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Breast multiparametric ultrasound: a single‑center experience

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Abstract

Purpose To evaluate the role of multiparametric ultrasound (mpUS) in the characterization of focal breast lesions (FBLs). **Methods** This prospective study enrolled patients undergoing multiparametric breast ultrasound for FBLs. An experienced breast radiologist evaluated the following ultrasound features: US BI-RADS category, vascularization pattern (internal, vessels in rim and combined) and presence of penetrating vessels with each Doppler method (Color-Doppler, Power-Doppler, Microvascular imaging), strain ratio (SR) and Tsukuba score (TS) with Strain Elastography (SE), E_{max} , E_{mean} , E_{min} and E_{ratio} with 2D-shear wave elastography (2D-SWE). Core biopsy for all BI-RADS 4-5 FBLs and 24-month follow-up for all BI-RADS 2-3 FBLs were considered for standard of reference. The diagnostic performance was assessed with the area under curve (AUCs) and cut-off values were determined according to the Youden's index.

Results A total of 139 FBLs were included with 75/139 (53.9%) benign and 64/139 (46.1%) malignant FBLs. Internal vascularization patterns ($p < 0.001$), penetrating vessels ($p < 0.001$), TS 4-5 ($p < 0.001$) and all 2D-SWE parameters ($p < 0.001$) were signifcantly diferent between benign and malignant FBLs. The BI-RADS score provided an AUC of 0.876 (95% CI 0.810–0.926) for the diagnosis of malignant FBLs. Among the 2D-SWE measurements, an excellent diagnostic performance was observed for *E*_{max} with an AUC of 0.915 (95% CI 0.856–0.956) and *E*_{mean} of 0.908 (95% CI 0.847–0.951). Optimal cutoff for the diagnosis of malignant FBLs were US BI-RADS > 3, Strain Ratio > 2.52, Tsukuba Score > 3, E_{max} > 82.6 kPa, E_{mean} > 66.0 kPa, E_{min} > 54.4 kPa and E_{ratio} > 330.8.

Multiparametric ultrasound, particularly SWE, can improve specifcity in the characterization of FBLs.

Keywords Breast · Ultrasonography · BI-RADS · Doppler · Microvascular imaging · Elasticity imaging techniques

Introduction

Breast ultrasound (US) is considered, in association with mammography and magnetic resonance imaging, a valuable tool in breast imaging [\[1](#page-7-0)], especially in young women with dense breasts [\[2](#page-7-1)].

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Whereas B-Mode US features are still considered fundamental for the characterization of of focal breast lesions (FBLs), recently technological advances have enabled the spread of multiparametric ultrasound (mpUS), which allows the association of the conventional B-Mode assessment with other tools for analyzing specific features, such as the assessment of vascularization and elasticity of FBLs. The

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application of Color-Doppler (CD), Power-Doppler (PD) and new developments, such as Microvascular Flow Imaging (MFVI), provides important information on the vascularization of FBLs $[3, 4]$ $[3, 4]$ $[3, 4]$ $[3, 4]$ $[3, 4]$, which is related to the underlying phenomenon neoangiogenesis [[5\]](#page-7-4). Breast elastography [[6\]](#page-7-5) is a noninvasive method for measuring the elasticity of a FBLs through two diferent technique: the Strain Elastography (SE) [\[7](#page-7-6)], which allows qualitative assessment methods such as the Tsukuba Score (TS) [[8\]](#page-7-7) and semi-quantitative methods such as the Strain Ratio (SR) [[9\]](#page-7-8), and the shear-wave elastography (SWE) [\[10](#page-7-9)], which ensures a quantitative evaluation of the elasticity of each point of the area examined (2D-SWE) in terms of absolute data, such as maximum elasticity (E_{max}) , mean elasticity (E_{mean}) and minimum elasticity (E_{min}) expressed in kPa, or relative data, such as elasticity ratio (E_{ratio}) . Several studies have shown that the breast mpUS approach can improve diagnostic performance, particularly it increased the specifcity and reduced the number of unnecessary biopsies in low-suspicion FBLs [\[11](#page-7-10)[–14](#page-7-11)]. It can be also useful in the assessment of US BI-RADS 3 and 4 FBLs, suggesting a strategy for down- and up- grading [[15](#page-7-12), [16\]](#page-7-13). In addition, breast mpUS could be useful in the evaluation of some tumors that are sometimes difficult to distinguish from benign FBLs because both appear as smooth-surfaced masses, such as mucinous carcinoma [[17\]](#page-7-14) and triple negatives [[18\]](#page-7-15). However, many of these studies did not evaluate and directly compare both qualitative and quantitative parameters in the multiparametric breast ultrasound approach.

The purpose of this study was to evaluate the role of mpUS in the characterization of FBLs by analyzing the multiparametric features, both qualitative and quantitative, of the US fndings.

Methods

Study participants

The institutional Ethic Committee approved this prospective, single-center study and all regulatory approvals were granted (N°022019). All patients included gave their full written informed consent. Our study complied with the terms of the Declaration of Helsinki [\[19\]](#page-7-16).

This study included 1200 patients women who underwent US evaluation between January 2019 and December 2019 by a radiologist with 20 years of experience in breast imaging, including ultrasound, at the Breast Unit of the Policlinico Universitario "P.Giaccone" in Palermo, Italy. Inclusion criteria were: (1) a palpable mass detected on physical examination; (2) a detected lesion from adjunct mammography examination; (3) dense breasts; (4) mastodynia; (5)

young patients having family history or (6) in a follow-up for benign breast nodules.

Exclusion criteria included negative examination (BI-RADS 1), lack of adequate standard of reference, namely refusal to undergo biopsies for FBLs classifed as BI-RADS 4–5 or inconsistent follow-up for FBLs classifed as BI-RADS 3, and the lack of even multiparametric assessment techniques of vascular imaging, and elasticity, and 2D-SWE.

Standard of reference

The standard of reference of this study was considered USguided core-biopsy for all the FBLs classifed as BI-RADS 4 or 5, either before or after mpUS assessment, and US followup at 6, 12 and 24-months for all FBLs classifed as BI-RADS 2 and 3. In particular, stability or size decrease during follow-up was considered typically benign US fndings. FBLs with size increases during follow-up were considered malignant and US-guided core-biopsy was performed.

Ultrasound measurements

The breast radiologist assessed the following mpUS features of all FBLs: B-Mode, CD, PD, MVFI, SE, 2D-SWE, blinded to the pathological results. An ultrasound unit (RS80A+, Samsung Medison, Co. Ltd.) provided with high-frequency linear transducers (LA 5–12 MHz and LA 2–9 MHz) was used. For each FBL, the following parameters were recorded: US BI-RADS category, maximum diameter of the lesion, vascularization pattern and presence of penetrating vessels with each vascular imaging method (CD, PD, MVFI), Strain Ratio and Tsukuba Score evaluated with SE, *E*max, *E*mean, E_{min} and E_{ratio} acquired with by 2-D SWE analysis.

To obtain vascular information, a Doppler box was used and the parameters were adjusted to increase the sensitivity to low-velocity fow with a low wall flter and gain as high as possible but still minimizing fash artefacts. Soft pressure was applied to the transducer to preserve the fow of small blood vessels. The parameters for CD and PD US were velocity scale<2.3 cm/s, dynamic range of 45 dB, and frame average rate of eight and nine frames per second. The parameters for MVFI were velocity scale<1.3 cm/s, dynamic range of 56 dB and frame rate of 40 frames per second. The vascularization patterns recorded as "absent", "internal" and "vessels in rim", according to the BI-RADS US lexicon, and "combined", with both internal and vessels in rim; the latter, although not included in US BI-RADS analysis, it is often encountered in clinical practice and widely reported in literature [\[4,](#page-7-3) [20](#page-7-17)]. In addition, the radiologist was asked to report the presence of a "penetrating vessel", defned as a radially aligned or marginally oriented vessel within the tumor [\[20](#page-7-17)].

The SE was performed applying the probe only with soft pressure and placing a target lesion in the center of a box that superiorly included the subcutaneous fat, inferiorly included the pectoralis muscle and on both sides included more than 5 mm of normal breast parenchyma from the lesion's borders. A real-time elastography image was obtained using a color map that showing the degree of displacement for all pixels within the box, representing the amount of strain in a scale ranging from red (greatest strain, softest area) to green (average strain, intermediate component) and blue (no strain, hardest area). To calculate the Strain Ratio, a ROI within the lesion and a ROI outside the lesion (in the context of surrounding fat tissue) were placed, in order to measure the relative density of the lesion.

The 2D-SWE was performed by placing the probe vertically on the skin, avoiding applying heavy pressure. A real-time assessment of the lesion was performed in a dual screen mode, displacing at the same time a conventional B-mode observation and a qualitative elasticity assessment. A specifc box is superimposed on the lesion, allowing a two-dimensional colorimetric map in real time, ranging from dark blue (lower retyping) to red (higher rigidity). A circular ROI sized 2 mm was placed within the lesion in the stifest area as depicted by a color-coded map in a rectangular box, ranging from 0 (dark blue: soft) to 180 kPa (red: stiff). To calculate E_{ratio} , another circular ROI of the same size was placed at the same level in the surrounding breast tissue.

Statistical analysis

Continuous variables were reported medians and interquartile ranges after testing for normal distribution with the Shapiro–Wilk normality test and they were compared with the Mann–Whitney *U* test. Categorical variables were reported as numbers and percentages and they were compared with the Pearson's chi-squared test of Fisher's exact test. The diagnostic performance of mpUS measurements was assessed with the area under the receiver operating characteristics curve (AUC) with 95% confdence interval (95% CI). Optimal cutofs for the diagnosis of malignant lesions were determined with the Younden index with their sensitivity and specifcity [[21\]](#page-7-18).

Statistical significance level was set at $p < 0.05$. Statistical analyses were performed using IBM SPSS software version 26.0 (Armonk, NY, USA: IBM Corp) and MedCalc Statistical Software version 14.8.1 (Ostend, Belgium).

Results

The study included a total of 139 FBLs (size range 3.5–50 mm; mean size \pm SD: 14.9 \pm 8.3 mm) in 134 women (age range $21-87$ years, mean age \pm SD: $53.6\pm$ 14.5 years) who underwent mpUS. According to the standard of reference, 75/139 (53.9%) FBLs were benign and 64/139 (46.1%) were malignant (Table [1](#page-2-0)); among benign FBLs, the most prevalent lesion was fibroadenoma $(n=62)$, while among

Table 1 Benign and malignan focal breast lesions (FBLs) and respective histotypes, as by standard of reference, for each BI-RADS class

	Benign FBLs $(75/139)$			Malignant FBLs (64/139)			<i>p</i> values		
Vascular imaging method	CD	PD	MVFI	CD	PD	MVFI	CD	PD	MVFI
Presence of vascularization	30(40.0)	29(38.7)	47(62.7)	42(65.6)	45(70.3)	57 (89.1)	0.003	${}_{0.001}$	< 0.001
Internal pattern	15(20.0)	13 (17.3)	14(18.7)	40(62.5)	42(65.6)	50(78.1)	< 0.001	< 0.001	< 0.001
Vessels in rim pattern	7(9.3)	6(8.0)	10(13.3)	0(0)	1(1.6)	2(3.1)	0.015	0.124	0.033
Combined pattern	8(10.7)	10(13.3)	23(30.7)	2(3.1)	2(3.1)	5(7.8)	0.108	0.033	0.001
Penetrating vessels	1(1.3)	1(1.3)	5(6.7)	30(46.9)	31(48.4)	45(70.3)	< 0.001	< 0.001	< 0.001

Table 2 Vascularization pattern and presence of penetrating vessels for benign and malignant focal breast lesions (FBLs) assessed with each vascular imaging method

Categorical variables are provided as numbers and percentages

Table 3 Comparison between benign and malignant focal breast lesions (FBLs) of Strain Ratio, maximum elasticity (E_{max}), mean elasticity (E_{mean}), minimum elasticity (E_{min}) and elasticity ration (E_{ratio})

	Benign FBLs	Malignant FBLs	<i>p</i> value
Strain ratio	2.23(1.41, 3.02)	3.81(2.84, 6.73)	< 0.001
$E_{\rm max}$	56.5 (36.0, 78.4)	137.3 (97.4, 173.2)	< 0.001
E_{mean}	45.9 (28.6, 62.9)	115.1 (81.3, 150.3)	< 0.001
$E_{\rm min}$	35.3 (20.5, 47.3)	91.8 (64.6, 127.5)	< 0.001
E_{ratio}	237.7 (145.8, 396.0)	366.1 (226.4, 657.2)	< 0.001

Continuous variables are provided as median and interquartile range (25th to 75th percentile)

malignant FBLs, the most prevalent was invasive ductal carcinoma ($n=49$).

According to BI-RADS assessment, two (1.4%) FBLs were classifed as BI-RADS 2, 55 (39.6%) as BI-RADS 3, 29 (20.9%) as BI-RADS 4a, 12 (8.6%) as BI-RADS 4b, 14 (10.1%) as BI-RADS 4c and 27 (19.4%) as BI-RADS 5.

Regarding the vascular pattern (Table [2](#page-3-0)), presence of vascularization was signifcantly more common in malignant FBLs compared to benign FBLs for all the vascular imaging methods ($p \le 0.003$). The internal vascular pattern and the presence of penetrating vessels were signifcantly more common in malignant FBLs for all the vascular imaging methods (all $p < 0.001$). Contrarily, benign FBLs demonstrated more commonly the vessel in rim pattern in

CD $(p=0.015)$ and in MVFI $(p=0.033)$ and the combined pattern in PD ($p = 0.033$) and in MVFI ($p = 0.001$).

All the quantitative measurements acquired with SE and 2D-SWE (Table [3\)](#page-3-1) were signifcantly higher in malignant FBLs compared with benign FBLs (all $p < 0.001$). Regarding the qualitative assessment of SE there were signifcant diferences in the TS, with 67/75 (89.3%) benign FBLs showing a TS 1-3, while 8/75 (10.7%) showing a TS 4-5; on the other hand, 46/64 (71.9%) malignant FBLs showed a TS 4–5, while 18/64 (28.1%) showed a TS 1–3 $(p < 0.001)$.

Table [4](#page-3-2) reports the performance and the cut-off values obtained using the Youden method for the mpUS measurements with their sensitivity and specifcity. The BI-RADS score provided an AUC of 0.876 (95% CI 0.810–0.926). In SE, TS had the highest diagnostic performance for the diagnosis of malignant FBLs with an AUC of 0.874 (95% CI 0.807–0.924). Among the 2D-SWE measurements, an excellent diagnostic performance was observed for *E*_{max} with an AUC of 0.915 (95% CI 0.856–0.956) and *E*_{mean} of 0.908 (95% CI 0.847–0.951). AUCs are illus-trated in Fig. [1.](#page-4-0) Optimal cutoff for the diagnosis of malignant lesions were US BI-RADS > 3, strain ratio > 2.52, Tsukuba score > 3, *E*max > 82.6 kPa, *E*mean > 66.0 kPa, $E_{\text{min}} > 54.4$ kPa and $E_{\text{ratio}} > 330.8$. Examples of lesions with mpUS assessment are provided in Figs. [2,](#page-4-1) [3](#page-5-0) and [4.](#page-5-1)

Table 4 Area under the curve (AUC) with cutoff values, sensitivity and specifcity of US BI-RADS categories, Strain elastography and shear-wave measurements

Cutoff values were determined according to the Youden index

 E_{max} maximum elasticity, E_{mean} mean elasticity, E_{min} minimum elasticity, E_{ratio} elasticity ratio

Fig. 1 Receiver operating curves of diagnostic performance for distinguish benign from malignant FBLs of strain ratio, Tsukuba score and 2D-shear wave parameters in comparison with US BI-RADS

Discussion

US B-mode imaging is a widely used technique for the characterization of FBLs, and the anatomic morphologic descriptors provided by this technique are included in the BI-RADS lexicon of the American College of Radiology [[22](#page-7-19)]. The exclusively morphologic assessment guaranteed by the B-mode approach, however, does not allow the evaluation of the many phenotypic features acquired by a heterogeneous disease such as breast cancer [\[23](#page-7-20)]. The latest available edition of the BI-RADS lexicon (dated 2013), however, considers associated features both vascularization (absent, internal vascularization, vessels in rim) and elasticity assessment (soft, intermediate, hard), although it specifes not to use them as the only diagnostic feature in interpretation nor to override morphologic features more predictive of malignancy for patient management. On the other hand, in accordance with the updated 2018 EFSUMB guidelines and the 2015 WFUMB guidelines, biopsy is suggested for a FBLs classifed BI-RADS 3 that shows high stifness on breast ultrasound elastography [[15](#page-7-12), [24\]](#page-7-21). In addition, the 2015 WFUMB guidelines indicate the downgrading of a US BI-RADS 3 or 4a FBLs on the basis of stifness on breast ultrasound elastography, while downgrading of a US BI-RADS 4b, 4c, or 5 FBLs is not recommended; this approach confrmed by recent prospective studies $[16, 25]$ $[16, 25]$ The application of such arrangements in clinical practice could reduce unnecessary biopsies and allow to avoid expensive and relatively invasive procedures.

The results of this study demonstrated a signifcant difference between benign and malignant FBLs in quantitative 2D-SWE parameters, with signifcantly higher values in malignant FBLs (all $p < 0.001$), confirming previously reported data performed with diferent ultrasound equip-ment [[26,](#page-7-23) [27](#page-7-24)]. The cut-off values for $E_{\text{min}}-E_{\text{mean}}-E_{\text{max}}$ and their corresponding AUC were higher than BI-RADS assessment alone; these results were in accordance with the results of the multicentric study of Berg et al. [[26](#page-7-23)]. The 2D-SWE analysis also resulted in increased specifcity for all four parameters studied compared to BI-RADS

Fig. 2 Asymptomatic 38-yearold woman; on B-Mode US examination (**A**): hypoechoic oval mass with circumscribed margins, parallel orientation and no posterior fndings, classifed as BI-RADS 3. The microvascular fow imaging shows mild internal vascularization (**B**). Strain elastography (**C**) characterizes the lesion as soft, with a predominant green pattern (Tsukuba score 1). 2D-shear wave elastography colorimetric map (D) shows a soft lesion with a peripheral stiffer area (green), with an E_{max} of 82.6 kPa. The multiparametric US features described are consistent with the diagnosis of fbroadenoma

Fig. 3 79-year-old woman with known calcifc fbroadenoma. On B-mode US examination (**A**): hypoechoic oval mass with circumscribed margins and some course calcifcations (indicated by arrowhead), responsible for a posterior shadowing (thin arrows). The microvascular fow imaging (**B**) reveals the absence of internal or vessels in rim vascularization. Strain elastosonography (**C**) shows a predominantly blue pattern with green areas at the periphery (Tsukuba score 3); on 2D-shear wave elastography analysis (**D**), the colorimetric map (lower right) shows heterogeneity of stifness with the highest values corresponding to intralesional calcifcations

Fig. 4 A 59-year-old woman with a palpable lump in her left breast. B-mode US examination (**A**) shows the presence of a hypoechoic mass with irregular shape and indistinct, spiculated margins. Intralesional microcalcifcations (thin arrows), posterior shadowing (thick arrows) and a perilesional "echogenic halo" (arrowheads) are present. The study of vascularization shows the presence of fow within the lesion with all three techniques Color Doppler (**B**), Power Doppler (**C**) and microvascular fow imaging (**D**): the latter technique also shows the presence of a "penetrating vessel" (arrowhead) penetrating from the periphery into the lesion. Elasticity assessment with strain (*E*) and 2D shear wave elastography (**F**) reveals a lesion harder than the surrounding tissue, with E_{min} , E_{mean} , E_{max} and E_{ratio} values above the identifed cut-ofs. Histopathology of US core biopsy: invasive ductal carcinoma

assessment alone, particularly for the E_{max} parameter, with a decrease in sensitivity only for *E*ratio. Consequently, these data suggest that 2D-SWE assessment would have led to a signifcant reduction in unnecessary biopsies, without a signifcant increase in breast cancer missed, except for the *E*ratio parameter alone.

TS was the mpUS parameter with the highest specifcity, and despite the suboptimal sensitivity, the data on correlation with benign and malignant FBLs agree with those in the literature [\[28](#page-7-25)].

Compared with BI-RADS assessment alone, SR showed lower sensitivity and overlapping specificity. Elia et al., using a similar cut-of (2.49) for SR, reported comparable sensitivity and specificity values [[29\]](#page-7-26).

MVFI showed a superior ability to visualize microvessels and, in general, in identifying the presence of vascularization, compared with conventional CD and PD, in diferent clinical settings, including the breast [[4,](#page-7-3) [30,](#page-7-27) [31\]](#page-7-28). Therefore, the MVFI was considered, in this study and in previous studies [\[31\]](#page-7-28), the most reliable vascular imaging technique in assessing the vascularization patterns most frequently associated with benign FBLs and malignant FBLs. The results of the current study showed a statistically signifcant prevalence of the absence of vascularization, vessels in rim pattern and combined pattern in benign FBLs compared with malignant FBLs. In our experience, lack of vascularization demonstrated by MVFI outperformed the CD fndings of the prospective study by Watanabe et al. in the characterization of benign FBLs [[20\]](#page-7-17). On the other hand, in our series the presence of internal vascularization as revealed by MVFI improved breast cancer characterization when compared to the study of Svensson et.al, performed with CD assessment alone [[3](#page-7-2)]. Regarding the combined pattern, in our series, it was signifcantly more frequent in benign FBLs. These data are in accordance with the study by Watanabe [[20\]](#page-7-17).

According to standard of reference, a small but not negligible number of breast carcinomas $(N=4)$ would have been missed with exclusive use of the US BI-RADS lexicon; in particular, one triple negative invasive ductal carcinoma, one luminal B/Her negative invasive ductal carcinoma, one lobular carcinoma in situ (CLIS) and one mucinous carcinoma would have been missed. The frst two cases, initially classifed as BI-RADS 3, appeared suspicious on both vascular (particularly on MVFI) and elastographic evaluations. CLIS appeared suspicious on SE (TS 5) and on 2D-SWE (*E*min, *E*mean, *E*max of 59.3, 80.45, 101.6, respectively). Mucinous carcinoma, on the other hand, also initially classifed as BI-RADS 3, showed values of the quantitative 2D-SWE parameters below the cut-ofs identifed in our case series and a combined vascularization, in the absence of penetrating vessels; however, it appeared suspicious on SE (TS 4 and an SR 3.8). Lower values of E_{max} and E_{mean} than for other types have already been reported in the literature [\[32](#page-8-0)].

In our series, 22 unnecessary biopsies of benign FBLs would have occurred using the US BI-RADS lexicon alone. Among them, a number ranging from 6 to 16 would have been suspicious taking into consideration the quantitative parameters 2D-SWE and SR, particularly fbroadenomas; indeed, previous studies have stated that fbroadenomas, especially if calcifc, giving false-positive SWE [[33\]](#page-8-1). On the other hand, among the above false positives, a TS greater than 3 was recorded in only 2 FBLs, confrming that an exclusively qualitative assessment sometimes correlates better with the BI-RADS classifcation [[33](#page-8-1)].

Our study has some limitations. Firstly, we did not perform a direct comparison of vascularization and tumor elasticity by histologic analysis. Such analyses could have provided more information about the true correspondence between vascularization pattern and/or presence of penetrating vessels with the true degree of angiogenesis, or between SE and 2D-SWE elastographic analyses with tumor stifness, but would not have directly afected the results of our study. In addition, we did not perform histologic analysis for all FBLs, because for clearly benign FBLs on imaging the standard of reference was followup imaging. Second, inter- and intra-reader agreement reproducibility was not calculated. Finally, it is a singlecenter study that included a limited population of women; therefore, further studies, involving multiple centers and operators, are needed to include diferent populations to evaluate the reproducibility of our results in other geographical areas.

In conclusion, mpUS enables noninvasive real-time analysis of focal breast lesions. The multiparametric approach, with the technological improvement of B-mode imaging, the refnement of microvascular imaging systems and the introduction of elastography techniques enable the physician to obtain quantitative and reproducible parameters, improving diagnostic accuracy. In our experience, among the various methods, the E_{max} parameter of 2D-SWE showed the best results in terms of specifcity, with similar sensitivity compared with BI-RADS classifcation.

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Data availability Not applicable.

Declarations

Conflict of interest The authors have no relevant fnancial or non-fnancial interests to disclose.

Trial registration Trial registration number and date of registration for prospectively registered trials: N°022019.

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