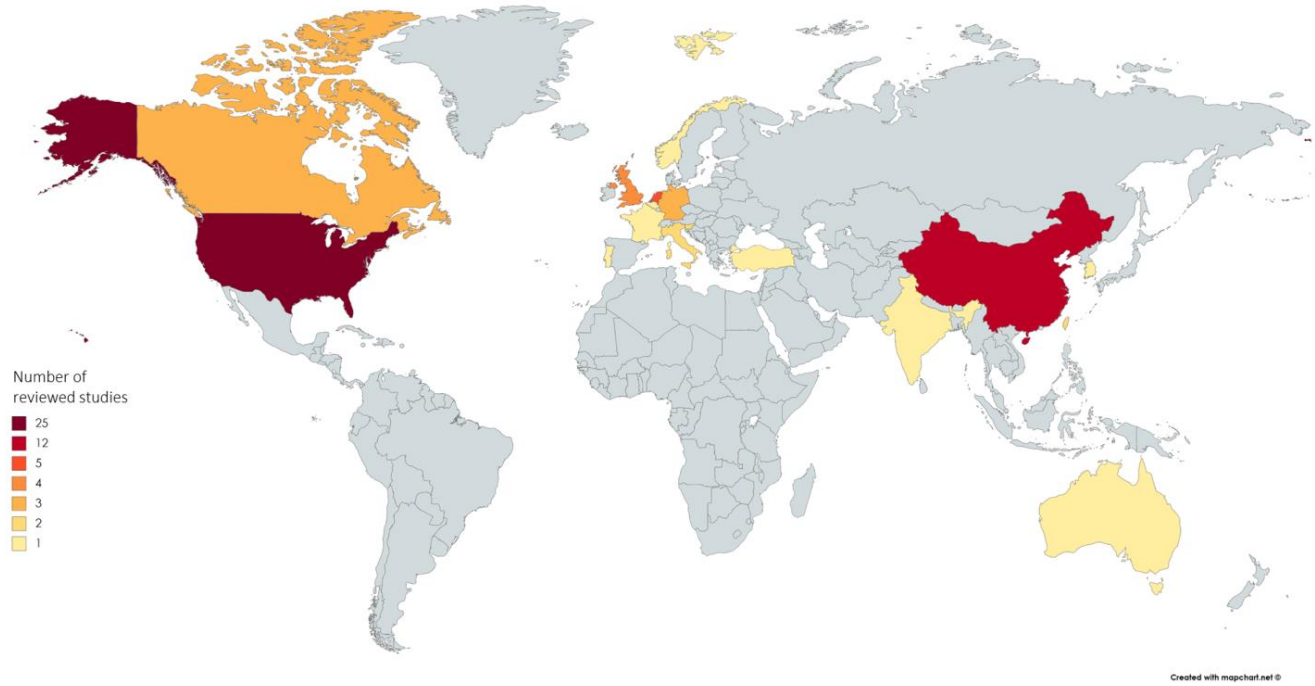

Figure 4. *Geographic map of country of affiliation of first authors of reviewed studies.*

For most of the studies (37 studies; 55%), MRI scans were collected using 1.5-T scanners only. Eleven studies (16%) used images acquired using 3-T scanners only. Finally, 14 studies (21%) used both 1.5-T and 3-T scanners, whereas four studies did not provide this information. Of the different MRI sequences used for breast imaging, CE sequences were used most often. In particular, in 50 studies (75%), only CE images were used, whereas in seven studies (10%), CE images were combined with other MRI data, such as T2-weighted, diffusion-weighted, and MR spectroscopy images. Images acquired using the Dixon method were also used in three studies (4%); in one of these studies, it was used alone, and in the other two, it was combined with other MR images (T1-, T2-, and proton density–weighted images). Finally, three studies (4%) were performed using diffusion-weighted images only.

Different aims were addressed in various studies. We grouped the aims of the studies reported in each article into four subgroups: breast lesion classification (i.e., differentiation of malignant versus benign lesions) (36 studies [54%]); image processing (14 studies [21%]), including tissue and lesion segmentation and image quality improvement; prognostic imaging (nine studies [13%]); and response to neoadjuvant therapy (NAT) (eight studies [12%]). The lesion classification subgroup included all studies that tried to differentiate between two or multiple lesion categories (e.g., mass, nonmass, benign, or malignant). The image processing subgroup comprised all studies that focused on image segmentation or image quality improvement. The prognostic imaging subgroup included all studies correlating MRI enhancement parameters, extracted through ML algorithms, with indicators of prognosis, namely molecular subtype (luminal A cancers), the pathologic marker of aggressiveness (Ki-67 labeling index and histologic grade), multigene assay classification (MammaPrint [Agendia], Oncotype DX [Genomic Health], and PAM50 [Prosigna]), and

lymph node status. Finally, the NAT response subgroup consisted of all studies analyzing the pretreatment prediction of response to therapy, early prediction of NAT response after one cycle, and residual tumor assessment. Figure 5 shows in detail the article distribution according to these different subgroups.

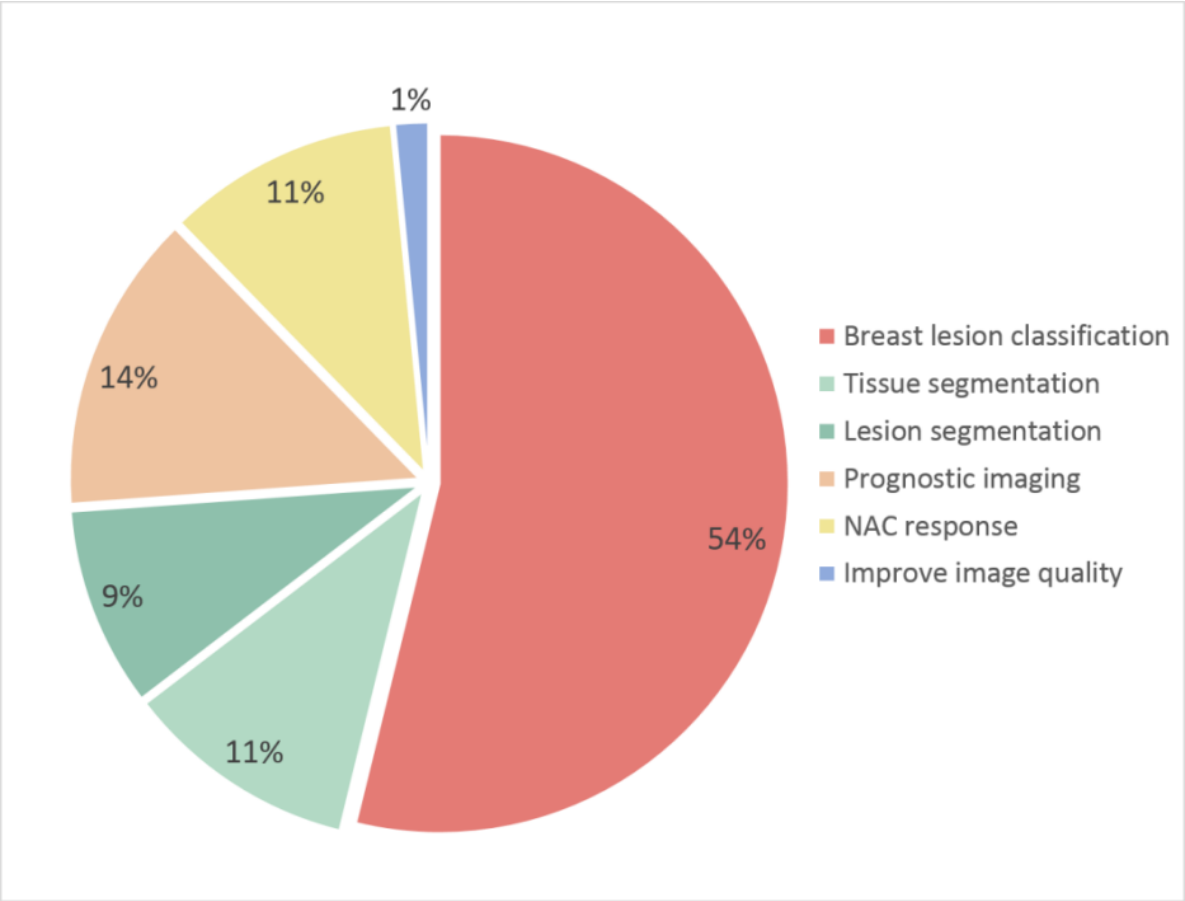

Figure 5. *Pie chart of percentage distribution of original articles on application of artificial intelligence to breast MRI, according to different clinical aims. NAT = neoadjuvant therapy.*

To address these aims, different algorithms falling under the umbrella of AI were applied. Multiple algorithms were frequently combined to address the final aim of the study. Among the techniques used, ANN, SVM, and clustering approaches were the most frequently used algorithms, accounting for 66% of the studies. Comprehensive distribution of the methods used is provided in Figure 6, whereas Figure 7 shows their distribution as stratified by the aim pursued.

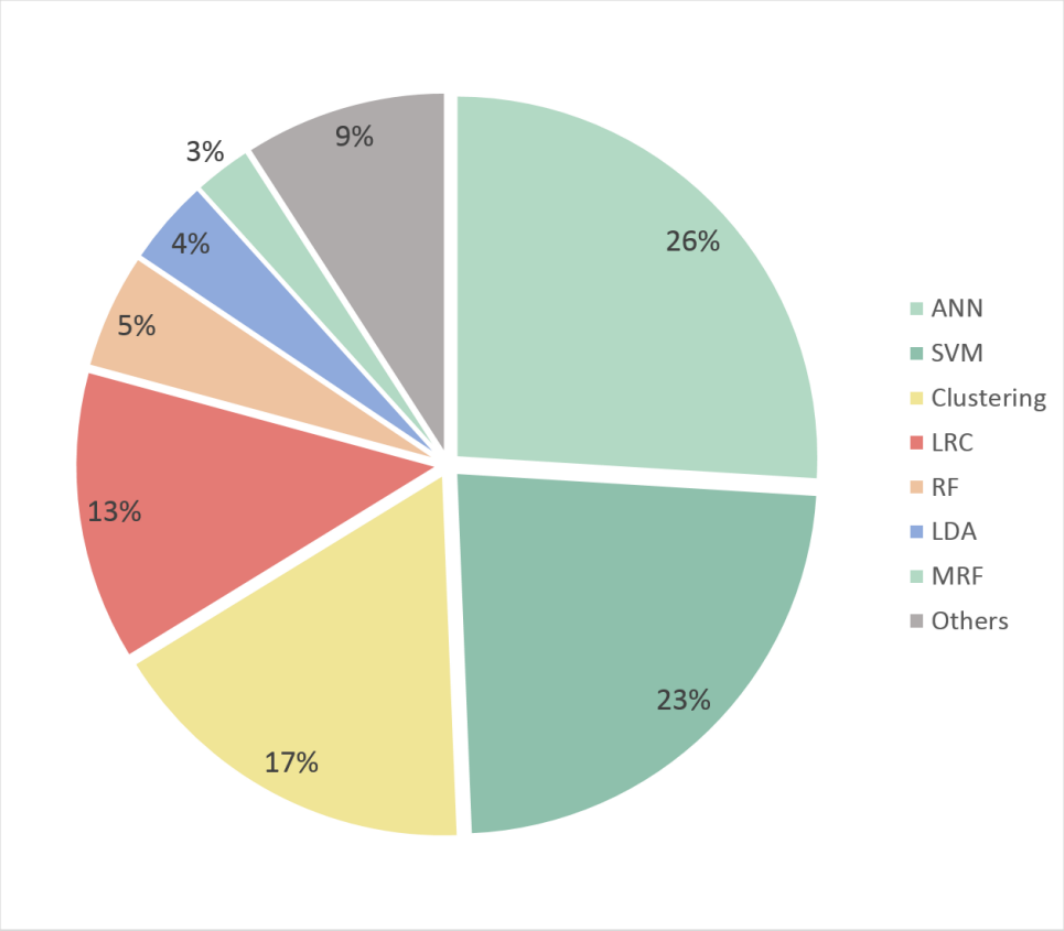

Figure 6. *Pie chart of percentage distribution of used machine learning approaches to process breast MRI data in articles included in this review. "Others" denotes techniques used in less than 2% of studies.*

Taking into account only ANNs, which were used in 21 studies, conventional ANNs were used in 48% of the studies [21–30], Bayesian ANNs in 24% [31–35], convolutional neural networks in 24% [36–40], and Markov-Chain Monte-Carlo Bayesian neural net classifier in 5% [41]. Regarding clustering techniques, which were applied in 13 studies, fuzzy C-means clustering algorithm was the technique most often applied, accounting for 77% of the studies [40, 42–50].

Lesion Classification

The median size of the dataset was 120 patients (range, 41–325 patients; IQR, 88.5–234 patients) and 132 lesions (range, 41–690 lesions; IQR, 94–259 lesions). SVM was the most frequently used algorithm, used in 15 of 36 studies (42%) [36, 37, 51–64]. The diagnostic performance was evaluated primarily on the basis of AUC value from ROC analysis, which ranged from 0.74 [60] to 0.96 [57] (median AUC value, 0.88; IQR, 0.83–0.91). Overall, after all methods of lesion classification (SVMs [36, 37, 51–64], ANNs [21–25, 31–34, 36, 37], clustering [42, 43], LRCs [24, 42, 65, 66], and the RF algorithm [67–69]) were considered, the AUC value ranged from 0.74 [60] to 0.98 [21] (median, 0.87; IQR, 0.84–0.91). Ground truth was established on the basis of pathologic analysis in 34 studies and radiologic reports in two studies.

Image Processing

The median size of the dataset was 21 patients (range, 4–361 patients; IQR, 10–82 patients) and 98.5 lesions (range, 60–137 lesions; IQR, 79–118 lesions). The most frequently used approach was clustering, which occurred in six of 14 studies (43%) [40, 44–47, 70]. Several measures of performance were used: the Dice similarity coefficient [38, 71], accuracy [70], sensitivity and specificity [26, 27, 40, 70, 71], the overlap ratio [40, 44, 66, 71], true-positive findings [72], correlation [38, 47], the intraclass correlation coefficient (ICC) [46], and the Jaccard similarity coefficient [73]. Ground truth was established by manual segmentation in 11 studies and by radiologic report in two studies.

Prognostic Imaging

The median size of the dataset was 178 patients (range, 66–318 patients; IQR, 90–228 patients) and 192 lesions (range, 84–508 lesions; IQR, 170–318 lesions). Different algorithms were applied. ANNs were used in three studies [28, 35, 41], clustering was used in three studies [48–50], LRCs were used in four studies [49, 50, 74, 75], and an SVM [76], Markov random fields [49], and LDA [48] were used in one study each. The measure of performance was the AUC value in all but one [76] study, and the AUC value ranged from 0.62 [35] to 0.88 [41, 75] (median 0.80; IQR, 0.76–0.85). Ground truth was established on the basis of pathologic findings in seven studies and multigene assay classification in two studies.

Neoadjuvant Therapy Response

The median size of the dataset was 63 patients (range, 28–151 patients; IQR, 50.75–81 patients). ANNs were used in two studies [29, 30], LRCs were used in two studies [77, 78], and an SVM [79], LDA [80], clustering [81], and Bayesian classifier [82] were used in one study each. The statistical measure of performance that was used most often (used in all but one [82] study) was the AUC value. AUC values ranged from 0.74 [80] to 0.96 [29] (median, 0.85; IQR, 0.83–0.90). In half the studies, the ground truth was established on the basis of pathologic analysis; in the other half, it was established on the basis of Response Evaluation Criteria in Solid Tumors [83].

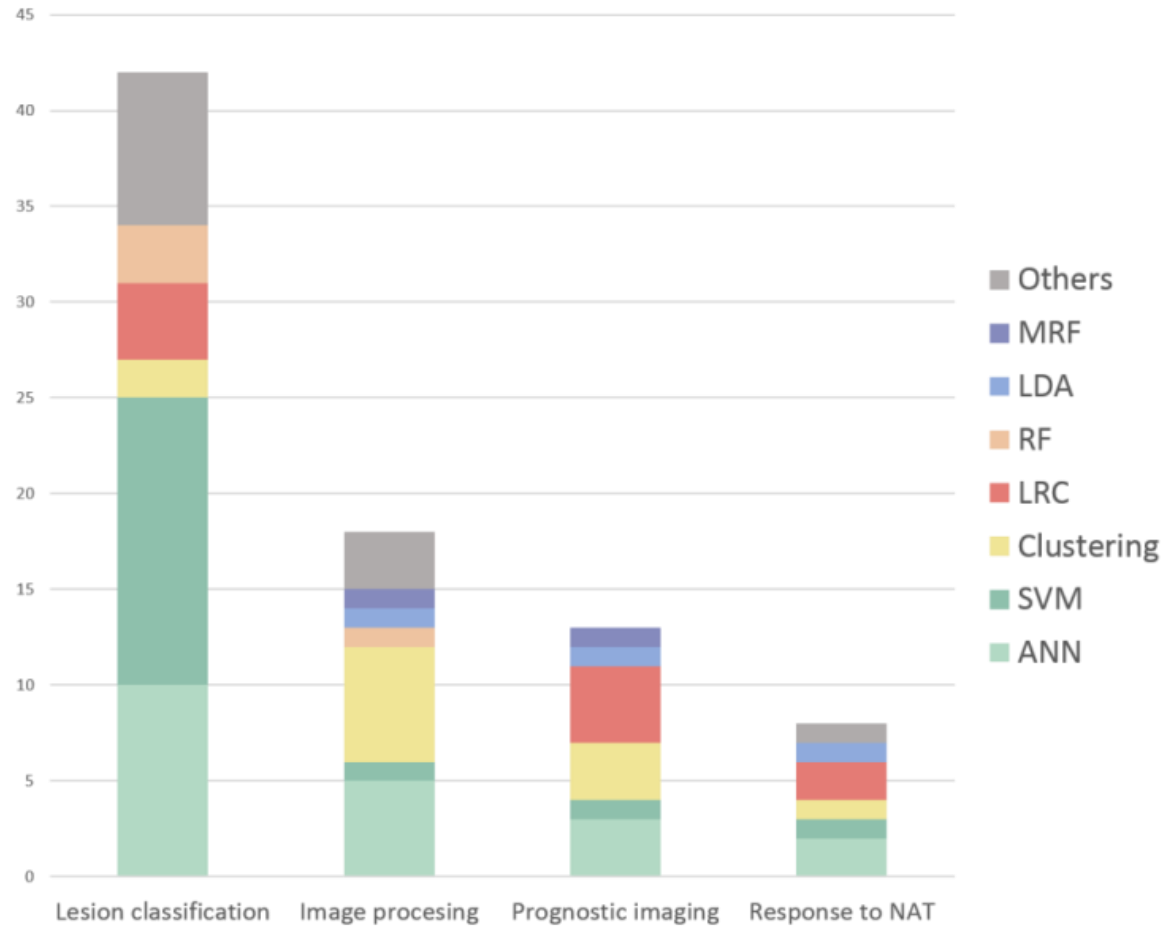

Figure 7. *Bar graph of distribution of machine learning algorithms used (alone or in combination with another algorithm) in published articles included in this review, according to clinical aim. "Others" denotes techniques that were used in less than 2% of cases. NAT = neoadjuvant therapy*

Discussion

Today, all over the world, AI is one of the most compelling and complex challenges faced by the medical community. Radiologists are already—or soon will be—directly involved in using AI. Therefore, efforts have to be made to become familiar with the phenomenon, and radiologists cannot put their heads in the sand regarding the existence of AI or be afraid to ask questions about it. The aim of this systematic mapping review was to evaluate the application of AI in breast MRI in a matter-of-fact manner. We primarily focused on clinical aims for which AI has been tested and then provided insights regarding applied ML methods, assessing where we stand and what we must expect. Web of Science Core Collection journal categories were also investigated to gain a better understanding of the current actors in the AI revolution.

As expected, in the past decade, several studies appeared that tested ML approaches in breast MRI. Researchers worldwide are working to exploit MRI data to improve breast cancer diagnosis and treatment. This is exemplified by the global coverage of published studies from many countries, with researchers in the United States and China having a leading role in producing these studies. Among European countries, The Netherlands and the United Kingdom have produced the largest number of publications. A fast nonlinear

increase in the number of published original studies is clearly visible (Fig. 2), reflecting the scientific community's growing interest in the application of the ML technique in MRI data processing. As pointed out in a recent report by Craft [84], interest in such applications is expected to grow within the next 5 years because, at present, most of these applications are nascent and not ready to be massively adopted.

Hard work has been expended on the development of innovative solutions to improve women's health care, as emphasized by the results of this review. Of note, only one-third of the articles identified were published in radiology journals, whereas 48% were published in engineering or computer science journals (Fig. 3). These findings suggest the existence of two concurrent circumstances and one emergent need. One circumstance, as would be predicted, is that radiologists are the target audience for and future users of AI-based applications in breast MRI. The other circumstance is that most AI methods are still in the technical development phase (or, as we may say, the preclinical phase, even though they are applied to breast MR images of humans). The emergent need involves close cooperation of radiologists and computer scientists and engineers as the key to success in the development of clinically usable AI-based solutions.

Moreover, breast imaging represents a breeding ground for ML implementation. First of all, early cancer diagnosis may be understood in several ways. There is a well-known population that is periodically screened involving millions of women all over the world who need to be confirmed healthy. BI-RADS is an accepted standard diagnostic categorical system globally [85]. Finally, there is room for improvement in risk prediction and prognostication using imaging. Increased positive predictive value of breast MRI is needed. Both this and multiparametric breast MRI for breast cancer prognosis are key areas of AI application.

In fact, when breast cancer diagnosis and treatment planning are performed on the basis of MRI data, radiologists are asked to integrate multiple types of information from multiple different images. As previously emphasized in the present study, CE, diffusion-weighted, and Dixon images provide the data most likely to be processed by ML algorithms. These MRI sequences have a common characteristic: they generate multiple image volumes for a single subject. Moreover, CE and DWI sequences are adopted to represent and investigate dynamic events, such as perfusion and, mainly, diffusion, respectively. This means that, by definition, breast MRI data include both spatial and morphologic information and temporal and dynamic information that must be integrated and processed to classify, detect, and characterize breast lesions. These data are prone to be processed with ML and, in particular, DL algorithms because of the heterogeneity and volume of the information included. Indeed, the successful application of these algorithms requires that overfitting and bias be avoided during model development, a goal that can be achieved using large and heterogeneous datasets. In this scenario, because of the large amount of morphologic and dynamic data that can be extracted, breast MRI offers one of the most appealing methods for the testing of AI and manifestation of its potential.

Despite lack of standardization of the breast MRI examination and the increasing use of DWI sequences, CE MRI is the sequence most as input data of ML algorithms for AI applications in nearly 60% of studies, whereas less than 5% of studies have involved diffusion images. This probably reflects not only the larger

confidence associated with use of a consolidated sequence—namely, CE MRI—but also the willingness to exploit its potential to discover more and more features that are helpful in achieving the best performance.

The present study emphasizes the four main applications of ML algorithms in breast MRI (lesion classification; image processing, mainly including tissue and lesion segmentation; prognostic imaging; and NAT response). These applications reflect the clinical settings in which the role of ML has increased. To date, the use of breast MRI for the four main indications has indeed increased [86], according to international guidelines [17, 87].

One of the most common indications is preoperative MRI examination of women with newly diagnosed breast cancer. Although debate on the topic still exists, obtaining the best local staging of the disease remains a crucial objective in providing optimal and successful treatment, as has been shown by surgeons'propensity to ask for preoperative breast MRI [88]. Image processing with the use of AI methods fits well with the aim of excluding multicentric or bilateral disease and the need to avoid false-positive findings that may result in unnecessary surgery or biopsies. MRI screening of high-risk patients largely has been shown to outperform mammography screening [89, 90]. AI-based applications may serve as a gatekeeper, with lesion and tissue segmentation possibly identifying women with a very low probability of harboring cancer. MRI has been proposed as a useful method for prediction of the early response to NAT [91]; however, no consensus yet exists regarding its widespread application, even if the number of women offered with a neoadjuvant approach is increasing because of expanding inclusion criteria [92]. In this clinical setting, the potential of image processing and automated tissue and lesion segmentation, in addition to automated classification of patients who do not respond to therapy, may help recognize women possibly benefitting from a more effective systemic regimen. Finally, there are great expectations for breast MRI biomarkers in predicting the prognosis of breast cancer [93, 94]. Extracting multiple functional and morphologic features from MR images could improve risk stratification of patients and allow a personalized approach to medicine by combining information on these features with demographic, genomic, and clinical data.

From the present study, it is clear that supervised learning approaches are the technique of choice for classification tasks, such as lesion characterization and prognostic imaging. Indeed, SVMs and ANNs are the approaches most often implemented to try to achieve these aims. This is reasonable because, for these specific tasks, the tumor presence and the clinical outcome (e.g., benign versus malignant status and molecular subtype classification) are already known. To the contrary, segmentation and detection of breast lesions are mainly performed using unsupervised clustering algorithms. This may be explained by the fact that, in segmentation tasks, tumor presence cannot be previously assumed, so the algorithm has to search for suspicious or unexpected patterns within the image data. When supervised approaches are used to accomplish segmentation tasks, an ANN seems to be the technique of choice, in particular after the introduction of CNNs. Deep CNNs represent an emerging subgroup of ANNs that have shown encouraging performance [36, 39]. However CNNs have been applied only recently, and for this reason they must be further investigated to exploit their true potential in breast MRI data processing. Diagnosis of and treatment

planning for breast cancer represent multifaceted challenges that breast radiologists must face on a daily basis. For example, breast tumor characterization must take into account the effect of multiple physiologic and pathologic phenomena that occur during tumor development and progression. This may be the reason for the successful application of SVMs and ANNs, both of which can model complex and nonlinear relationships within data. However, the approaches that have been developed must have very high performance levels because breast MRI is the most sensitive method for diagnosing breast cancer, with reported pooled sensitivity and specificity of 93.2% and 71.1%, respectively [95]. The key point will be the ability of AI to correctly change a BI-RADS diagnostic category assigned by a human from one recommending that biopsy be performed to a category not recommending biopsy, or vice versa, with a reliability very close to 100%, especially when the AI-based system suggests that biopsy should not be performed. AI applications in breast MRI, although encouraging, are still far from achieving the aforementioned goal, as based on their current performance. In the present study, we performed a systematic mapping review of articles on applications of ML methods in breast MRI published over the past decades. Although this kind of study allows the identification of gaps of knowledge within larger research topics, it usually leads to broad and descriptive characterization and does not usually include a quality assessment process [96]. This is especially true when we consider such large and heterogeneous categories as image processing, prognostic imaging, and NAT response, which group several specific subgoals with different tasks. Descriptive statistics were used only to support a narrative synthesis of current accomplishments, because of awareness that quantitative analysis is inappropriateness in such heterogeneous studies. For these reasons, the present mapping review can be considered the starting point for more focused investigations of specific in-depth literature reviews. We are only at the start of the era of the use of advanced AI methods for breast imaging. Despite the increase in published studies on this topic, the present mapping review provides a snapshot of a scenario that is expected to progress in the near future. Even if promising, AI-based applications still are not ready to be incorporated into clinical practice. On the basis of the results of the present study, we can reasonably expect that lesion classification and image processing will be the tasks benefitting most from the use of ML techniques. ML will help in the development of useful tools that will help radiologists in the detection, characterization, and treatment of breast diseases. Even though other breast imaging techniques will benefit from AI applications, the intrinsic multiparametric nature of MRI has the greatest potential to incorporate AI applications into personalized care for patients with breast cancer. AI can be a tool for extracting and using a larger portion of the huge amount of information associated with breast MR images. Breast radiologists must learn about AI methods before these methods can be used in the best interest of our patients.

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Conclusions

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Conclusions

Medical images represent imaging biomarkers of considerable interest in evidence-based clinical decision-making, for therapeutic development and treatment monitoring.

BAC have been recently described among “the top five women’s health issues in preventive cardiology, at the forefront of recent and ongoing research”, together with coronary microvascular dysfunction, hormone replacement therapy, calcium and vitamin D supplementation as well as metabolic considerations during pregnancy. Women entering screening program for breast cancer and otherwise not considered for CV risk will benefit doubly from mammography, aiming at secondary cancer prevention and primary and/or secondary CV prevention. This enormous potential needs to be exploited and awareness campaigns have to be promoted. Mammograms could screen women for CV disease, but not yet. A preventive action could be initiated only once a threshold will be defined by retrospective and prospective population studies.

Multiparametric breast MRI with different functional parameters may visualize and quantify the functional processes of cancer development and progression at multiple levels and provide specific information about the hallmarks of cancer. Numerous groups have developed sophisticated software to improve characterization of breast lesions, assessment and prediction of treatment response, and differentiation of biological cancer subtypes through MRI. Breast MRI is ready to candidate as a prognostic tool and more significant advances are expected, which will further aid the development of novel personalized approaches in the management of breast cancer.

Breast imaging represents a promising area for the application of AI both for screening and diagnostics.

In particular, MRI images are a fertile ground for machine learning processing due to their complex information content, holding the greatest potential to incorporate AI applications into the so called *precision medicine*. Nevertheless, several investigations focus on the application of AI to breast imaging but we are still far from clinical practice due to the lack of validation studies.

Scientific curriculum

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Certifications

- National Scientific Qualification (Abilitazione Scientifica Nazionale) for associate professor. Discipline: Diagnostica per immagini, radioterapia e neuroradiologia. Valid through 2024.

Publications since the start of PhD

(total publications 30; Citations 297; h-index 10, update on December 30, 2019)

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