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ORIGINAL ARTICLE

The clinical value of hepatojugular reflux on congestive heart failure: A meta-analysis

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Abstract

Background: Hepatojugular reflux is a cardiac physical examination with a long history of use in heart failure diagnosis across many clinical settings. However, the development of new diagnostic methods has thrown the clinical role of hepatojugular reflux into question. Our meta-analysis aimed to determine the diagnostic accuracy of hepatojugular reflux and assess its usefulness in diagnosing congestive heart failure among at-risk patients.

Methods: This meta-analysis of studies reporting diagnostic hepatojugular reflux values of patients at risk for congestive heart failure followed PRISMA guidelines. We searched MEDLINE, EMBASE, Web of Science, CENTRAL, and Google Scholar for eligible studies from inception through February 1, 2021. After QUADAS-2 quality assessment, we conducted data synthesis using the random effects model and a hierarchical summary receiver operating characteristic model. As an additional analysis, we sorted the studies by clinical setting and performed synthesis again. We submitted our protocol to PROSPERO (International Prospective Register of Systematic Reviews; ID No. CRD42020215004).

Results: The literature search provided 4121 studies for evaluation. Seven studies and their 5195 participants were deemed eligible for synthesis. Clinical diagnosis was the most frequent reference standard. Bivariate random-effects analysis found hepatojugular reflux sensitivity of 0.12, 95% confidence interval (CI) [0.07–0.19], and specificity of 0.96, 95% CI [0.95–0.97]. The DOR was 29.7, 95% CI [18.4–45.3]. The additional analysis of the emergency settings provided a sensitivity of 0.14, 95% CI [0.12–0.17] and specificity of 0.95, 95% CI [0.93–0.96].

Conclusions: Our meta-analysis suggests that hepatojugular reflux has practical value for diagnosis of congestive heart failure with high specificity.

KEYWORDS
congestive heart failure, diagnostic meta-analysis, hepatojugular reflux, physical examination

(Ms. Ikehara has not tile).

1 | INTRODUCTION

Hepatojugular reflux (HJR) was first described by W. Pasteur (1885), and it remains one of the most common physical exanimations used in diagnosing heart failure.[1,2] Defined as a jugular venous pressure (JVP) increase >3 cm lasting more than 15 s upon abdominal compression, HJR suggests that the right ventricle is not accommodating the increased venous return. HJR differs from other cardiac physical examinations in its high positive likelihood ratio and specificity for heart failure. Marantz et al.[3] reported that HJR has a low sensitivity of 0.24 and high specificity of 0.96 for congestive heart failure (CHF) in 1990. Despite the many advances in the field of CHF diagnosis, HJR remains on some lists of clinical heart failure diagnostic criteria, such as the Framingham Diagnostic Criteria.[4]

CHF continues to hospitalize vast numbers of patients worldwide despite modern developments in medical therapy.[5,6] The world hospitalizes more than 37.7 million patients for CHF annually, with 1 million hospitalizations occurring in the United States.[7,8] Given the vast number of patients, CHF diagnosis and treatment involves cardiologists, internists, emergency and family physicians, and other clinicians who may confirm CHF based on a positive HJR sign.

Despite its long history, there is a paucity of robust evidence supporting the clinical value of HJR in the modern clinical context. Advances in diagnostic equipment and methodology have led to declines in cardiac examination skills.[9] Moreover, many studies supporting HJR have had serious limitations in terms of methodological quality and statistical power. Many key HJR studies, including Marantz et al.,[3] were conducted over 30 years ago with fewer than 50 participants. Although Martindale et al.[10] conducted a meta-analysis, reporting HJR sensitivity of 0.14 and specificity of 0.93, limitations in their methodology may constrain the generalizability of their results, in particular to non-emergency patients. Crucially, their literature search covered 20 cardiac diagnostic topics, rather than focusing on HJR, only four studies were eligible for synthesis, and they did not provide quality assessment specified to HJR or publication bias assessment results. We believe that some studies potentially appropriate for meta-synthesis remained uninspected. Furthermore, given that there is no non-invasive universal gold standard for diagnosing all types of heart failure, a meta-analysis should ideally have a statistical method for handling heterogeneity and imperfect reference standards. Thus, previous studies have not clearly established the clinical diagnostic value of HJR, because of methodological issues such as using narrow literature searches, reporting the results of single-center studies, and failing to account for heterogeneity.

In the present meta-analysis, we conducted a comprehensive systematic literature search in order to confidently evaluate the diagnostic value of HJR on CHF. In addition to standard analysis using a bivariate random-effects model, we implemented a Bayesian hierarchical model analysis to support the main analysis, enabling us to produce more robust estimates of diagnostic values of HJR for CHF while coping with heterogeneity.[11] Through this research, we hope to emphasize the importance of physical examinations, especially for primary care physicians or nurse practitioners in clinical situations when access to diagnostic testing equipment is limited.

2 | METHODS

We submitted our study protocol to PROSPERO (the International Prospective Register of Systematic Reviews, ID No. CRD42020215004) on 11 December 2020.[12] We followed the guidelines of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) Diagnostic Test Accuracy (DTA) statement[13] (Table S1).

2.1 | Inclusion and exclusion criteria

Studies were selected for analysis based on the following criteria: (1) original studies assessing HJR as an index test and providing sufficient data to fill two-by-two tables (true-positive, false-positive, true-negative, and false-negative) for diagnosis of CHF or heart failure; (2) study types including clinical trials, cross-sectional, case–control, cohort, or diagnostic studies, which were performed to confirm CHF or heart failure; (3) reference standards including clinical criteria or clinical assessment; and (4) patients with dyspnea or suspected heart failure in any clinical setting. We defined CHF as heart failure necessitating hospitalization, oxygenation, and diuretics, whereas we excluded studies whose target disease was any other type of heart failure such as ischemic or valvar. Our study outcome measures were true-positive, false-positive, true-negative, and false-negative rates. If an eligible study showed only the diagnostic values such as sensitivity and specificity instead of true-positive, false-positive, true-negative, and false-negative rates, we calculated the true-positive, false-positive, true-negative, and false-negative rates and used them for synthesis.

Studies were excluded if they were deemed potential sources of bias, based on the following criteria: (1) studies where CHF or heart failure is not the primary disease; (2) studies using only a single non-universal test as a reference standard; (3) studies with sample sizes of 10 or fewer (such as case reports, case series), review studies, letters, editorials, gray literature, duplicate or series publications, non-diagnostic studies, or non-human studies; (4) studies using HJR as both an index and reference standard; (5) studies duplicating data from the same patient cohort; (6) studies deemed to be potential sources of bias in our diagnostic meta-analysis and lacking in appropriate scientific rigor; and (7) studies in languages other than English.

2.2 | Systemic literature search method

We conducted a literature search with MEDLINE (PubMed), EMBASE, Web of Science, and CENTRAL from inception through February 1, 2021, followed by a manual search using Google Scholar. We tried to contact authors for further information. Librarians in the academic

information center at the Jikei University School of Medicine provided support. Search terms were a combination of HJR diagnostic terms and heart failure or CHF, including their thesaurus matches. Two independent teams performed the first screening. We excluded languages other than English in order to precisely perform quality assessment.[14] While our research target is CHF, many studies use the terms heart failure and CHF interchangeably. Next, we did full text reviews. Discrepancies of inclusion or exclusion were resolved by all authors. No studies were excluded for improper reference standards.

2.3 | Quality assessment with QUADAS-2

We implemented a quality assessment of the remaining articles with Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2), assessing applicability and risk of bias.[15] For data synthesis, there were various clinical reference standards for diagnosis of heart failure. If each study's method for diagnosing heart failure was deemed valid clinically by the authors, we defined them as the same reference standard. We attempted to contact all authors whose studies had unclear points.

2.4 | Statistical methods

We performed bivariate random-effects analysis using the Reitsma method, producing sensitivity, specificity, diagnostic odds ratio (DOR), positive likelihood ratio, and negative likelihood ratio.[16,17] DOR, positive likelihood ratio, and negative likelihood ratio were also calculated with the DerSimonian-Laird random-effects model.[18,19] Diagnostic area under the curve (AUC) was also calculated.[20] We plotted the hierarchal area under the curve (HSROC) showing the 95% confidence region and 95% predictive region.[17,21] For additional analysis, we sorted the eligible studies by clinical setting and reported the diagnostic values for each setting. If any clinical setting had more than 3 studies, we conducted analysis again. Further, we conducted a sensitivity analysis using a set of studies of which more than half were determined to have low risk of bias on quality analysis.

We performed data synthesis with STATA version 15.0 [StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC] and R version 3.5.2 [R Core Team (2020). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/]. Quality assessment was performed with Review Manager.

(RevMan) [Computer program]. Version 5.4. The Cochrane Collaboration, 2020.

2.5 | Bias and heterogeneity assessment

Bias assessment was performed using QUADAS-2. Although publication bias is the most well-known meta-analysis bias, the methodology for detecting publication bias is not well settled. Lin et al.[22] suggested applying multiple tests for publication bias, and thus we evaluated publication bias with Begg's, Egger's, and Deeks' tests, as well as by visual assessment.[20,23] Deeks' test was calculated by plotting the ln (DOR) against 1/effective sample size (ESS)1/2 and testing for asymmetry of this plot. The ESS can mitigate the effects of unequal total numbers of disease and non-disease participants. In contrast, Begg's method uses rank correlation of lnDOR with the variance of the lnDOR and Egger's method uses a linear regression model with lnDOR with the standard error of the lnDOR weighted by the inverse variance of the lnDOR.[24] Heterogeneity analysis was conducted using the I^2 method, describing the percentage of total variation across studies attributable to the heterogeneity.[20,25]

3 | RESULTS

The study selection process is shown in Figure 1. There were 4121 potentially eligible articles after removing obvious duplications. We added 10 articles through a manual Google Scholar search. Title and abstract screening excluded 3954 articles. Among the remaining 167 articles, 160 were ineligible for the following reasons: insufficient data, not using original data, series publications, primary disease not heart failure or CHF, and inappropriate comparison of differing severities of heart failure. Finally, 7 studies were eligible for quality assessment. We implemented QUADAS-2 to assess the risk of bias and applicability (Figure S1). Four of the studies [ID 1, 3–5] were determined to have low risk of bias, consistent with studies conducted in emergency settings. The other three studies did not have high-risk concerns, despite having inconclusive quality analysis results overall. Thus, over half of the studies included had low risk of bias. As a result, 7 studies were included in our meta-analysis.[3,26–31]

The characteristics and results of individual studies are shown in Table 1. There are some differences among the 7 studies, which were published between 1990 and 2015. Three of the studies were prospective. Designs ranged from including cross-sectional to case–control. The clinical setting was emergency care in four studies, primary care in three studies, and a nursing home in one study. Average participant age ranged from 64 to 82. Sensitivity ranged from 0.04 to 0.20, and specificity ranged 0.94 to 0.99. DOR ranged from 0.87 to 30.0. The studies included 2291 and 2904 total disease and non-disease participants, respectively.

We performed synthesis using 7 studies, ID numbers 1–7. The results for HJR are shown in Table 2.

The bivariate random effects model with Reitsma analysis found sensitivity of 0.12, 95% CI[0.07–0.19] and specificity of 0.96 95% CI [0.95–0.97]. The AUC was 0.93 95% CI [0.90–0.97]. The DerSimonian and Laird random effects model produced a mean DOR of 29.7, 95% CI [18.4–45.3], a mean positive likelihood of 4.06 95% CI [3.26–4.99], and a mean negative likelihood of 0.15 95% CI [0.08–0.23].

We found studies conducted in three different clinical settings. Among the four studies conducted in the emergency setting, mean

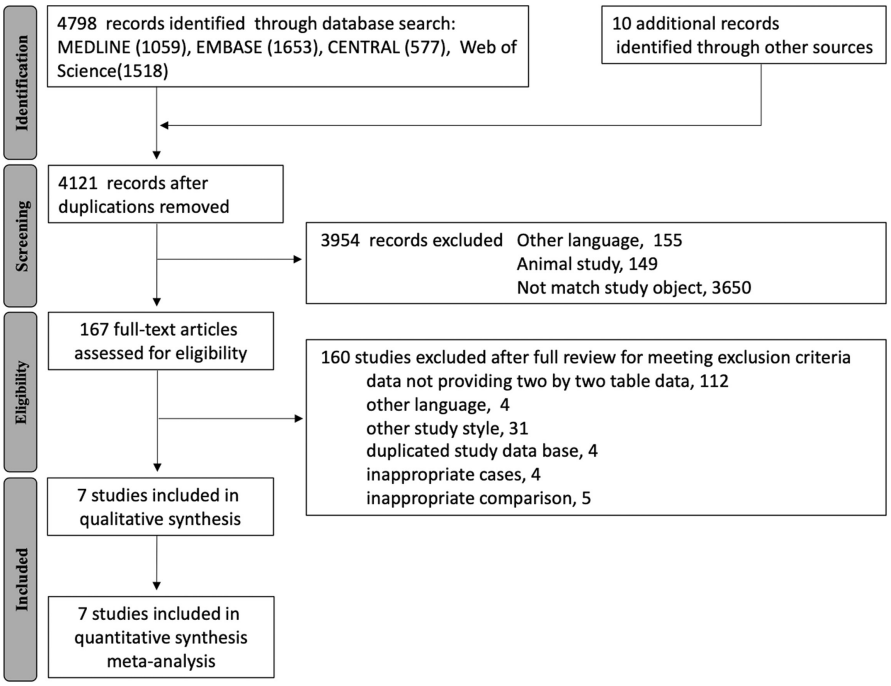

FIGURE 1 PRISMA literature search flowchart. We show a flowchart depicting our literature search, based on the PRISMA flowchart. After quality assessment with QUADAS-2, seven studies were eligible for the synthesis

sensitivity and specificity ranged from 0.12 to 0.24, and from 0.94 to 0.96., respectively. Two studies were conducted in the primary care setting, and their mean sensitivity and specificity were 0.04–0.29 and 0.95–0.99, respectively. A single study was conducted in a nursing home setting, and its mean sensitivity and specificity were 0.06 and 0.95, respectively. Because there were 4 studies conducted in the emergency setting, we conducted analysis again, though we did not create a HSROC model in the "metandi" package, owing to the small number of studies. The bivariate random effects model with Reitsma analysis found sensitivity of 0.14, 95% CI [0.12–0.17] and specificity of 0.95 95% CI [0.93–0.96]. The AUC was 0.68, 95% CI [0.64–0.72]. The DerSimonian and Laird random effects model produced a mean DOR of 3.16, 95% CI [2.08–4.79], a mean positive likelihood of 3.00 95% CI [1.50–5.90], and a mean negative likelihood of 0.92 95% CI [0.85–0.99] [Figure 2].

4 | DISCUSSION

In the present study, we systematically reviewed previous research to assess the diagnostic accuracy of HJR on CHF using a combination of statistical methods, finding high specificity and low sensitivity. Our results suggest that clinicians should strongly suspect CHF based on a positive HJR sign.

Our meta-analysis supports the high specificity of HJR and its practical use as a physical examination for the diagnosis of CHF. The high specificity is consonant with HJR's pathophysiologic mechanism. Added abdominal pressure generates negative intrathoracic pressure, increasing venous return to the right atrium and ventricle. This leads to decreased JVP in healthy adults; in contrast, obstruction of flow in the right-sided chambers increases JVP in patients with right ventricular failure.[32] A positive HJR test reflects increased pulmonary artery wedge pressure (PCWP), suggesting CHF.[33] Conversely, the low sensitivity of HJR implies that negative HJR cannot screen out CHF, probably because HJR does not directly test left ventricular pressure. Even PCWP measured with right heart catheterization provides an indirect estimate of left atrial pressure. In mild-to-moderate left-sided heart failure, the right-sided chambers may remain unaffected, resulting in a negative HJR sign, which may explain the low sensitivity of HJR for CHF.

Our results are consistent with previous studies reporting HJR diagnostic values, and are likely robust for the following reasons.[3,10] Firstly, our systematic literature search focused on HJR and CHF, and was conducted with the assistance of an experienced health sciences librarian who applied systematic search terms. Secondly, all eligible studies showed high specificity and low sensitivity in a small range. Thirdly, clinical assessment is a suitable reference standard because there is no non-invasive universal gold standard test to diagnose heart failure. All reference standards in our eligible studies were clinical criteria or clinical assessment, rather than a single test.

Furthermore, our analyses provided the HSROC curve shown in Figure 2. The HSROC model provided confidence and prediction intervals. Our prediction area was in a small range, supporting the robustness of our estimation. The Reitsma bivariate random model is feasible for estimating summary diagnostic values, such as sensitivity and specificity. On the other hand, the HSROC model is suitable for SROC curve estimation to evaluate test accuracy and for evaluating how the curve's position and shape vary in order to address between-study variability.[11]

In the HSROC model, the confidence region and prediction region are used to describe uncertainty about summary sensitivity and specificity. The confidence region shows the summary estimates of sensitivity and specificity jointly in the HSROC space while also

TABLE 1 The characteristics and data of the 7 studies eligible for synthesis

ID	Year	Author	Country	Prospective or not	Study type	Disease	Study population	Index test	Reference standard	Age	Participants	CHF	Non-CHF	TP	FP	FN	TN	Sensitivity	Specificity	DOR
1	1990	Marantz et al.	US	NR	NR	CHF	Emergency patients with dyspnea	HJR	Clinical criteria	64	48	21	27	5	1	16	26	0.24	0.96	8.13
2	2004	Fonseca et al.	Portugal	NR	CS	HF	Primary care patients	HJR	Clinical	68	318	14	304	4	4	10	300	0.29	0.99	30.0
3	2005	Mueller et al.	Switzerland	Pros	NR	CHF	Emergency patients with dyspnea	HJR	Clinical	71	452	217	235	34	15	183	220	0.16	0.94	2.72
4	2005	Steg et al.	US, France, Norway	Pros	NR	CHF	Emergency patients with dyspnea	HJR	Clinical	66.4	709	492	217	68	10	424	207	0.14	0.95	3.32
5	2010	Potocki et al.	Switzerland	Pros	NR	HF	Emergency patients with dyspnea	HJR	Clinical	77	287	154	133	18	5	136	128	0.12	0.96	3.39
6	2014	Vijayakrishnan et al.	US	Retro	CC	HF	Primary care patients	HJR	Clinical criteria	70.7	2880	1227	1653	54	83	1173	1570	0.04	0.95	0.87
7	2015	Daamen et al.	Netherlands	NR	CS	HF	Nursing home residents	HJR	Clinical	82	501	166	335	10	16	156	319	0.06	0.95	1.28

Abbreviations: CC, case–control; CHF, congestive heart failure; CS, cross-sectional; DOR, diagnostic odds ratio; FN, false negative; FP, false positive; HF, heart failure; NR, not reported; Pros, prospective; Retro, retrospective; TN, true negative; TP, true positive.

addressing their inverse association based on the included studies. However, the confidence region does not show between-study heterogeneity.[11,34] In contrast, the prediction region shows potential future sensitivity and specificity by describing the full extent of the summary points' uncertainty, reflecting between-study heterogeneity.[11]

Our results expand on the meta-analysis by Martindale et al.,[10] adding to the evidence for the clinical value of HJR. First, meta-analysis should be updated regularly in pursuit of more robust and precise results.[35] As of 2022, roughly 7 years has passed since Martindale et al. was published. Secondly, our analysis attempted to improve on some possible weaknesses in their methods. Martindale et al. did not select search terms focusing on HJR and was limited to emergency settings. HJR is not useful only in emergency medicine but also for outpatients, inpatients, and home care. Our literature search and quality assessment led to the inclusion of four studies in addition to the three studies in the Martindale et al. analysis. In addition, the four eligible studies in the Martindale et al. study were published from 1990 to 2010, while the seven studies in our analysis were published from 1990 to 2015. The total number of participants of HJR in Martindale et al. was about 1500, but our study included about 5000 participants. Further, our method of synthesis allowed us to better address heterogeneity among the original studies and the imperfectness of heart failure diagnosis. We also included an assessment of publication bias. Moreover, methods for coping with heterogeneity are still developing and pose a challenge for diagnostic meta-analysis. We applied some conventional methods in order to produce more reliable results. Finally, our meta-analysis may

TABLE 2 Hepatojugular reflux results of 7 eligible studies

	Mean	Standard error	95% Confidence interval
Sensitivity	0.12	0.03	0.07–0.19
Specificity	0.96	0.006	0.95–0.97
Diagnostic odds ratio (DOR)	3.28	1.23	1.57–6.85
Positive likelihood ratio	3.01	1.02	1.55–5.85
Negative likelihood ratio	0.92	0.034	0.85–0.99
Area under the curve	0.93		0.90–0.95

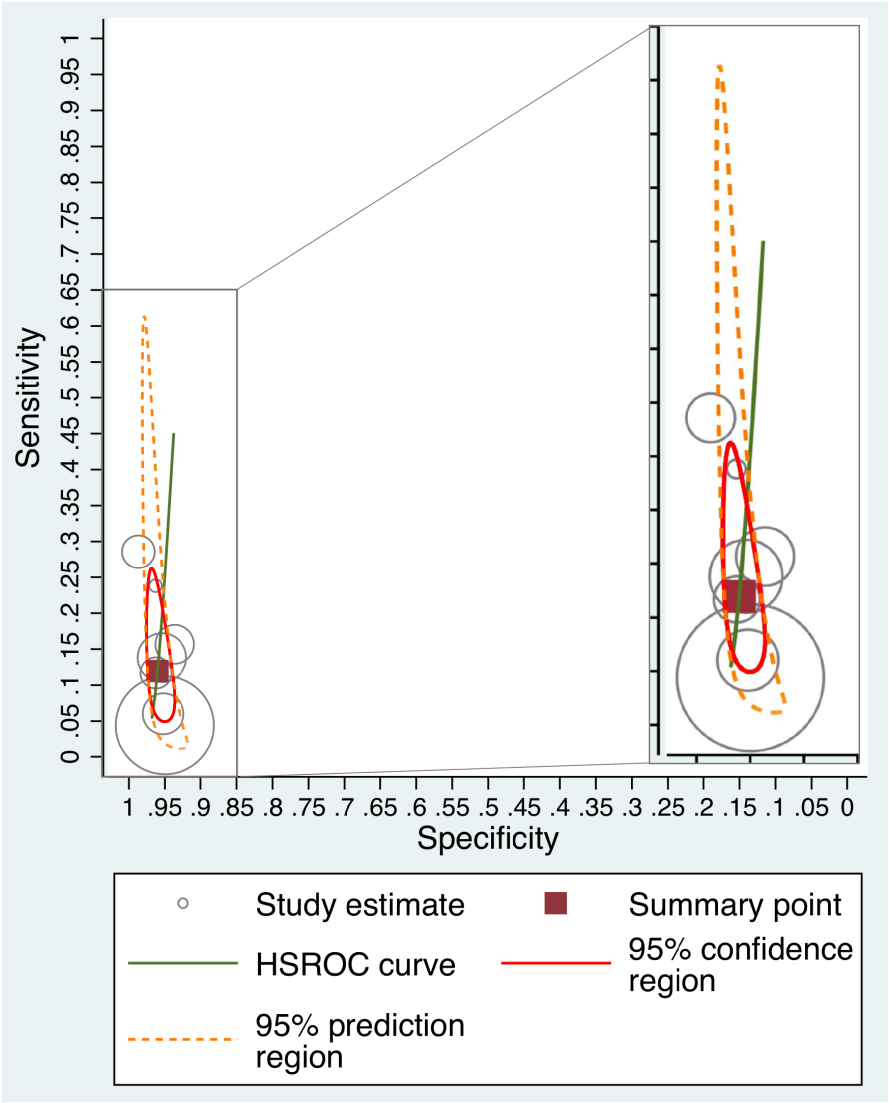

FIGURE 2 Hierarchical summary receiver operating characteristic curve (HSROC) of hepatojugular reflux on congestive heart failure. The 95% confidence and prediction region of our synthesis shows a narrow range

contribute to reassessment of the value of physical examinations in clinical practice.

Furthermore, over its long history, HJR has had a broad role in clinical practice. A recent study suggests that HJR has value as a prognostic marker for post-discharge outcomes in hospitalized patients with heart failure.[36] Another study also supports the clinical significance of HJR in that it may help assess heart failure with preserved ejection fractions.[37] Our results support the usefulness of positive HJR for confirming CHF without relying on imaging studies. HJR therefore has potential applications in a diverse range of clinical settings, where it may help reduce health expenditures while maintaining a high standard of care.

Regarding publication bias, Deeks' method produced the ESS, which makes it possible to conduct analysis while accounting for unequal total numbers of disease and non-disease participants. Our study included 2291 and 2904 disease and non-disease participants, respectively. This difference in group size may have led to a finding of publication bias via Deeks' method, which was not detected by Egger's method or Begg's method. Thus, the hypothesis that there is no publication bias cannot be rejected.

Our meta-analysis included 7 studies and 3 clinical settings: emergency, primary care, and nursing home. The differences in clinical setting caused strong heterogeneity among the included studies and may have biased our results. However, all 7 studies supported high specificity and low sensitivity. The additional synthesis of the emergency settings also supports these tendencies toward high specificity and low sensitivity. Although the diagnostic value of HJR may differ in clinical settings, we hope that HJR contributes to diagnosis of heart failure in a range of settings.

This study has more several limitations. First, we restricted our literature search to English language publications. If we had included non-English studies, additional results may have appeared. Next, because the eligible studies included various methods of heart failure diagnosis, strong heterogeneity was a concern. However, we employed the HSROC method to support our bivariate random-effects analysis and address heterogeneity among the studies. Next, while visual assessment did not reveal publication bias, and there was low statistical heterogeneity, both supporting the reliability of our results, Deeks' test implied some publication bias. However, a reliable method for assessing publication bias in diagnostic meta-analysis has not been established.[22] Moreover, there is disagreement about how to assess and respond to potential publication bias. There are still residual concerns about publication bias in our study.

5 | CONCLUSION

Our meta-analysis found high specificity for HJR, in line with previous studies, implying its usefulness in clinical practice. Evidence from our study indicates that HJR can still contribute to reliable CHF diagnosis in various clinical settings.

AUTHOR CONTRIBUTIONS

HI: conceptualization, data curation, quality assessment, formal analysis, methodology, writing original draft, YM: conceptualization, data curation, data curation, writing original draft, YI: data curation, formal analysis, writing original draft, TY: quality assessment, supervision, writing original draft, SU: data curation, conceptualization, methodology, project administration, supervision, writing original draft.

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CONFLICT OF INTEREST

HI, YM, YI, and TY do not have any competing interests related to this study. SU, A peer-reviewed project grant from Bristol Myers Squibb.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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