Association Between Monocyte Levels and Breast Lump Detected By Ultrasound Among Chinese Women: A Longitudinal Study

Ying Gao
Tianjin Medical University General Hospital
Shu Li
Tianjin University of Traditional Chinese Medicine
Wei Wei
Tianjin Medical University General Hospital
Yujing Jin
Tianjin Medical University General Hospital
Junfang You
Tianjin Medical University General Hospital
Xiaoqian Xu
Tianjin Medical University General Hospital
Shaomei Sun
Tianjin Medical University General Hospital
Li Liu
Tianjin Medical University General Hospital
Qing Zhang (zhangqing@tmu.edu.cn)
Tianjin Medical University General Hospital

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Abstract

Background

Few studies have focused on the relationship between monocyte and breast lump. To explore whether absolute monocyte count (AMC) or monocyte percent (%MONO) could be used as a new circulation tumor marker for breast lump detection by ultrasonography among Chinese women.

Methods

A total of 3,231 women who had at least two breast ultrasonography examinations were followed up from January 2014 to December 2019. Adjusted Cox proportional hazards regression models were used to evaluate the relationships between AMC and %MONO and the incidence of breast lump.

Results

During a total of 6,037 person-years of follow-up, 803 participants developed a breast lump. In the final multivariable adjusted models, using the lowest quartile as the reference group, the HRs (95%CIs) of breast lump were 1.18 (0.95, 1.45), 1.33 (1.08, 1.65), and 1.28 (1.02, 1.61), respectively, for AMC in the 2nd, 3rd, and 4th quartiles (P_{trend} < 0.001). The corresponding HRs (95%CIs) for %MONO in the 2nd, 3rd, and 4th quartiles were 1.03 (0.83, 1.28), 1.28 (1.03, 1.29), and 1.62 (1.30, 2.02, P_{trend}< 0.001), respectively. The multivariable adjusted HRs for breast lump per unit increase of AMC and %MONO were 3.19 (1.38, 7.38; P = 0.007) and 1.14 (1.08, 1.21; P < 0.001), respectively. The effect of high monocyte levels on increased risks of breast lump were more remarkable in younger women.

Conclusion

This study demonstrated that increased monocyte levels can be used as an indicator of the incidence of breast lump, especially for younger women.

Introduction

Worldwide, breast cancer is the most commonly diagnosed cancer and the leading cause of cancer death among females [1]. In 2015, it was estimated that there were about 268,000 newly diagnosed invasive breast cancer cases among Chinese women [2], with 68,500 deaths [2], making breast cancer a major threat to women’s health in China. Breast lump are the most dreaded signs in women; even though most breast lump are benign, breast lump have a relatively high probability of being malignant [3, 4]. In addition, even in women with proven benign breast disease (BBD) (e.g., fibroadenosis and fibroadenoma), the benign breast lump indicates an increased risk of developing breast cancer compared with women without BBD [3, 5]. Therefore, the presence of breast lump can be an indicator of breast cancer or an early indicator of an increased risk of breast cancer. Mammography and core needle biopsy are the most reliable detection methods for breast lump, but these techniques are not sufficiently sensitive for use in dense breasts or for detection of small breast lump, and they are uncomfortable and invasive for women to select as routine examinations [6, 7]. In contrast, ultrasound is more accurate at detecting small tumors, even in dense breasts, and repetitive evaluation over a short interval is more feasible because it does not involve radiations and is non-invasive [8]. Owing to the increasing development and frequency of use of breast ultrasound in breast cancer screening, the incidence of breast lump is rising [9].

Since Rudolf Virchow noted "lymphoreticular infiltrate" in neoplastic tissues in 1863, inflammation has been associated with cancer [10–13]. As a major component of the infiltrates of most tumors, tumor-associated macrophages (TAMs) are derived from monocytes and recruited to the tumor microenvironment, where they play an important role in the development of tumors [14, 15]. In solid tumors, TAMs have seemingly contradictory roles. On the one hand, they can kill tumor cells and, when appropriately activated, elicit tumor tissue destructive reactions centered on the vascular endothelium; on the other hand, TAMs can stimulate tumor-cell proliferation and tumor growth, promote angiogenesis, and favor invasion and metastasis [16, 17]. Proinflammatory processes in adipose tissue contribute to breast cancer development [18]. In turn, many studies have previously reported that malignant neoplasms adversely affect monocyte function and could hinder the immune-mediated destruction of malignant cells (i.e., the infamous immune escape) [19–21]. Many studies have previously reported monocyte levels or monocyte-related markers of inflammation as predictive and prognostic biomarkers of breast cancer [22–27] or malignant neoplasms adversely affect monocyte function and could hinder immunologically mediated destruction of malignant cells [19–21]. However, the relationship between absolute monocyte count (AMC) or monocyte percentage (%MONO), as systemic indicators of monocyte activity and breast lump, is not well understood [3, 28].

Therefore, this longitudinal study aimed to explore the association between AMC and %MONO with the breast lump detected by ultrasound in a large sample of Chinese with a long follow-up period. The results could provide additional markers for the risk management of women undergoing breast screening.

Methods

Study design and population

This was a retrospective study of female patients who underwent comprehensive health examinations at Tianjin Medical University General Hospital from January 2014 to December 2019. The protocol of this study was approved by the institutional review board of Tianjin Medical University General Hospital. The need for individual consent was waived by the board.

The inclusion criteria were 1) >18 years of age, and 2) no abnormality in the first breast ultrasound examination, and 3) had at least two subsequent breast ultrasound examinations. The repeat examinations were recognized by their individual health examination ID. The exclusion criteria were 1) with history of breast cancer, or 2) with history of breast surgery, or 3) with abnormal AMC or %MONO, or 4) with incomplete blood routine examination data from the first health examination, or 5) with a chronic inflammatory disease such as cholecystitis, chronic nephritis, rhinitis, pharyngitis, bronchitis, gastritis, rheumatoid arthritis, myocarditis, or others, at the first health examination.

Assessment of breast lump

For the routine breast examination, all participants underwent a whole breast ultrasound scan in the supine position. The presence of a breast lump was defined as the detection of a three-dimensional lesion, such as a breast cyst, solid or mixed lump, or intraductal lump, that occupied space within the breast (Fig. 1) [29]. Experienced board-certified radiologists performed all breast ultrasound examinations using a 5-12 MHz linear probe (OXANA 2, Siemens, Erlangen, Germany) or 5-12 MHz linear probe (XARIO, Toshiba Corp., Tokyo, Japan); they also performed the subsequent evaluations.

Data collection

This study used data from the cohort of Tianjin Chronic Disease Risk and Health Management. Basic information, including age and sex, was checked before health examinations. Blood pressure and anthropometric parameters (height, weight, and waist circumference) were measured by experienced medical staff following standard procedures. Body mass index (BMI) was calculated as weight (kg) divided by the square of height (m^2). All blood samples were taken after at least an 8-h fast and analyzed at the Department of Laboratory Medicine. The following blood values were collected: total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), fasting blood glucose (FBG), uric acid (UA), white blood cell (WBC) count, absolute neutrophil count (ANC), percentage of neutrophil (%NEUT), absolute eosinophil count (AEC), percentage of eosinophil (%EO), absolute basophil count (ABC), percentage of basophil (%BASO), absolute lymphocyte count (ALC), percentage of lymphocyte (%LY), AMC, %MONO, red blood cell (RBC) count, hemoglobin (Hb), and platelet (PLT) count. Data regarding self-reported marital status, smoking status, drinking status, history of chronic disease, and family disease were also collected using a detailed questionnaire.

Follow-up

All patients were followed by ultrasound examinations in the context of annual physical examinations until December 31, 2019. All examinations were conducted by doctors and nurses and breast ultrasound scan were performed by radiologists in the ultrasound imaging department. Based on the results of the ultrasound scan, the patients were grouped according to whether a breast lump was found during follow-up.

Statistical analysis

Patient baseline characteristics are presented as median (interquartile range) for continuous variables and as number (percentage) for categorical variables. All continuous variables were examined for normality using the Shapiro-Wilk test; for non-normal distribution variables, the differences among breast lump categories were examined using the Mann-Whitney U test, and categorical variables were examined using the chi-squared test. The incidence of breast lump was used as the dependent variable, and AMC and %MONO were used as the independent variable. The Cox proportional hazards regression model was used to examine the association between AMC or %MONO and the presence of breast lump initially, using the lowest quartile as the reference group. We also analyzed AMC and %MONO as continuous variables in all regression models. In model 1, crude hazard ratios (HRs) with corresponding 95% confidence intervals (CIs) were calculated. Model 2 was further adjusted for age and BMI as potential confounding variables. Model 3 was adjusted for age, BMI, WC, SBP, DBP, TC, TG, LDL-C, HDL-C, FBG, UA, marital status, smoking status, drinking status, family history of cancer, hypertension, diabetes, history of cancer, history of hypertension, and history of diabetes. Tests for trend across quartiles of AMC and %MONO were examined using the median value of each quartile as an ordinal variable in the Cox proportional hazards regression models. The cumulative incidence of breast lump stratified by age was analyzed using the Kaplan-Meier method, and the differences between groups were compared using the log-rank test. STATA 13.0 (StataCorp LP, College Station, TX, USA) was used in all analyses. All P-values are two-sided, and $P<0.05$ is defined as statistically significant.

Results

Characteristics of the patients

A total of 5760 patients were screened for eligibility, and 2602 were excluded: 48 with a history of breast cancer, 879 with a history of breast surgery, 401 with chronic inflammation at baseline, 1141 with incomplete blood routine data at the first health examination, and 133 with abnormal absolute monocyte counts or percentage of monocyte. Therefore, the final study population includes 3158 participants. During a total of 6037 person-years of follow-up (median follow-up time, 2.35 years), breast lumps were found in 803 patients (Fig. 2).

Table 1 presents the baseline characteristics of the participants according to the breast lump status during follow-up. Compared with women without a breast lump, those with a breast lump were younger, more likely to have a lower BMI, WC, SBP, DBP, TC, TG, LDL-C, FBG, UA, %LY, and a history of hypertension and diabetes and more likely to have a higher AMC and %MONO (all $P<0.05$). No significant differences were observed between the two groups for HDL-C, WBC, ANC, AEC, ABC, ALC, AMC, %NEUT, %EO, %BASO, RBC, Hb, PLT, marital status, drinking status, family history of cancer, hypertension, diabetes, and history of cancer (all $P>0.05$).

Table 1 Characteristics of the participants according to the presence of a by breast lump

Characteristics	Breast Lump		P value
	No (N=2355)	Yes (N=803)	
Age (years)	46.6 (36.7, 56.3)	45.2 (38.2, 52.2)	0.01
BMI (kg/m^2)	23.60 (21.40, 26.06)	23.38 (21.30, 25.60)	0.05
WC (cm)	80.0 (73.0, 86.0)	77.0 (72.0, 84.5)	<0.01
SBP (mmHg)	120 (110, 135)	109 (100, 118)	<0.01
DBP (mmHg)	75 (68, 84)	75 (66, 80)	<0.01
TC (mmol/L)	5.03 (4.40, 5.75)	4.91 (4.29, 5.57)	<0.01
TG (mmol/L)	1.11 (0.80, 1.58)	1.04 (0.77, 1.49)	0.01
LDL-C (mmol/L)	2.90 (2.34, 3.49)	2.77 (2.24, 3.38)	<0.01
HDL-C (mmol/L)	1.47 (1.26, 1.71)	1.49 (1.27, 1.72)	0.30
FBG (mmol/L)	4.9 (4.6, 5.3)	4.8 (4.6, 5.2)	<0.01
UA (mmol/L)	267 (233, 311)	260 (227, 300)	<0.01
WBC (×10^9/L)	5.36 (4.58, 6.32)	5.39 (4.61, 6.34)	0.68
ANC (×10^9/L)	3.05 (2.46, 3.77)	3.08 (2.49, 3.85)	0.40
%NEUT (%)	57.0 (51.9, 62.5)	57.8 (52.6, 63.1)	0.08
AEC (×10^9/L)	0.08 (0.05, 0.13)	0.08 (0.05, 0.14)	0.96
%EO (%)	1.6 (1.0, 2.5)	1.6 (1.0, 2.5)	0.92
ABC (×10^9/L)	0.03 (0.02, 0.04)	0.03 (0.02, 0.04)	0.75
%BASO (%)	0.5 (0.4, 0.7)	0.5 (0.4, 0.7)	0.79
ALC (×10^9/L)	1.79 (1.49, 2.12)	1.77 (1.49, 2.11)	0.21
%LY (%)	34.0 (28.8, 38.6)	32.8 (28.4, 38.0)	0.01
AMC (×10^9/L)	0.34 (0.28, 0.41)	0.35 (0.29, 0.41)	0.03
%MONO (%)	6.3 (5.4, 7.3)	6.5 (5.5, 7.5)	0.03
RBC (×10^{12}/L)	5.36 (4.58, 6.32)	5.39 (4.61, 6.34)	0.70
Hb (g/L)	135 (129, 141)	134 (127, 141)	0.50
PLT (×10^9/L)	251 (216, 288)	257 (217, 294)	0.65
Marital status[a]			

Married	1857 (78.9)	628 (78.2)	0.10
Unmarried	155 (6.6)	39 (4.8)	
Others†	24 (1.0)	13 (1.6)	
Smoking status[b]			
Never	2232 (94.8)	771 (96.0)	0.06
Ever	38 (1.6)	8 (0.9)	
Now	18 (0.8)	1 (0.1)	
Drinking status[c]			
No	2108 (89.5)	707 (88.0)	0.34
Yes	180 (7.6)	73 (9.1)	
Family history of disease			
Cancer	244 (10.4)	90 (11.2)	0.50
Hypertension	921 (39.1)	32.8 (40.8)	0.38
Diabetes	477 (20.3)	173 (21.5)	0.44
History of chronic disease			
Cancer	26 (1.1)	11 (1.4)	0.55
Hypertension	291 (12.4)	67 (8.3)	<0.01
Diabetes	89 (3.8)	14 (1.7)	<0.01

BMI, body mass index; WC, waist circumference; SBP, systemic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein; HDL-C, high-density lipoprotein; FBG, fasting blood glucose; UA, uric acid; WBC, white blood cell; ANC, absolute neutrophil count; NEUT, neutrophil percentage; AEC, absolute eosinophils count; %EO, eosinophils percentage; ABC, absolute basophil count; %BASO, basophil percentage; ALC, absolute lymphocyte count; %LY, lymphocyte percentage; AMC, absolute monocyte count; %MONO, monocyte percentage; RBC, red blood cell; Hb, hemoglobin; PLT, platelet.

Data are presented as medians (ranges) or n (%).

P-values <0.05 are considered statistically significant.

†Others includes separated, divorced, and widowed.

[a]data about marital status were missing in 123 patients with a breast lump and 319 patients without breast lump;

[b]data about smoking status were missing in 23 patients with a breast lump and 67 patients without breast lump;

[c]data about drinking status were missing in 23 patients with a breast lump and 67 patients without breast lump.

Association of AMC and %MONO with breast lump

Table 2 presents the crude and adjusted associations of AMC and %MONO with the incidence of a breast lump. AMC and %MONO levels (both as quartiles and as continuous variables) were positively associated with the incidence of breast lump in all models. In the final multivariable-adjusted models, using the lowest quartile as the reference group, the HRs (95%CIs) of breast lump were 1.18 (95%CI: 0.95, 1.45), 1.33 (95%CI: 1.08, 1.65), and 1.28 (95%CI: 1.02, 1.61), respectively, for AMC in the 2nd, 3rd, and 4th quartiles (P for trend <0.001). The corresponding HRs (95%CI) for %MONO in the 2nd, 3rd, and 4th quartiles were 1.03 (95%CI: 0.83, 1.28), 1.28 (95%CI: 1.03, 1.29), and 1.62 (95%CI: 1.30, 2.02), respectively (P for trend <0.001). The multivariable-adjusted HRs for breast lump per unit increase of AMC and %MONO were 3.19 (95%CI: 1.38, 7.38; P=0.007) and 1.14 (95%CI: 1.08, 1.21; P<0.001), respectively.

Table 2 Adjusted relationships of absolute monocyte count and percentage of monocyte to the incident of the breast lump.

	Level 1	Level 2	Level 3	Level 4	P for trend	Continuous	P value
Absolute monocyte count							
Range	≤ 0.29	0.30-0.35	0.36-0.42	≥ 0.43	-	-	-
Person-years of follow up	1793	1591	1404	1248	-	-	-
No. of breast lump	203	221	203	176	-	-	-
Model 1	1.00 (reference)	1.23 (1.01, 1.48)	1.34 (1.11, 1.63)	1.28 (1.05, 1.57)	0.002	3.15 (1.51, 6.58)	0.002
Model 2	1.00 (reference)	1.23 (1.02, 1.49)	1.40 (1.15, 1.70)	1.34 (1.09, 1.65)	<0.001	3.88 (1.83, 8.26)	<0.001
Model 3	1.00 (reference)	1.18 (0.95, 1.45)	1.33 (1.08, 1.65)	1.28 (1.02, 1.61)	0.007	3.19 (1.38, 7.38)	0.007
Monocyte percentage							
Range	≤ 5.40	5.41-6.40	6.41-7.50	≥ 7.51	-	-	-
Person-years of follow up	1687	1675	1503	1172	-	-	-
No. of breast lump	199	195	212	197	-	-	-
Model 1	1.00 (reference)	1.05 (0.86, 1.28)	1.32 (1.09, 1.60)	1.64 (1.35, 2.00)	<0.001	1.15 (1.09, 1.21)	<0.001
Model 2	1.00 (reference)	1.05 (0.86, 1.28)	1.33 (1.09, 1.62)	1.69 (1.39, 2.07)	<0.001	1.16 (1.10, 1.22)	<0.001
Model 3	1.00 (reference)	1.03 (0.83, 1.28)	1.28 (1.03, 1.59)	1.62 (1.30, 2.02)	<0.001	1.14 (1.08, 1.21)	<0.001

Confidence intervals (CIs) not including 1.00 are considered statistically significant.

Model 1: crude hazard ratios (HRs) with corresponding 95% CIs were calculated.

Model 2: adjusted for age and BMI as potential confounding variables.

Model 3: adjusted for age, BMI, WC, SBP, DBP, TC, TG, LDL-C, HDL-C, FBG, UA, marital status, smoking status, drinking status, family history of cancer, hypertension, diabetes, history of cancer, history of hypertension, and history of diabetes.

Cumulative incidence of breast lump stratified by age

Figure 3 shows the cumulative incidence of breast lump stratified by age and quartile of AMC and %MONO; these data indicated that the effect of high monocyte levels on increased risks of a breast lump was more remarkable in women <60 years of age (both $P<0.05$), while no significant differences were observed for women >60 years of age (both P 0.05).

Discussion

The relationship between monocytes and breast cancer is well-established [22–27], but their relationship with BDD is not well understood [3, 28], and fewer studies examined those markers in relation to breast lumps, irrespective of their malignancy status. This study suggests that increased monocyte levels were independently associated with breast lump and might be used as an indicator of the incidence of breast lump, especially for women <60 years. Those results suggest additional markers for the risk management of women undergoing breast screening.

Previous studies reported a relationship between monocyte-related markers of inflammation and monocyte activation in BBD tissue. For instance, in an age-matched control study, Degnim et al. [3] found that a higher density of macrophages is observed in BBD tissues compares with that in normal mammary gland tissue. Moreover, BBD stromal tissues are far more frequently inflamed than normal breast tissues [30]. Charles et al.[31] demonstrated that the re-calcification time, an indicator of monocyte' generation of pro-coagulant products, was significantly shorter in breast cancer patients than in patients with cystic hyperplasia, which in turn was significantly shorter than in healthy women. However, unlike risk factors for breast cancer, risk factors for breast lump (irrespective of their malignancy status) development are not clear. This study revealed that increased monocyte levels were independently associated with breast lump. Taken together, those results suggest that breast lump, irrespective of their benign/malignant status, are more likely to display elevated monocyte-related markers. Those results could help the management of women with breast lump under ultrasound. Women with higher monocyte-related markers could benefit from shorter screening intervals without harm. Of course, additional cohort studies are necessary to examine this hypothesis. Furthermore, additional studies are necessary to verify whether monocyte-related markers at baseline could help predict the development of benign vs. malignant breast lump.

We also analyzed the association of AMC and %MONO with the incidence of breast lump stratified by age and found high monocyte levels display a more pronounced effect on breast lump risk in women <60 years of age. A previous study had also found that a high density of TAM infiltration was significantly related to younger age (≤ 50 years) [32]. Furthermore, data suggested that the total number of immune cells does not change between younger (< 40 years) and middle-aged (40-60 years) groups, but it significantly decreased at an older age (>60 years)[33]. The decreased levels of immune cells, especially platelet-derived beta-2 microglobulin, shifts monocytes and macrophages to a pro-reparative phenotype and reduce the risk of pro-fibrotic responses [34].

Notable strengths of this study include its large sample size and the initial report regarding the causal associations between monocytes and breast lump, including standardized assessment of outcomes over a 5-year follow-up period. Nevertheless, there are some potential limitations to this study. First, the participants were patients from the Health Management Center rather than from the general population; thus, the representativeness is limited. Moreover, the prevalence of breast lump in the general population could not be determined. Second, all enrolled subjects were Chinese women from Tianjin city, and racial and epidemiologic factors should be considered when interpreting our findings. Third, the AMC and %MONO are easily available markers obtained from a simple blood draw, but they might not necessarily represent the exact monocyte infiltration of the breast tissue. Future studies should examine the correlations between blood AMC/%MONO and monocytes in breast biopsies. Last, although there is a lack of information concerning reproductive factors in the present study, we adjusted for a variety of other potential confounders and achieved robust results. These limitations can be addressed in future studies.

Conclusions

In summary, increased AMC and %MONO increase the risk of developing a breast lump. And we encourage the implementation of prevention measures as breast lump can be either malignant or be a marker of increased breast cancer risk. Future studies are needed to explore monocytes as a circulation marker for the incidence of BBD and breast cancer.

Declarations

Ethics approval and consent to participate

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Institutional Review Board of Tianjin Medical University General Hospital (IRB2020-WZ-201) and informed consent was waived. All methods were carried out in accordance with relevant guidelines and regulations under Ethics approval and consent to participate.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available due ethical/privacy reasons. Upon request the analyses generated from the data are available from the corresponding author.

Competing interests

The authors have no conflict of interest to declare.

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Authors' Contributions

YG and QZ initiation of the study. YG and SL analyses of the data and wrote the manuscript text. JYJ and WW performed and interpreted the breast ultrasound scan. JFY and XQX supervised data collection and prepared the tables and figures. SMS and LL supervised the study's implementation. All authors reviewed and approved the final manuscript.

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Figures

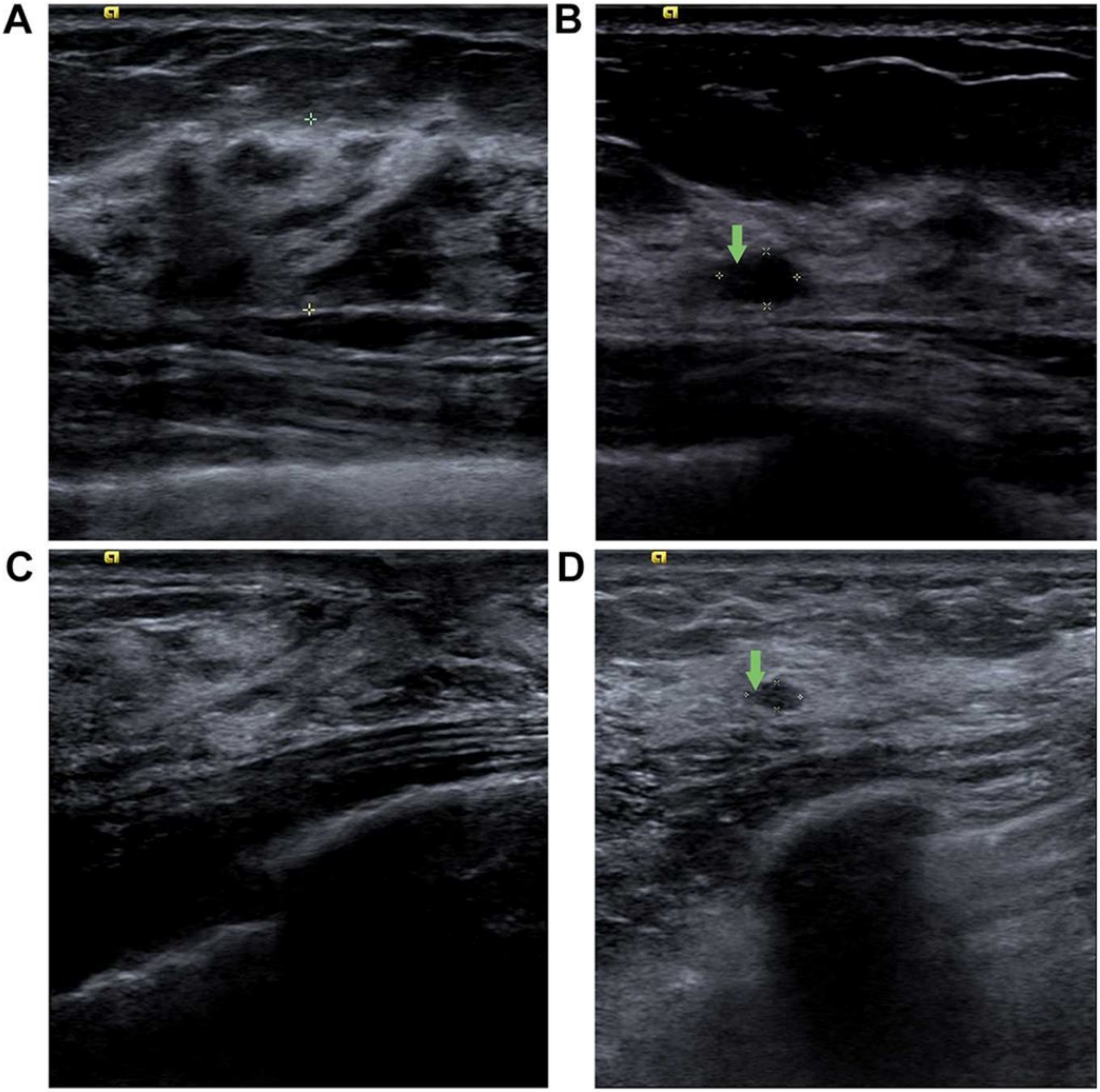

Figure 1

Breast ultrasound images of 2 patients enrolled in study. A/B: breast ultrasound images of a 46-year-old woman. A: normal on the first examination; B: breast lump on the subsequent examination (green arrow). C/D: breast ultrasound images of a 71-year old woman. C: normal on the first examination; D: breast lump on the subsequent examination (green arrow).

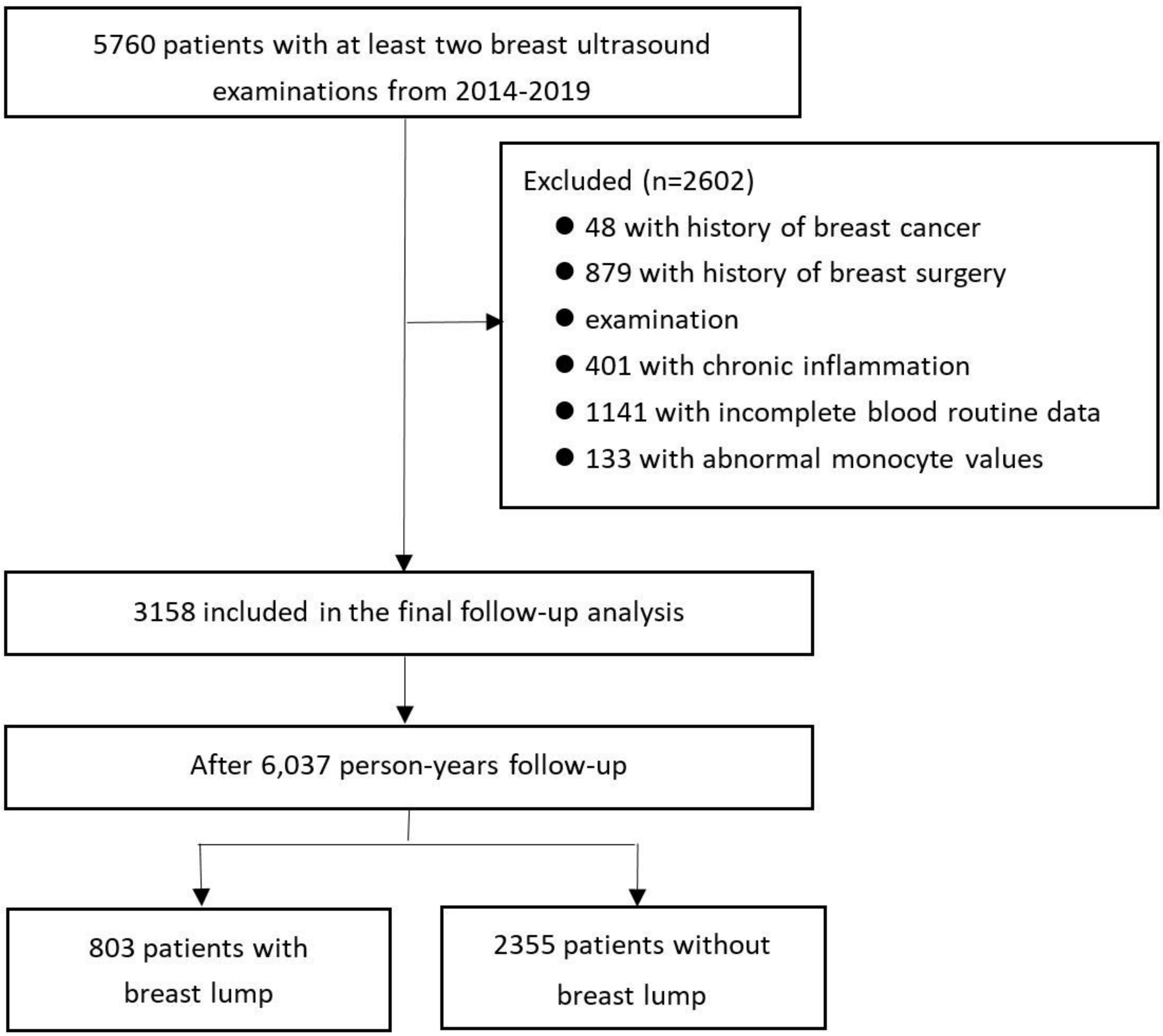

Figure 2

Flow diagram showing the selection of study population

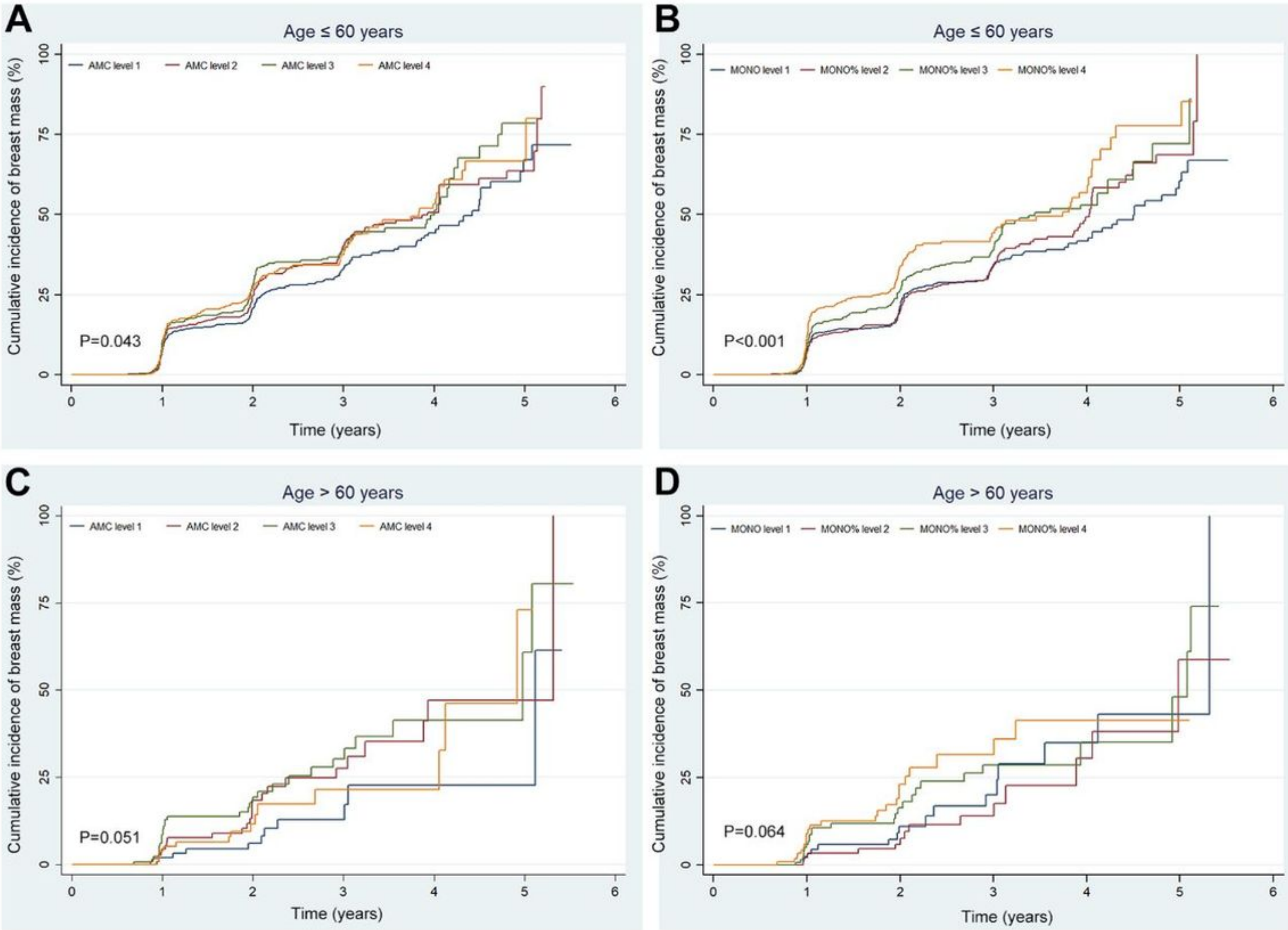

Figure 3

Cumulative curves of incidence of breast lump stratified by age and quartile of AMC and %MONO. A/C: incidence of breast lump according to the quartiles of absolute monocyte count for age ≤60 years (A) or for age >60 years (C); B/D: incidence of breast lump according to the quartile of the percentage of monocyte for age ≤60 years (B) or for age >60 years (D). P-values <0.05 are considered statistically significant.