Chapter

A Short Communication: Non-acid Nucleic Blood Multi-Factors Panels for Primary Breast Cancer Detection - A Systematic Review and Network Meta-Analysis

Vahid Raja, Ziba Farajzadegan, Marjan Mansourian, Khojaste Ghasemi, Mohammad Sadegh Aboutalebi, Rasool Nouri and Fariborz Mokarian

Abstract

This study aimed to compare the non-acid nucleic blood multi-factor panels together and with mammography in terms of sensitivity, specificity, and accuracy in primary breast cancer detection (I, II, III, and IV). We systematically reviewed studies assessing non-acid nucleic blood tumor markers panels' diagnostic value in both healthy women and patients (before any anticancer treatment) for the detection of primary breast cancer. Out of the 2358 titles initially identified, 12 studies and 9 panels were included in the network meta-analysis. Panels I (MSA + B2m) and J (GATA3 + E-cadherin) had the highest sensitivity in all stages of primary breast cancer but had no significant difference with mammography. Panels L (MSA + CA15–3) and B (M-CSF- + CA15–3) had the highest specificity in all stages compared to other panels but no remarkable difference with mammography. Panels J (GATA3 + E-cadherin) and I (MSA + B2m) respectively had the highest accuracy in primary breast cancer detection but no considerable difference with mammography in terms of accuracy. Panel J, including GATA3 + E-cadherin, demonstrated a higher diagnostic value for primary breast cancer detection (I, II, III, and IV) than the rest of the panels.

Keywords: primary breast cancer, blood tumor markers, timely diagnosis, sensitivity and specificity, multi-factor panels, network meta-analysis

1. Introduction

Based on our previous study [1], the necessity of a noninvasive, accessible, cost-effective, and reliable method for breast cancer detection based on blood factors was proved. Furthermore, blood multi-factor panels can be the best choice for such a

method thanks to improving the sensitivity and specificity of cancer detection considerably compared to the individual state. In that study [1], we had determined the best non-acid nucleic blood multi-factor panels for breast cancer detection in early stages and locoregional breast cancer (I, II, and III). In this brief study, however, we compared the best non-acid nucleic blood multi-factor panels in primary breast cancer detection (I, II, III, and IV) by conducting a network meta-analysis. In fact, this study aimed to offer new insight into the diagnostic value of the best panels of non-acid nucleic blood tumor markers to detect primary breast cancer along all stages not only in early stages. The breast malignancy that emerges and can be diagnosed for the first time is named primary breast cancer, and if it recurs after primary treatment including surgery, chemotherapy, hormone therapy, and radiotherapy individually or collectively, it will be named secondary breast cancer [2]. Primary breast cancer comprises locoregional (I, II, III) and metastatic stages (IV) [3].

2. Materials & method

The systematic reviews of the observational studies were conducted based on PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-analysis) [4]. Eligibility criteria, search strategy (supplementary material 1 B), databases, study selection, data extraction, and statistical analysis conformed to our former study [1]. The difference is that, in this brief study, we systematically reviewed the studies that have simultaneously assessed several tumor markers in the form of a panel to diagnose and detect breast cancer in all stages of primary breast cancer (I, II, III, and IV).

The included panels were **B**: M-CSF + CA15–3, **C**: VEGF + CA15–3, **D**: VEGF + M-CSF + CA 15–3, **E**: VEGF+ M-CSF, **F**: p16+ c-MYC+ P53, **G**: CA15–3 + CEA, **I**: MSA + B2m, **J**: GATA3 + E-cadherin and **L**: MSA + CA15–3.

All these panels were made based on simultaneous measurement of two or three blood tumor markers in patients and healthy people using a compatible linear combination method [5]. Panels (B, C, D, E, F, G) were assessed in more than one study (multiple studies), and panels (I, J, L) were only assessed in one study (single study). We conducted direct and indirect paired comparisons of the sensitivity, specificity, and accuracy of the included blood tumor markers panels for diagnosing primary breast cancer in all stages. All the investigations were conducted in comparison to mammography (M) as the gold standard [6–8], like our previous study (**Figure 1**) [1].

3. Results and discussion

3.1 Study selection

Study selection conformed to our former study [1]. However, in this brief study, among the 54 studies relevant to our research question which contained 86 unique blood tumor markers panels (supplementary material 2) conforming to our eligibility criteria, only 12 studies and 9 panels presented enough data for estimating sensitivity and specificity in all stages (I, II, III, and IV) of primary breast cancer and could be included in the systematic review and network meta-analysis. These 12 studies were similar in terms of pre-analytical procedures and analytical methods (**Table 1**).

All the included and excluded studies are presented in **Figure 2**.

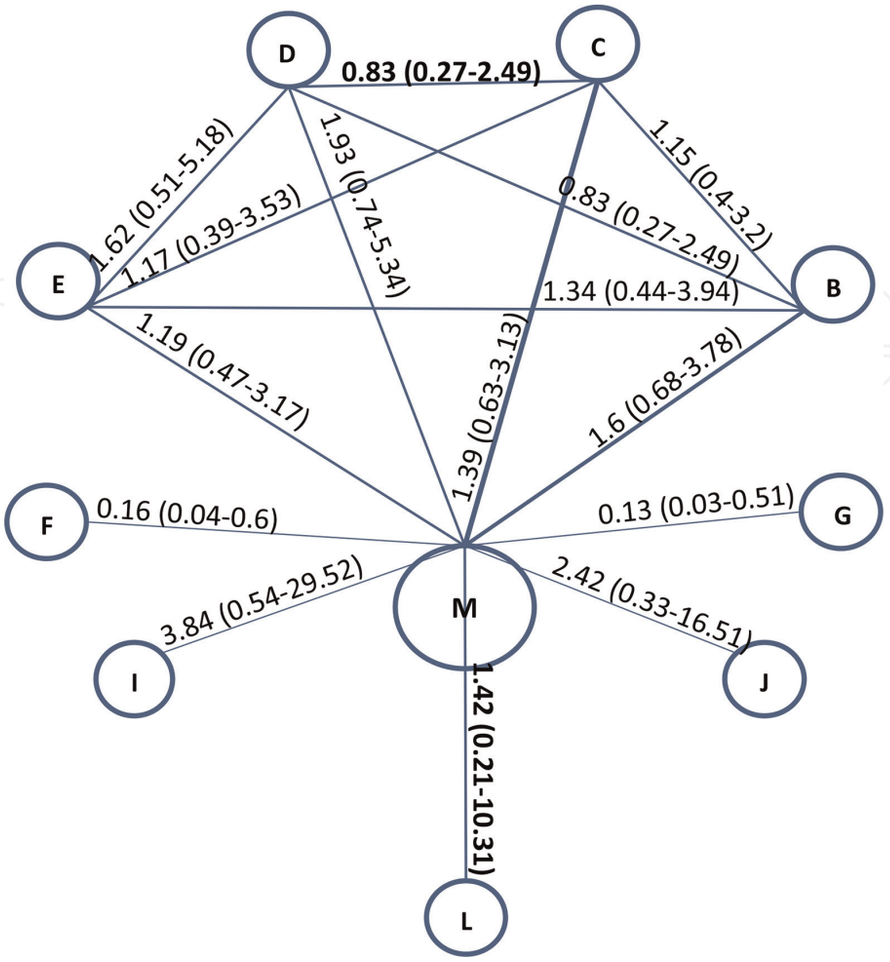

Figure 1.
Multiple comparison of different panels for sensitivity. B: M-CSF + CA15–3, C: VEGF + CA15–3, D: VEGF + M-CSF + CA 15–3, E: VEGF+ M-CSF, F: p16+ c-MYC+ P53, G: CA15–3 + CEA, I: MSA + B2m, J: GATA3 + E-cadherin. L: MSA + CA15–3 M = mammography.

Association between diagnosis of primary breast cancer and blood tumor markers panels:

Panels I (MSA + B2m) and J (GATA3 + E-cadherin) had the highest sensitivity in primary breast cancer but did not have noticeable differences with mammography. Panels G (CA15–3 + CEA) and F (p16+ c-MYC+ P53) had the lowest sensitivity than the rest of the panels and mammography as mammography exhibited a remarkably better function than them, with OR = 0.13 and 95% CL (0.04–0.46) and OR = 0.15 and 95% CL (0.04–0.52) (**Figure 3a**, **Table 2**). In diagnostic tests, sensitivity had a vital role in screening diseases [21]. As a result, we can claim that the panels which had the highest sensitivity can be promising diagnostic tests in primary breast cancer screening, which included panels I and J in all stages of primary breast cancer. Panels L (MSA + CA15–3) and B (M-CSF + CA15–3) had the highest specificity but did not have remarkable differences with mammography. Panels G (CA15–3 + CEA) and D (VEGF + M-CSF + CA 15–3) had the lowest specificity as mammography demonstrated a superior function in specificity, with OR = 0.06 and 95% CL (0.01–0.39) and OR = 0.06 and 95% CL (0.02–0.19) (**Figure 3b**, **Table 3**). Mammography had a better function in specificity than a large number of panels, since it exhibited the highest specificity after panel L with OR = 2.54 and 95% CL (0.1–177.46) in diagnosing

First author and year	Country	Study design	Sample size and population	Clinical stages	Panel	Number of panel components	Sensitivity	Specificity	Accuracy	Method of chemical evaluation	Type of sample	Score
S Zajkowska, M.. 2016 [9]	Poland	Case–control	240 Bc:120 B:60 H:60 Median age (range) 54 (34–72)	I:29 II:30 III:31 IV:30	VEGF + CA 15–3 M-CSF + CA 15–3 VEGF + M-CSF + CA 15–3 VEGF+ M-CSF*	2 2 3 2 VEGF M-CSF CA 15–3	96.25 91.25 96.25 90 76.25 60 83.75	65 67.5 57.5 76 85 90 75	80.6 79.3 76.8 83	ELISA CMIA	plasma	11
Sacks, N. P. 1987 [10]	Australia.	Case–control	131 **Bc:72** **B:13** **H:46**	I/ II:34 III/ IV:38	MSA + CA15–3	2	84	100	89.2	ELISA	serum	11
Liu, Y. 2017 [11]	China	Case–control	248 **Bc102** **H146** **50.88 ± 7.12**	I/ II:57 III/ IV:45	*p16+ c-MYC + TP53	3 p16 c-MYC TP53	30 27.5 11.8 24.5	90 90 90 90	65.3	ELISA	serum	10
Molina, Rafael 1998[12]	Spain	Case–control	292 **Bc186** **B56** **H50**	I/ II:118 III/ IV:68	Ca15.3 + CEA	2 Ca15.3 CEA	29.2 15.6 18.3	90	51.2	ELISA	serum	9.5
Ławicki, Sławomir 2016 [13]	Poland	Case–control	200 **Bc100** **B50** **H50** **48(20–78)**	I/ II/ III:77 IV:23(with metastases)	VEGF +CA15–3	2 VEGF CA 15–3	84 61 65	90 96 96	87	ELISA	plasma	11
Lawicki, S. 2017 [14]	Poland	Case–control	200 **Bc100** **B50** **H50** **48(20–78)**	I/ II/ III:77 IV:23	VEGF+ CA 15–3	2 VEGF CA 15–3	83 60 64	90 95 95	86.5	ELISA	plasma	11.5

First author and year	Country	Study design	Sample size and population	Clinical stages	Panel	Number of panel components	Sensitivity	Specificity	Accuracy	Method of chemical evaluation	Type of sample	Score
Tjandra, JJ 1988 [15]	Australia	Case–control	161 **Bc109** **B31** **H21**	I:32 II:24 III/ IV:53	MSA + B2m	2 MSA B2m	93 88 39	90 95 90	90.3	Radioimmunoassay + ELISA	serum	12
Ławicki, S 2013 [16]	Poland	Case–control	190 **Bc110** **B40** **H40** **44 (30–78)**	I:25 II:35 III:25 IV:25(with metastases)	M-CSF + CA15–3	2 M-CSF CA 15–3	85 60 53	90 95 95	87.1	ELISA	plasma	11
Ławicki, Sławomir 2013 [17]	Poland	Case–control	200 **Bc100** **B50** **H50** **51 (40–70)**	I/ II/ III:75 IV:25(with metastases)	VEGF+ CA 15–3 M-CSF+ CA 15–3 VEGF+ M-CSF VEGF+ M-CSF+ CA 15–3	2 2 3 VEGF M-CSF CA 15–3	61 67 63 75 44 53 36	86 86 86 78 92 94 92	73.5 76.5 74.5 76.5	ELISA	plasma	11
Luo, M. 2019 [18]	China	Case–control	200 **Bc120** **H80** **59.88 ± 9.05 (32–70)**	I/ II:47 III/ IV:73	GATA3 + E-cadherin GATA3 E-cadherin	2	90 87.5 82.5	91.7 73.3 87.5	90.6	ELISA	serum	11.5
Looi, Koksun 2006 [19]	China	Case–control	123 **Bc41** **H82** **Multi cancer**		p16 + c-MYC + P53	3	43.9	97.6	79.6	ELISA	serum	8

First author and year	Country	Study design	Sample size and population	Clinical stages	Panel	Number of panel components	Sensitivity	Specificity	Accuracy	Method of chemical evaluation	Type of sample	Score
Guadagni, Fiorella 2001 [20]	Italy	Case–control	2191 **BC 1453 B738 mean age, 57 years (range 25–97 years**	I:392 II:562 III:153 IV:48 Metastatic:240 Local recurrence:58	CEA + CA 15.3	2 CA 15.3 CEA	39 33 16.7	85	54	RIA kit	serum	9.5

B: benign; H: Healthy; ELISA: the enzyme-linked immunosorbent assay; CMIA: luminescent microparticle immunoassay; RIA: radioimmunoassay.
The scoring system based on the CASP checklist (specified for diagnostic studies) was applied to all studies.
The sensitivity, specificity, and accuracy of all studies were evaluated in all stages of primary breast cancer (I, II, III, and IV).
[*] Based on linear combination (5).

Table 1.
Characteristics of articled included in network meta-analysis.

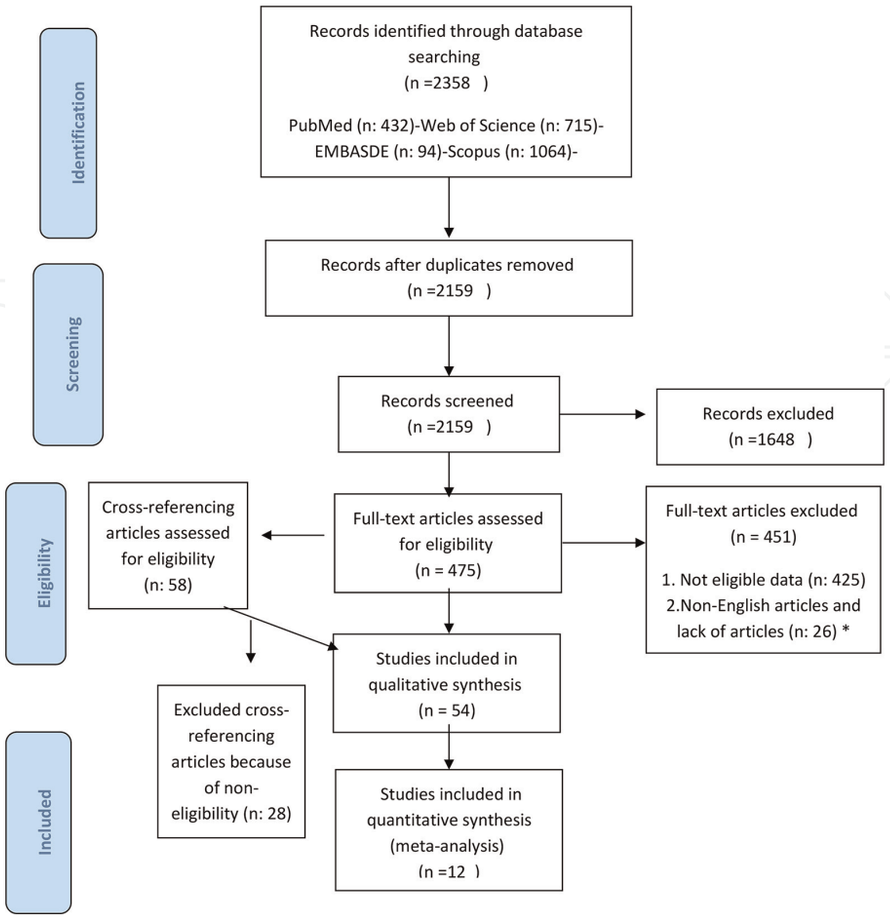

Figure 2.
*Flow diagram of included and excluded articles. *Although we sent emails to articles' authors to get their full texts, we did not receive any answers.*

primary breast cancer. Panels J (GATA3 + E-cadherin) and I (MSA + B2m) possessed the highest accuracy in primary breast cancer but did not show significant differences with mammography. Panel L (MSA + CA15–3) did not demonstrate considerable differences with panel I; therefore, we could consider them approximately similar regarding accuracy. Panels G (CA15–3 + CEA) and F (p16+ c-MYC+ P53) possessed the lowest accuracy in primary breast cancer as mammography exhibited a considerably superior function in accuracy, with OR = 0.15 and 95% CL (0.07–0.3) and OR = 0.37 and 95% CL (0.17–0.74) (**Figure 3c**, **Table 4**).

The best panels based on total function: **J: GATA3 + E-cadherin, I: MSA + B2m.**

In diagnosing primary breast cancer, panels J and I exhibited the highest accuracy and total function compared to other panels. Overall, we recommend panel J because it had an even better function in accuracy than panel I, despite being minor (**Table 1**) and its study had a larger sample size (200). Panel J was made of GATA3 and E-cadherin. GATA3 is a transcription factor that plays a crucial role in the development and progression of breast cancer and can reverse the epithelial-mesenchymal transition. It also regulates the proliferation, differentiation, and development of cells. E-cadherin is a member of the cadherin family mainly expressed in epithelial cells. E-cadherin mediates the adhesion of allogeneic epithelial cells and plays a key role in epithelial cell aggregation and adhesion. Studies have demonstrated that the expression of cadherin is closely related to the invasion of breast cancer [18].

Figure 3.
Estimated rank probability of all panels' sensitivity, specificity, and accuracy. B: M-CSF + CA15–3, C: VEGF + CA15–3, D: VEGF + M-CSF + CA 15–3, E: VEGF+ M-CSF, F: p16+ c-MYC+ P53, G: CA15–3 + CEA, I: MSA + B2m, J: GATA3 + E-cadherin. L: MSA + CA15–3 M = mammography.

4. Conclusion

In conclusion, panel J including GATA3 + E-cadherin with a sensitivity of 90 and specificity of 91.7 demonstrated a higher diagnostic value for primary breast cancer than the rest of the panels as it exhibited higher function in accuracy than mammography, with OR = 1.38 and 95% CL (0.42–4.41), although it was not remarkable. After

	B	C	D	E	F	G	I	J	L	M
B	1									
C	1.18 (0.42–2.96)	1								
D	0.83 (0.28–2.29)	0.71 (0.25–2)	1							
E	1.73 (0.62–4.83)	1.47 (0.56–4.24)	2.09 (0.72–6.32)	1						
F	**10.52 (2.42–46.72)**	**9.01 (2.16–39.41)**	**12.73 (2.85–60.57)**	**6.13 (1.34–27.66)**	1					
G	**11.94 (2.69–56.3)**	**10.21 (2.36–46.39)**	**14.57 (3.07–70.46)**	**6.93 (1.49–32.44)**	1.12 (0.19–6.78)	1				
I	0.44 (0.05–3.44)	0.37 (0.05–2.95)	0.52 (0.06–4.22)	0.25 (0.03–2.01)	**0.04 (0.01–0.4)**	**0.04 (0.01–0.37)**	1			
J	0.64 (0.09–4.78)	0.54 (0.08–4.16)	0.77 (0.1–6.26)	0.37 (0.05–2.95)	**0.06 (0.01–0.57)**	**0.05 (0.01–0.52)**	1.46 (0.11–22.19)	1		
L	1.13 (0.16–7.97)	0.98 (0.14–6.79)	1.37 (0.19–10.07)	0.65 (0.09–4.78)	**0.11 (0.01–1)**	**0.09 (0.01–0.87)**	2.6 (0.18–36.26)	1.79 (0.13–22.86)	1	
M	1.59 (0.69–3.53)	1.35 (0.65–2.94)	1.91 (0.78–4.88)	0.91 (0.38–2.26)	**0.15 (0.04–0.52)**	**0.13 (0.04–0.46)**	3.63 (0.55–25.11)	2.47 (0.37–15.96)	1.4 (0.24–8.3)	1

B: M-CSF + CA15–3, C: VEGF + CA15–3, D: VEGF + M-CSF + CA 15–3, E: VEGF+ M-CSF, F: p16+ c-MYC+ P53, G: CA15–3 + CEA, I: MSA + B2m, J: GATA3 + E-cadherin L: MSA + CA15–3 M = Mammography.

Table 2.
Relative effects and its 95% credible interval of all pairwise panels for sensitivity based on Bayesian network meta-analysis method.

	B	C	D	E	F	G	I	J	L	M
B	1									
C	**4.75 (1.41–16.11)**	1								
D	**6.86 (1.97–25.88)**	1.46 (0.42–5.27)	1							
E	**5.19 (1.42–18.95)**	1.08 (0.31–3.99)	0.75 (0.2–2.74)	1						
F	2.8 (0.33–24.19)	0.58 (0.07–4.87)	0.4 (0.04–3.57)	0.53 (0.06–4.86)	1					

	B	C	D	E	F	G	I	J	L	M
G	6.82 (0.76–63.76)	1.43 (0.16–12.82)	1 (0.11–9.29)	1.33 (0.14–12.7)	2.62 (0.17–35.24)	1				
I	2.74 (0.16–61.57)	0.57 (0.03–12.81)	0.39 (0.02–8.77)	0.53 (0.03–12.6)	1 (0.04–30.25)	0.39 (0.02–13.06)	1			
J	2.4 (0.14–48.49)	0.51 (0.03–9.19)	0.34 (0.02–6.66)	0.46 (0.03–9.64)	0.85 (0.03–22.94)	0.34 (0.01–9.86)	0.87 (0.02–42.75)	1		
L	0.16 (0.01–4.92)	0.03 (0.01–1.04)	**0.02 (0.01–0.72)**	**0.03 (0.01–0.89)**	0.06 (0.01–2.68)	**0.02 (0.01–0.96)**	0.06 (0.01–3.68)	0.07 (0.01–4.26)	1	
M	0.42 (0.14–1.2)	**0.09 (0.03–0.24)**	**0.06 (0.02–0.19)**	**0.08 (0.02–0.25)**	**0.15 (0.02–0.96)**	**0.06 (0.01–0.39)**	0.16 (0.01–2.05)	0.18 (0.01–2.3)	2.54 (0.1–177.46)	1

B: M-CSF + CA15–3, C: VEGF + CA15–3, D: VEGF + M-CSF + CA 15–3, E: VEGF+ M-CSF, F: p16+ c-MYC+ P53, G: CA15–3 + CEA, I: MSA + B2m, J: GATA3 + E-cadherin L: MSA + CA15–3 M = Mammography.

Table 3.
Relative effects and its 95% credible interval of all pairwise panels for specificity based on Bayesian network meta-analysis method.

	B	C	D	E	F	G	I	J	L	M
B	1									
C	1.11 (0.65–1.9)	1								
D	1.24 (0.7–2.18)	1.11 (0.65–1.97)	1							
E	1.03 (0.59–1.81)	0.92 (0.54–1.64)	0.83 (0.46–1.46)	1						
F	1.8 (0.77–4.42)	1.61 (0.7–4)	1.45 (0.61–3.77)	1.78 (0.73–4.23)	1					
G	**4.42 (1.92–10.23)**	**3.98 (1.74–9.25)**	**3.58 (1.44–8.49)**	**4.32 (1.79–10.29)**	2.45 (0.85–6.76)	1				
I	0.54 (0.15–1.81)	0.48 (0.14–1.62)	0.44 (0.12–1.48)	0.53 (0.15–1.84)	0.3 (0.07–1.15)	**0.12 (0.03–0.47)**	1			
J	0.48 (0.13–1.74)	0.43 (0.12–1.55)	0.39 (0.1–1.43)	0.46 (0.13–1.84)	0.26 (0.06–1.1)	**0.11 (0.03–0.43)**	0.91 (0.17–4.57)	1		
L	0.58 (0.17–2.09)	0.52 (0.16–1.92)	0.47 (0.13–1.71)	0.57 (0.16–2.1)	0.32 (0.08–1.35)	**0.13 (0.03–0.51)**	1.09 (0.22–5.35)	1.22 (0.25–6.06)	1	

	B	C	D	E	F	G	I	J	L	M
M	0.66 (0.42–1.05)	**0.59 (0.39–0.92)**	**0.53 (0.32–0.87)**	0.64 (0.38–1.06)	**0.37 (0.17–0.74)**	**0.15 (0.07–0.3)**	1.22 (0.4–3.84)	1.38 (0.42–4.41)	1.1 (0.34–3.45)	1

B: M-CSF + CA15–3, C: VEGF + CA15–3, D: VEGF + M-CSF + CA 15–3, E: VEGF+ M-CSF, F: p16+ c-MYC+ P53, G: CA15–3 + CEA, I: MSA + B2m, J: GATA3 + E-cadherin L: MSA + CA15–3 M = Mammography.

Table 4.
Relative effects and its 95% credible interval of all pairwise panels for accuracy based on Bayesian network meta-analysis method.

panel J, panel I (MSA + B2m) with a sensitivity of 90 and specificity of 90.3 and panel L (MSA + CA15–3) with a sensitivity of 84 and specificity of 100 had the best function in primary breast cancer detection than the rest of the panels. However, more experimental studies are required with larger samples, on different populations, and using other chemical measurement methods to verify these results.

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Author contributions

Vahid Raja had the idea for the research. The literature search was performed by Vahid Raja, Mohammad Sadegh Aboutalebi, and Rasool Nouri. The data analysis was performed by Marjan Mansourian and Khojaste Ghasemi. The article was drafted by Vahid Raja and Ziba Farajzadegan. The article was critically revised by Vahid Raja, Ziba Farajzadegan, and Fariborz Mokarian.

Conflict of interest

Not applicable.

Data availability

The data used to support the findings of this study are available from the corresponding author upon request.

Ethical statement

Our study did not require an ethical board approval because it did not contain human or animal trials.

Supplementary material

Including traditional meta-analysis of all panels, nod-splitting analysis of inconsistency for sensitivity, specificity and accuracy, ranking of different panels in sensitivity, specificity and accuracy, the search strategy for each data base, and 54 studies were identified relevant to our research question.

Author details

Vahid Raja[1*], Ziba Farajzadegan[2*], Marjan Mansourian[3], Khojaste Ghasemi[3], Mohammad Sadegh Aboutalebi[4], Rasool Nouri[5] and Fariborz Mokarian[6]

1 Clinical Laboratory Sciences, Amin Hospital, Isfahan university of Medical sciences, Isfahan, Iran

2 Community and Preventive Medicine, Isfahan University of Medical Sciences, Isfahan, Iran

3 Department of Biostatistics and Epidemiology, School of Public Health, Isfahan University of Medical Sciences, Isfahan, Iran

4 Faculty of Nursing and Midwifery, Isfahan University of Medical Sciences, Isfahan, Iran

5 Department of Medical Library and Information Sciences, Isfahan University of Medical Sciences, Isfahan, Iran

6 Hematology and Oncology Department of Internal Medicine, Isfahan University of Medical Sciences, Isfahan, Iran

*Address all correspondence to: www.mahantajhizs@gmail.com
and farajzadegan@med.mui.ac.ir

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