



Cardiac Complications in Pregnancy: A Systematic Review and Meta-Analysis of Diagnostic Accuracy of BNP and N-Terminal Pro-BNP

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ABSTRACT

Introduction: Serum brain-type natriuretic peptide (BNP) levels may be involved in detecting the breakdown of defense mechanisms in pregnant women. BNP and N-terminal pro-BNP (NT-proBNP) levels can be used in emergency settings as a biomarker to rule out or confirm cardiac complications. The present study was conducted as an attempt to evaluate the performance of BNP and NT-proBNP as diagnostic tools for cardiac complications, including heart failure and pre-eclampsia, in pregnant and recently-delivered women.

Methods: This meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. To extract the data, articles meeting the inclusion criteria were directly reviewed by two of the authors. Disputes were resolved through discussion with all authors before data mining. In cases of unresolved disagreement, a third reviewer was consulted to achieve consensus. A quantitative analysis of the total bias of publications was performed

using Stata software version 14.0, using funnel plots and Deek's test.

Results: Overall, 13 unique studies were included in this review. The pooled sensitivity, specificity and positive and negative predictive values for diagnosing cardiac complications in pregnant women when BNP level was ≤ 100 ng/L, were determined to be 95, 62, 71 and 91%, respectively. The corresponding measures when the BNP levels were 100–500 ng/L were calculated to be 98, 92, 97 and 92%, respectively. The pooled sensitivity, specificity and positive and negative predictive values for diagnosing cardiac complications in pregnant women using NT-proBNP were 78, 74, 20.5 and 97%, respectively.

Conclusion: Our results suggest that both BNP and NT-proBNP levels can be used as diagnostic tools among pregnant and newly-delivered women to diagnose cardiac complications, including heart failure and pre-eclampsia. While BNP showed a relatively better diagnostic accuracy compared to NT-proBNP, it must be noted that the number of studies evaluating NT-proBNP included in this meta-analysis was low and the studies were inconsistent in terms of cutoff value. Further studies are required to confirm the prospective use of BNP and NT-proBNP in assessing common symptoms that indicate cardiac complications during labor. Moreover, the clinical use of the NT-proBNP test in this field requires further study.

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Keywords: Brain-type natriuretic peptide; N-terminal pro-BNP; Pregnancy; Cardiac complications

Key Summary Points

Serum brain-type natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP) levels can be used as diagnostic tools to diagnose cardiac complications in pregnant and newly-delivered women.

There is a significant correlation between high levels of NT-proBNP and the development of pre-eclampsia.

BNP levels of 100–500 ng/L, showed a positive and negative predictive value of 92 and 97% for diagnosing cardiac complications in pregnancy.

The high sensitivity of BNP (98%) makes it a good diagnostic method for screening purposes.

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to <https://doi.org/10.6084/m9.figshare.14769672>

INTRODUCTION

A number of hemodynamic alterations are associated with pregnancy, including increases in cardiac output, plasma volume and heart rate. Excessive volume loading is often regarded as a major pathogenic mechanism predisposing harmful maternal events during pregnancy. In response to volume overload, B-type natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP) levels increase in non-pregnant women; consequently, increased BNP and NT-proBNP levels can be used as biomarkers to

predict the risk of cardiovascular complications [1–6]. However, despite the identification of clinical predictors of cardiac complications during pregnancy and the use of diagnostic tools such as echocardiography [7, 8], current risk stratification is insufficient as it does not include evaluation of maternal heart adequacy and its adaptation during pregnancy. Moreover, as the signs and symptoms of pregnancy can highly mimic the signs of cardiac decompensation, the clinical diagnosis of cardiac disease is complicated still further in pregnant patients; as such, additional tools, such as serum BNP levels, may be useful diagnostic markers to detect the breakdown of defense mechanisms. BNP is a neurohormone that is secreted when ventricular volume and pressure increase [9]. It has a very high sensitivity and specificity for diagnosing cardiac disease that are not influenced by subjective factors. In recent years, studies on the manifestation and role of BNP in heart disease have consistently indicated that it is heavily featured in the appraisals of heart failure [10]. It has been reported that BNP and NT-proBNP levels can be used in emergency settings as a biomarker to rule out or confirm heart failure [12, 13]. However, due to the large number of cardiovascular changes in pregnancy that can affect BNP levels, the use of BNP as a diagnostic marker of heart failure is currently almost entirely limited to the non-pregnant population despite that fact that the level of BNP tends to remain stable throughout all pregnancy trimesters and the postpartum period (4–6 weeks), with the levels of BNP slightly higher in pregnant women and women who have recently delivered (median values ranging from 15.5 to 19 pg/mL have been reported) [14, 15] compared to non-pregnant women (median values of 10 pg/mL reported) [16, 17]. Increases in BNP and NT-proBNP levels during pregnancy are especially evident in the setting of pre-eclampsia, with median BNP levels in the range of 21.1–101 pg/mL [11, 15], with a more recent report of 37.1 pg/mL [17]. Therefore, the main purpose of this study was to assess the performance of BNP and NT-proBNP as diagnostic tools for cardiac complications, including heart failure and pre-eclampsia, in pregnant and recently-delivered women.

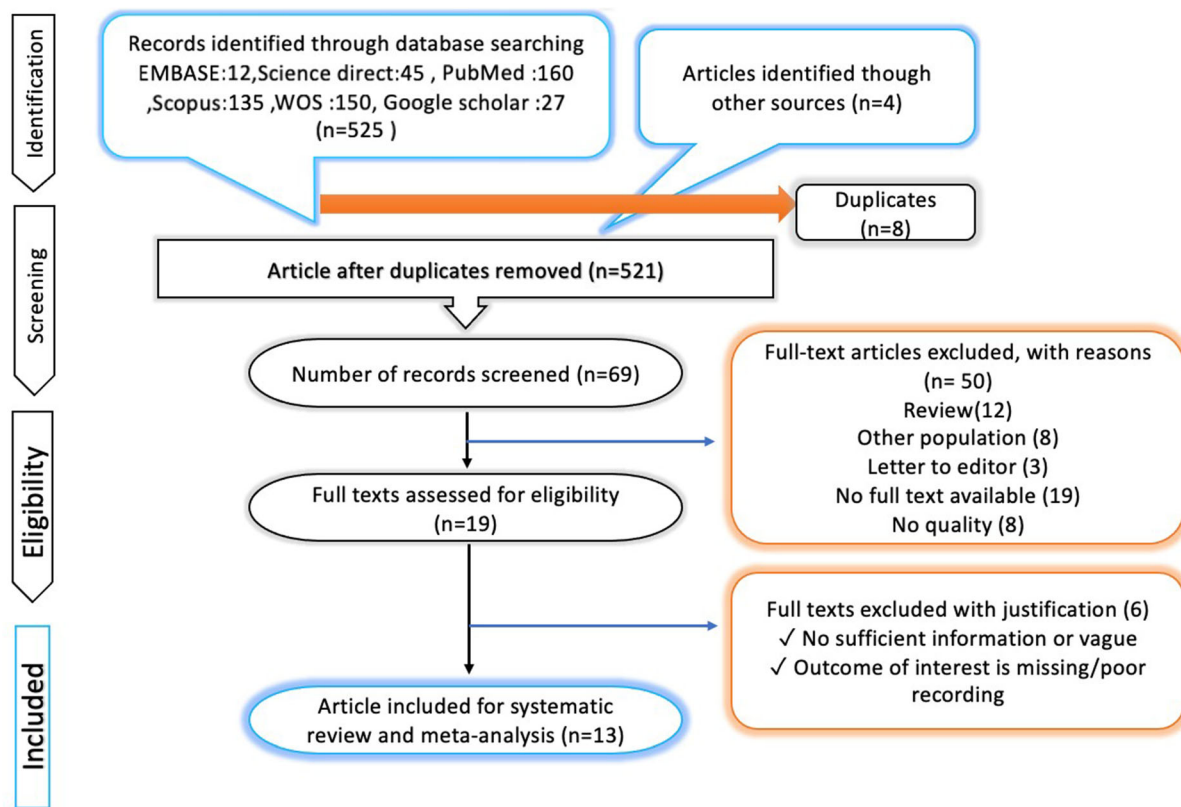


Fig. 1 PRISMA flow diagram

METHODS

This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [18, 19]. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Search Strategy Different databases, including the Web of Science, PubMed, Medline and ProQuest databases, were searched for relevant articles using the following keywords: “pregnancy,” “pre-eclampsia,” “heart failure,” “heart disease” or “congenital heart disease,” “cardiac complications,” “BNP” or “B-type natriuretic peptide” or “NT-proBNP”. Reference lists of the articles identified to be of interest were also manually searched.

Inclusion/Exclusion Criteria Women who were managed by a team of obstetricians and

cardiologists and who had valvular heart disease, congenital heart disease, left ventricular systolic disorder (LVSD) or pulmonary hypertension were eligible for inclusion in this study. Only full-text articles written in English were included. The following studies/articles were excluded: review articles, letters, case studies, expert opinions and conference papers. Also excluded were articles reporting research on animals other than humans and studies including patients with kidney disease, serum creatinine > 1.5 mg/dL, underlying lung disease, twin pregnancies and severe anemia.

Extraction of Data To avoid the inclusion of duplicate data, i.e. studies on the same research population in the same research center, only the largest of the duplicate studies with the longest follow-up time was considered. Also, for studies on different patients at the same research center, only one study was considered. To extract the data, articles meeting the

Table 1 Characteristics of the included studies

First author	Publication year	Study period	No. of patients	Age (in years) of patients (\pm SD)	Design	Prevalence	Reference standard	Country
Malhame [37]	2019	2007–2018	60	32 \pm 6.8	Retrospective	39 (65%)	Elevated BNP level (< 100 pg/mL)	USA
Tanouss [48]	2010	2006–2018	78	31 \pm 5	Prospective	66 (84%)	Elevated BNP level (> 100 pg/mL)	Canada
KAN [51]	2019	2016–2017	60	27.15 \pm 2.2	Prospective	–	\geq 500 ng/L	China
Singh [52]	2018	–	50	26.3 \pm 3.1	Prospective	38 (76%)	100–500 ng/L	India
Umazume [53]	2018	2014–2017	51	34.4 \pm 5.1	Prospective	–	Elevated BNP level (< 100 pg/mL)	Japan

SD Standard deviation

mentioned criteria were directly reviewed by two of the authors, with disagreement resolved by discussion. If the disagreement remained unresolved, consensus was achieved by consultation with a third author. Minimum, maximum and median measures were applied and the mean and standard deviations (SD) were obtained. Additional data was carefully extracted using a standardized data collection form.

Publication Bias A quantitative analysis on total bias was performed using Stata version 14.0 (StataCorp, College Station, TX, USA) to draw funnel plots and perform Deek's test. An asymmetric distribution of data points in the funnel diagram, together with a significance value of $p < 0.05$, indicated the existence of a potential publication bias [20].

Heterogeneity The Chi-square (χ^2) test was used to evaluate the heterogeneity in calculating the overall specificity and sensitivity. In

addition, Cochran's Q test was used to investigate heterogeneity in diagnostic odds ratio (DOR) pooling. When the results of these qualitative tests revealed a p value < 0.05 , we realized that there was a statistically significant heterogeneity. The I^2 test was also performed in each pooled analysis to quantitatively estimate the ratio of total changes throughout the study that could be attributed to heterogeneity versus chance. The value of I^2 , expressed as a value in the range between 0 and 100%, was $> 50\%$, indicating significant heterogeneity. The presence of a threshold effect is exhibited in the form of a curvilinear shape in summary receiver operating characteristic (SROC) curves.

RESULTS

Our search process identified 529 articles, of which 460 were excluded after review of the unrelated abstract and title. The full text of 69 articles was assessed, resulting in the exclusion

of another 50 articles for the following reasons: studies with no full text available ($n = 19$); studies evaluating other populations ($n = 8$); reviews ($n = 12$); cross-review for included references; letter to editors ($n = 3$); and studies with no reported quality estimate [8] (Fig. 1). Ultimately, 13 unique studies were included in this review. In two of the included studies, data (111 participants) were reported at the threshold of ≤ 100 ng/L, in two other studies (128 participants), the threshold was determined to be 100–500 ng/L and in one study (60 participants) data were reported at the threshold of ≥ 500 ng/L (Table 1). Three studies evaluated the diagnostic accuracy of NT-proBNP in diagnosing cardiac complications in pregnancy and six studies evaluated the association between NT-proBNP levels and development of pre-eclampsia. One study evaluated both cardiac complications and pre-eclampsia.

Diagnostic Accuracy of BNP and NT-proBNP

The overall sensitivity and specificity for BNP and NT-proBNP were 94 versus 78% and 75 versus 74%, respectively. The corresponding rates for positive and negative predictive values were 80 versus 20.5% and 93 versus 97%, respectively. In addition, the area under the curve for BNP and NT-proBNP was 0.96 and 83.5, respectively (Figs. 2, 3, 4) (Table 2). The high positive likelihood ratio (LR+; 3.95) and low rate of the negative LR (LR–; 0.091) of BNP was found to be associated with a lower the rate of misdiagnosis and a lower rate of missed diagnosis in the diagnostic test (Fig. 5). The pooled sensitivity, specificity, positive and negative predictive values of BNP within the level of ≤ 100 ng/L were calculated to be 0.95 (95% confidence interval [CI] 0.86–0.99), 0.62 (95% CI 0.48–0.74), 71% and 91%, respectively. The pooled sensitivity, specificity, positive predictive and negative predictive values of BNP

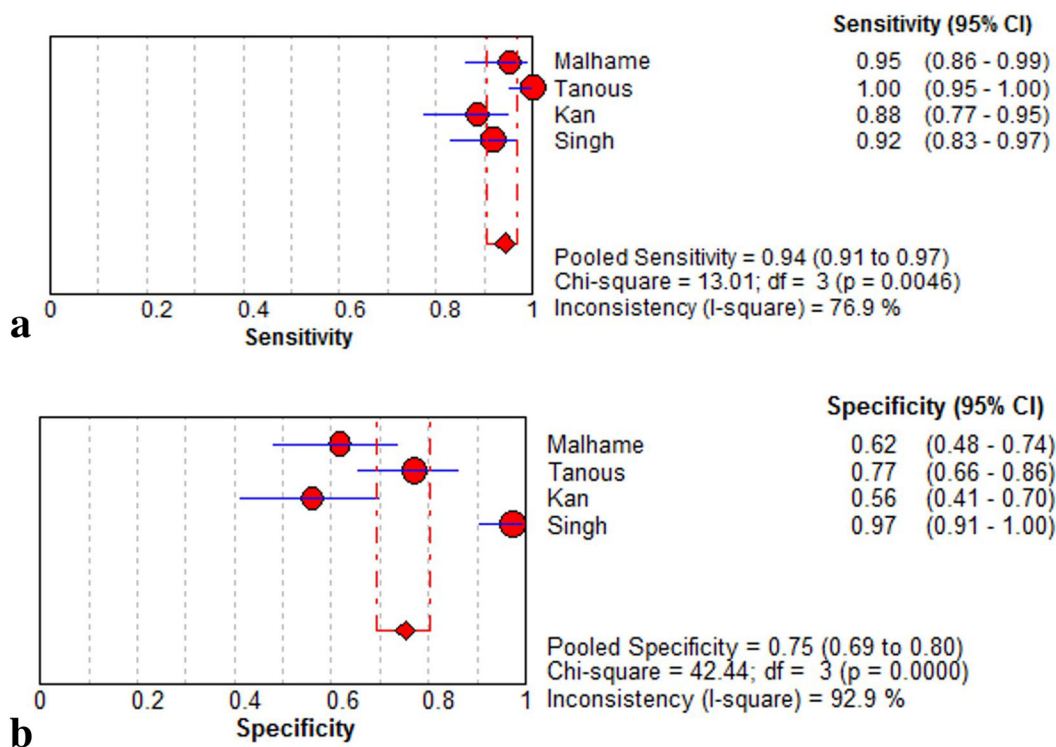


Fig. 2 Sensitivity (a) and specificity (b) of B-Type Natriuretic Peptide in diagnosing cardiac complications in pregnancy

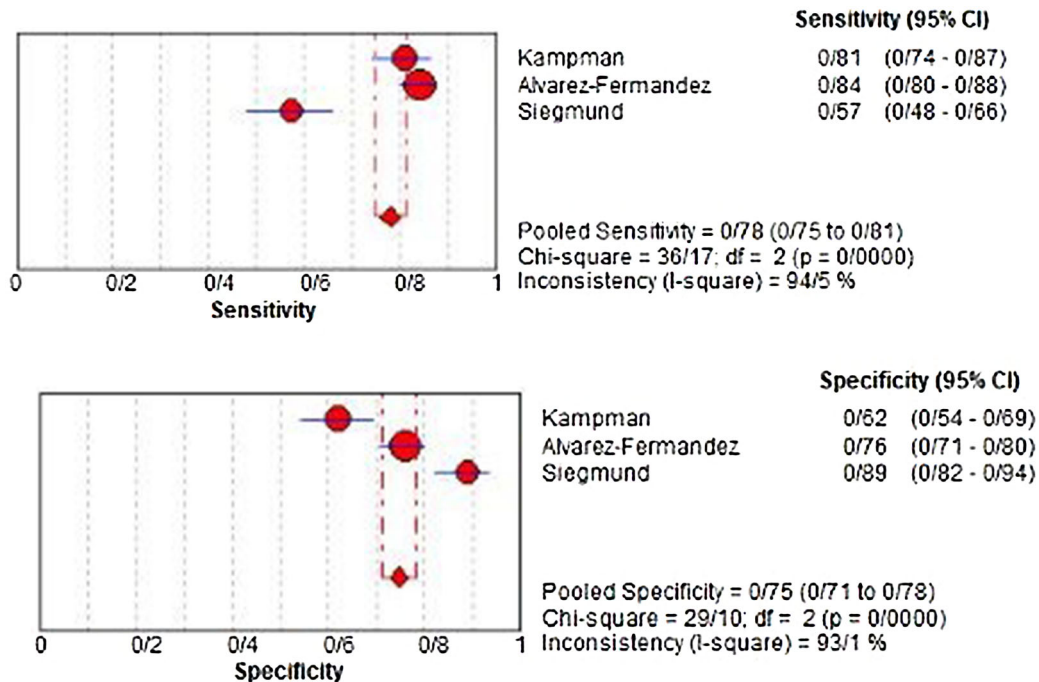


Fig. 3 Sensitivity (a) and specificity (b) of NT-proBNP in diagnosing cardiac complications in pregnancy

within the threshold of 100–500 ng/L were calculated to be 0.98 (95% CI 0.90–0.99), 0.92 (95% CI 0.83–0.95), 97% and 92%, respectively. Since only one study reported data for BNP at a threshold of ≥ 500 ng/L, this interval could not be analyzed in our meta-analysis; however, the sensitivity was more likely to decrease as the threshold increased (Table 3).

The Overall Mean NT-proBNP Levels

The overall mean NT-proBNP value was calculated to be 272.6 among women who developed pre-eclampsia compared to 72.3 among healthy pregnant women (Table 4). All included studies reported a significant correlation between high levels of NT-proBNP and the development of pre-eclampsia.

Diagnostic Accuracy of BNP According to Country

The best overall sensitivity of BNP for diagnosing cardiac complications during pregnancy was reported by Canadian authors (100%),

while the least sensitivity was reported in a study from China (88%). Specificity was the best in an Indian study (92%). However, an American study reported a specificity of 62% (Fig. 6).

DISCUSSION

The aim of this systematic review and meta-analysis was to examine the diagnostic accuracy of different BNP levels in the evaluation of pregnant and recently-delivered women with suspected cardiac failure. Women with cardiac disorders have higher BNP levels during their pregnancy compared to their non-pregnant counterparts, which may indicate an incomplete adaptation to the hemodynamic load of pregnancy. Pregnancy and physical exercise have a number of common characteristics in terms of hemodynamic alterations. Higher levels of BNP in non-pregnant women with underlying cardiac disease can be associated with some forms of latent ventricular dysfunction. However, this increase might only occur during physical exercise [21, 22], with the higher levels of BNP possibly indicative of

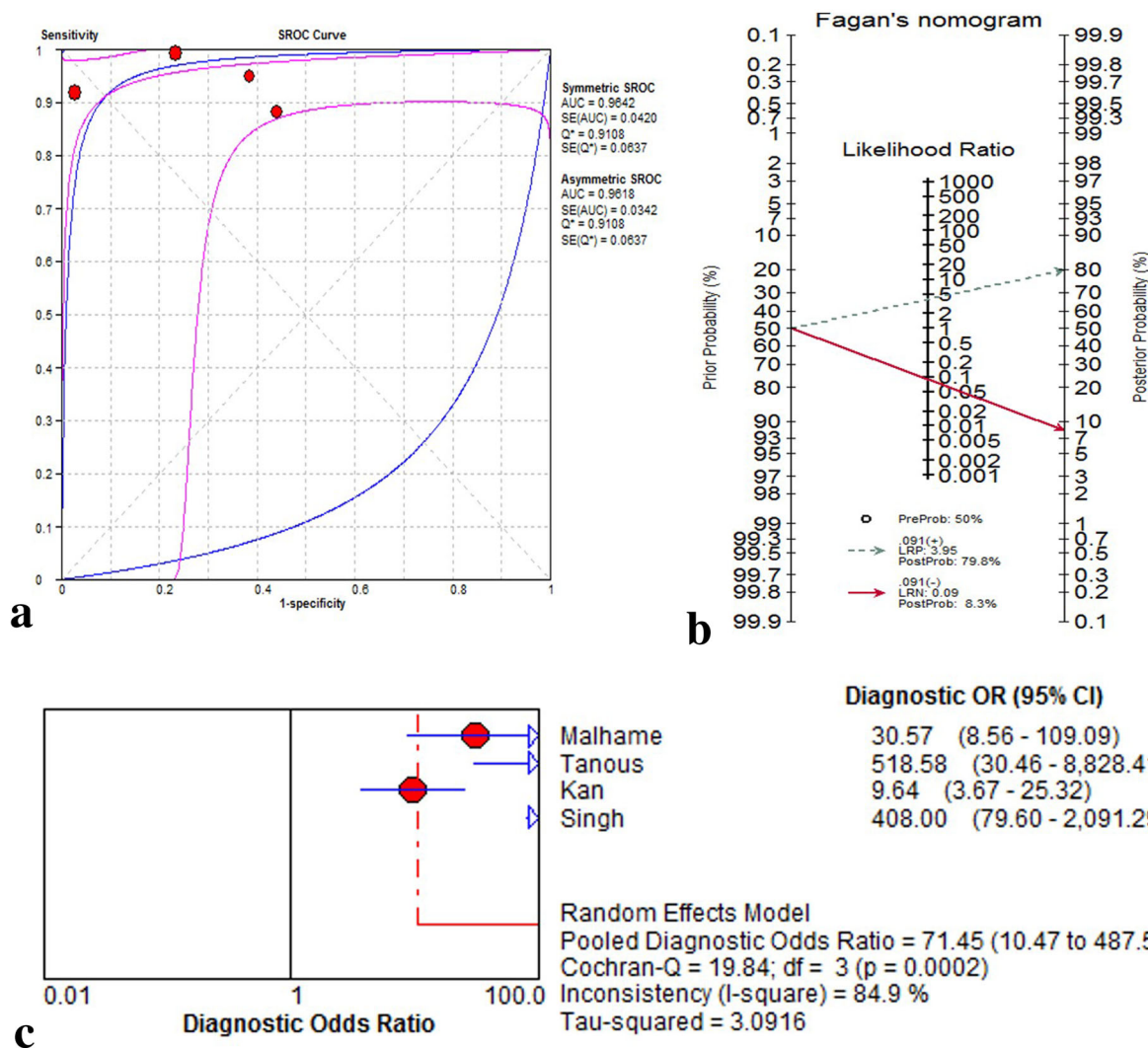


Fig. 4 Summary receiver (SROC) curve for B-Type natriuretic peptide in diagnosing Cardiac Complications in pregnancy (a). Fagan's nomogram for the calculation of post-test probabilities. A pre-test probability of 50% for diagnostic tool was fixed, which was estimated by the

number of symptomatic cases in selected studies. BNP had a post-test probability of 69.4% (b). Diagnostic odds ratio for B- natriuretic peptide in diagnosing Cardiac Complications in pregnancy (c)

subclinical disorders that present only with physical stress [23, 24]. This increase is paralleled by the increase in the mass of the left ventricular (LV) wall and the dimensions of the LV chamber [25, 26]. However, healthy women can generally compensate for the increased volume that occurs during pregnancy and have stable levels of BNP during their pregnancy [27, 28]. Increased levels of BNP during pregnancy, a physiological state that is associated

with volume overload and subsequent ventricular dilatation, can to some extent explain the mechanism which causes clinical deterioration. There is some evidence suggesting that pregnancy has a detrimental effect on the normal course of the cardiac disorder in women with LV systolic function [29] and may subsequently affect the performance of ventricles [30, 31]. Five related studies were included in this meta-analysis. Although these results were not

Table 2 Meta-analysis of accuracy of N-terminal pro-brain-type natriuretic peptide for diagnosing cardiac complications in pregnancy

Author/year	Positive predictive value (%)	Negative predictive value (%)	Specificity (%)	Sensitivity (%)	Mean—control (pg/mL)	Mean NT level—case (pg/mL)	Time of evaluation	Cutoff point (pg/mL)	Sample size (n)	Prevalence of complication (%)
Kampman/2014 [49]	18.3	96.9	61.8	81.3	100	173	20 weeks	128	169	10.3
Álvarez-Fernández/2016 [44]	N/A	N/A	76	84	N/A	N/A	N/A	219	340	N/A
Siegmund/2021 [50]	23.5	97.2	89.1	57.1	95	301	12 week	235 ng/mL	126	5.6
Overall	20.5	97	74	78	97.5	237	—	—	—	7.8

N/A Not available

consistent across all of the pooled results, the diagnostic performance of BNP in diagnosing cardiac complications showed a pooled sensitivity of 94% (95% CI of 0.91–0.97) and a pooled specificity of 75% (95% CI 0.69–0.80), as well as an AUC (\pm SD) value of 0.7991 ± 0.0164 . The sensitivity of BNP in detecting heart failure in the general population has been reported to be about 0.70, indicating the potential capacity of BNP to be used to diagnose heart failure [32].

The results of this systematic review and meta-analysis are comparable to those of other studies on non-pregnant populations [33, 34]. In the landmark study “Breathing Not Properly”, which evaluated BNP in patients presenting with acute dyspnea, the authors stated that BNP levels at a cutoff value of 100 pg/mL had a sensitivity of 90% (95% CI of 88–92) and an accuracy of 83% [33]. Therefore, when BNP was employed in the obstetric population, it was at least at the same levels of sensitivity and accuracy as in the non-pregnant population. Although the baseline levels of BNP were higher among pregnant and newly-delivered women [23, 35, 36], the cutoff values of BNP appeared to be relatively similar to those used in the non-pregnant population [33]. Thus, measuring the level of BNP might improve decision-making in terms of best management of the patient. Clinicians can test the level of BNP to detect the physiological signs of pregnancy along with early signs of cardiac failure. Assuming a 94% sensitivity and a 0.091 negative LR, a negative BNP test can be used to help prevent heart failure. Malhamé et al. argued that, assuming a positive LR of > 2 for BNP, a positive test may indicate the need for additional cardiac imaging [37]. The positive LR in this meta-analysis was calculated to be 3.95. The safest cutoff value used, in light of the findings of Malhamé et al., was 78 pg/mL, which can maximize sensitivity at the cost of lowering specificity.

Our results indicate a partially better sensitivity and specificity for BNP in comparison with NT-proBNP, which is consistent with the results reported by Hill et al. who compared the diagnostic accuracy of these biomarkers for the diagnosis of heart failure in the emergency department [37]. Some of the included studies

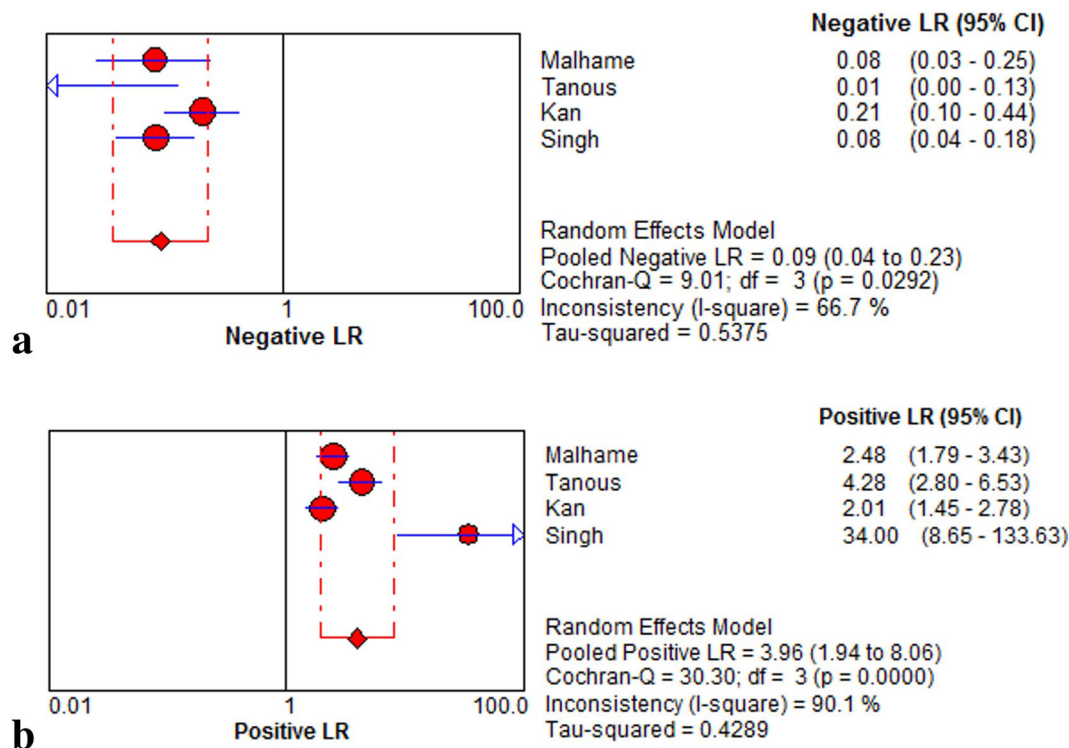


Fig. 5 Negative LR (a) and positive LR (b) of B-Type Natriuretic Peptide in diagnosing cardiac complications in pregnancy

Table 3 Meta-analysis of accuracy of brain-type natriuretic peptide in diagnosing cardiac complications in pregnancy

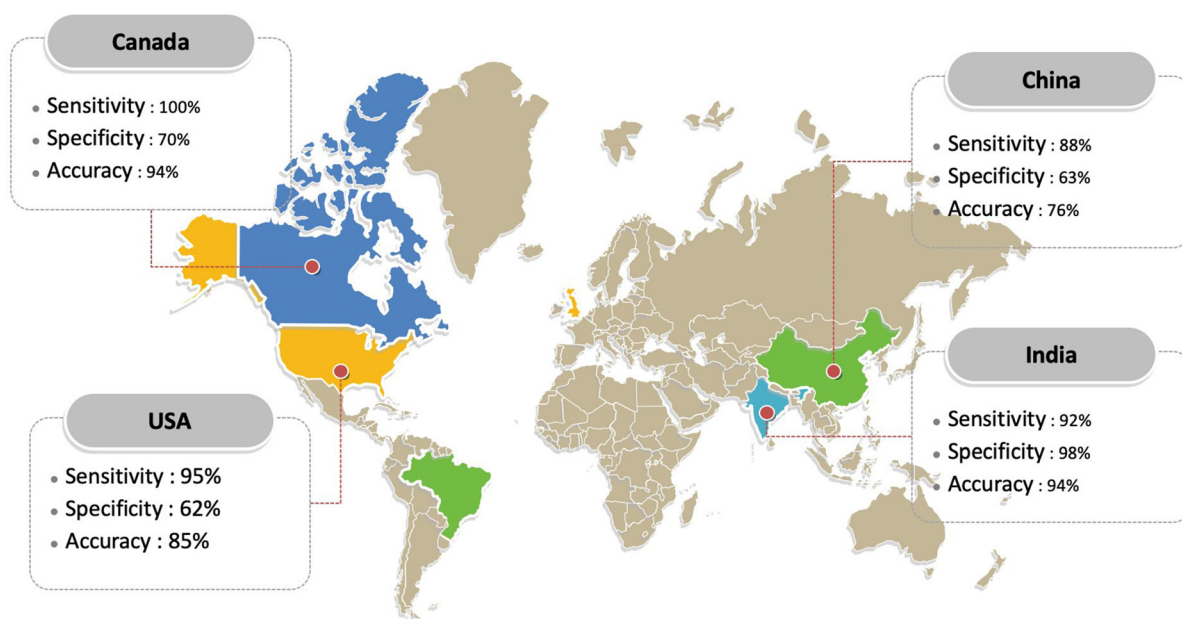
Parameter	All (95% CI)	cutoff ≤ 100 ng/L (95% CI)	cutoff 100–500 ng/L (95% CI)	≥ 500 ng/L (95% CI)	Prospective (95% CI)
Sensitivity (95% CI)	94% (0.91–0.97)	95% (0.86–0.99)	92% (0.83–0.95)	88% (0.77–0.95)	94% (0.89–0.96)
Specificity (95% CI)	75% (0.69–0.80)	62% (0.48–0.74)	98% (0.90–0.99)	63% (0.50–0.76)	80% (0.74–0.850)
PLR (95% CI)	3.95 (1.94–8.06)	2.47 (1.78–3.43)	34.0 (8.65–133.63)	2.40 (1.70–3.40)	5.63 (1.96–16.17)
NLR (95% CI)	0.09 (0.036–0.23)	0.081 (0.026–0.249)	0.08 (0.03–133.63)	0.18 (0.08–0.37)	8% (0.02–0.28)
DOR (95% CI)	71.44 (10.46–487.5)	30.56 (8.56–109.09)	408.00 (79.59–2091.3)	13.07 (5.07–33.71)	120.21 (7.26–1990)
PPV	80%	71%	97%	71%	83%
NPV	93%	92%	92%	84%	93%
Accuracy	85%	78.3%	94%	76%	87%
AUC-SROC	0.9842	0.9845	0.9867	0.9819	0.9854
I ²	76.9%	84.1%	85.6%	94%	81%

AUC-SROC Area under the curve-summary receiver operating characteristic curve, CI confidence interval, DOR diagnostic odds ratio, NLR negative likelihood ratio, NPV negative predictive value, PLR positive likelihood ratio, PPV positive predictive value

Table 4 Meta-analysis of mean levels of N-terminal pro-brain-type natriuretic peptide in association with pre-eclampsia

First author/year of publication	Sample size (<i>n</i>)	Mean—case (pg/mL)	Mean—control (pg/mL)
Hafiz/2021 [42]	60	673.50 ± 486.86	262.75 ± 457.04
Moghbeli/2010 [43]	63	197	58
Fernández/2016 [44]	340	169	34
Junus/2014 [45]	74	365	48
Giannubilo/2017 [46]	98	121.2 ± 26.3	42.5 ± 11.4
Bakacak/2015 [34]	76	110	37
Overall mean ¹	–	272.6	80.3

Values are presented as the mean (± SD where available)

**Fig. 6** Pooled sensitivity, specificity and accuracy for B-Type Natriuretic Peptide in diagnosing cardiac complications in pregnancy

indicated that when interpreting BNP levels in patients with pre-eclampsia, it is important to consider that BNP levels can be increased by hypertension, even if there are no signs of cardiac failure [23, 34, 39, 40]. However, it has been suggested that the increase in BNP level is clinically dependent on the degree of clinical and non-clinically detectable ventricular abnormalities and the inherited state of pre-eclampsia [34, 38]. All of our included studies

which evaluated NT-proBNP levels reported a significant correlation between the levels of this biomarker and the development of pre-eclampsia [42–47].

Tanous et al. found levels of BNP indicative of cardiac failure in 38% of pregnant women with underlying cardiac conditions [48]. These authors also reported that many of these women presented no signs of cardiac decompensation. Despite being inconclusive, this

reaction might be a sign of limited cardiac reserve. In addition, the levels of BNP were higher in pregnant patients with underlying cardiac disease than the healthy women. However, there was no significant difference between these levels in patients with and without clinical events [48]. These results indicate that these women, especially those who have elevated levels of BNP during their pregnancy, should maintain post-pregnancy care. Early detection of deterioration in such conditions, before any acute events occur, is of great importance in patients with underlying cardiac conditions, since both the mother and fetus will be endangered by acute conditions and the options for treating the patient can be limited due to pregnancy status. As early diagnosis is highly critical in such cases, studies have focused on risk stratification through prenatal and clinical echocardiographic variables [41, 42]. However, few studies have evaluated the application of biomarkers or other measurements capable of determining the adaptability of the heart with the hemodynamic load of pregnancy.

There are several limitations to our study which need to be addressed. First, as there were an insufficient number of studies that evaluated the diagnostic accuracy of both BNP and NT-proBNP in the same population, we had to include different studies with different samples, which could cause heterogeneity. Secondly, only three studies evaluated NT-proBNP, and each of these considered a different cutoff value which affected the accuracy of our pooled measurements. Thirdly, the studies investigating pre-eclampsia did not provide any data on the diagnostic accuracy of NT-proBNP and only reported the mean values.

CONCLUSION

In summary, the results of our study suggest that BNP as well as NT-proBNP levels can be used as a diagnostic tool among pregnant and newly-delivered women to diagnose cardiac complications, including heart failure and pre-eclampsia. BNP showed a relatively better diagnostic accuracy than NT-proBNP, but it should

be considered that the number of included studies evaluating NT-proBNP was low and the studies were inconsistent in terms of cutoff value. Further studies are required to confirm the prospective use of BNP and NT-proBNP for assessing common symptoms that indicate cardiac complications during labor. Moreover, the clinical use of the NT-proBNP test in this field requires further study.

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Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Disclosures. Mahboobeh Sheikh, Pouya Ostadrahimi, Morteza Salarzai and Fateme Parooie have nothing to disclose.

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Author Contributions. MSH and POR participated in the conception and design of the study, library searches and assembling relevant literature, critical review of the paper, supervising writing of the paper and database management. MS and FP participated in data collection, library searches and assembling relevant literature, writing the paper and critical review of the paper.

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