SUPPLEMENTAL MATERIAL:

APPENDIX 1

Evidence-based assessment of diagnostic accuracy of tissue Doppler echocardiographic index, E/e' for estimation of LV filling pressure and diastolic dysfunction/ heart failure with preserved ejection fraction.

Protocol for Systematic review and Meta-analysis study.

We will follow PRISMA guidelines [1] and Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy [2] in conducting this study.

Summary

Left ventricular Diastolic dysfunction (LVDD) causing heart failure with preserved ejection fraction (HFpEF) is a major clinical problem. Although echocardiography is recommended for noninvasive evaluation of LVDD/HFpEF and is currently routinely used in clinical practice and research, the diagnostic accuracy of echocardiographic variables is not well defined. We hypothesize that commonly utilized echocardiographic tissue Doppler index E/e' for estimating left ventricular filling pressure and diagnosis of LVDD/HFpEF is not very well validated.

Background

Target conditions being diagnosed

Diastolic dysfunction is an important cause of Heart failure (HF) with preserved ejection fraction (pEF) and a major medical and public health issue. [3–6] The diagnosis of HFpEF is more challenging than the diagnosis of HF with reduced EF because it is largely one of excluding other potential non-cardiac causes of symptoms suggestive of HF. Epidemiological studies indicate that varying severity of diastolic dysfunction is frequently present in asymptomatic population.[3] Diastolic dysfunction is predicative of developing overt heart failure and all-cause mortality. [3,4] Furthermore, there is increasing prevalence of HFpEF but no significant improvement in survival with time when compared to HF with reduced EF. [5,6]

Index tests

Echocardiography is the cornerstone for the noninvasive evaluation and quantitation of diastolic dysfunction.[7,8] Myocardial stiffness and relaxation abnormalities in diastolic dysfunction result in elevated LVFP that is indirectly evaluated by echocardiography. [7,8]

Pulsed-wave Doppler technique is performed in the apical 4-chamber view to obtain peak early (E) and late (A) mitral inflow velocities, which primarily reflect pressure gradient between the left atrium and left ventricle during early and late diastolic filling, respectively. [7] Tissue Doppler imaging (TDI) is implemented to acquire mitral annular velocities. [7,8] In conjunction with mitral peak early filling velocity E, the ratio of E/e' can be applied for the estimation of LVFP. [7] The American Society of Echocardiography (ASE) guidelines suggest that LVFP is elevated when E/e' > 12-15 (based on location) or normal when E/e' < 8. [7,8]

Reference tests

"Gold" or superior (standard) reference tests to evaluate LV diastolic function are based on invasive LV catheterization. These include LVFP measurements, LV relaxation time constant (tau) and parameters of LV myocardial and/or chamber stiffness. There are accepted cutoffs for each of invasive measurements, so that values above cutoff typically indicate elevated LVFP and/ LV diastolic dysfunction. For the LVFP, such cutoffs are LVEDP >16 mmHg or PCWP >12 mmHg; for LV myocardial wall diastolic relaxation time, it is Tau > 48 ms; for myocardial/chamber stiffness, corresponding cutoffs are based on specific parameter calculated. [7,9]

Rationale

Despite the clinical importance of mitral flow and tissue Doppler parameters in evaluating diastolic dysfunction, there is lack of rigorous evaluation of their diagnostic accuracy when compared to invasive standards. Apart from routine clinical use, these echocardiographic indices are extensively used in clinical trials and applied research to assess the changes in LV diastolic function or LVFP. [10–12] We therefore decided to evaluate diagnostic accuracy and clinical utility of E/e' in prediction LVFP and/or HFpEF.

Objectives

1. To perform a search of publications in medical scientific journals evaluating clinical evidence of the relationship between echocardiographic E/e' and LV filling pressure, LV relaxation time constant or LV myocardium/chamber stiffness in preserved ejection fraction. We consider the invasive measurements of LV diastolic function as a reference test.
2. To summarize the clinical evidences/ diagnostic accuracy of echocardiographic E/e' for estimating LV filling pressure and the diagnosis of LVDD/HFpEF.

Methods

Study search methodology:

Original clinical studies that evaluate invasive parameters of diastolic function including LVFP and echocardiographic tissue Doppler E/e' index at rest in patient cohorts with preserved ejection fraction will be screened and analyzed from PubMed, Scopus, Embase, and Cochrane databases (Figure 1). We will also review bibliography of important papers based on our clinical experience and book monographs. Only human medical studies published in English will be analyzed.

Search strategy:

We will develop the optimal search strategy for each library with assistance of UAB Reference Service of the UAB Lister Hill medical library.

Inclusion criteria for the studies:

The studies will be included if the study methodology stated that participants have preserved/normal LVEF (LVEF ≥40 %). For studies with mixed groups or studies with no a priori criteria for normal LVEF, the studies will be included if the dataset for LVEF corresponding to Mean-2SD ≥40 % is available or can be extracted. For a normal distribution, the latter condition assumes that about 98 % of participants have LVEF ≥ 40%. This approach allows for inclusion of all clinically relevant studies since LVEF threshold between 40-50% is typically used to distinguish normal/ preserved LVEF from reduced LVEF group. However the inclusion of studies for primary and secondary analysis will be based on the outline described in the statistical section.

Exclusion criteria for studies:

Studies will be excluded if the study group has >10% of patients with moderate to severe valvular heart disease, cardiomyopathy (hypertrophic, restrictive), age < 18 years, congenital heart disease, acute coronary syndrome, septic shock, cardiac transplant, significant arrhythmias that precluded from interpretation of index and / or reference test and less than 10 participants with preserved EF. Studies will be excluded if study reference tests are only based on non-invasive criteria of LVDD/HFpEF.

Index tests:

Ratio of echocardiographic mitral flow and tissue Doppler derived parameter- $E/e'_{lateral}$, E/e'_{septal} or E/e'_{mean}.

Reference tests:

Invasive LVFP measurements of LV end diastolic pressure (LVEDP), LV mean diastolic pressure (LVMDP), LV Pre-A diastolic pressure (LV pre-A DP) or pulmonary capillary wedge pressure (PCWP); LV relaxation time constant (Tau); LV stiffness parameters.

Clinical diagnosis of LVDD/HFpEF confirmed based on clinical sign and symptoms with evidence of elevated LVFP or impaired LV relaxation/ chamber stiffness with or without additional biochemical markers and/or other ancillary tests.

Data collection and analysis:

Selection of studies:

Studies will be screened from the list of citation pooled from PubMed, Scopus, Embase, and Cochrane databases based on search criteria. Other sources would also be evaluated for additional studies. Initial screening includes the analysis of the title and abstract of the cited study to identify studies that could contain data of our interest. A full text of these studies will be evaluated. If the study does not fit our conditions after in-depth text evaluation, the reason for study exclusion will be documented. Disagreements between reviewers will be solved by discussion.

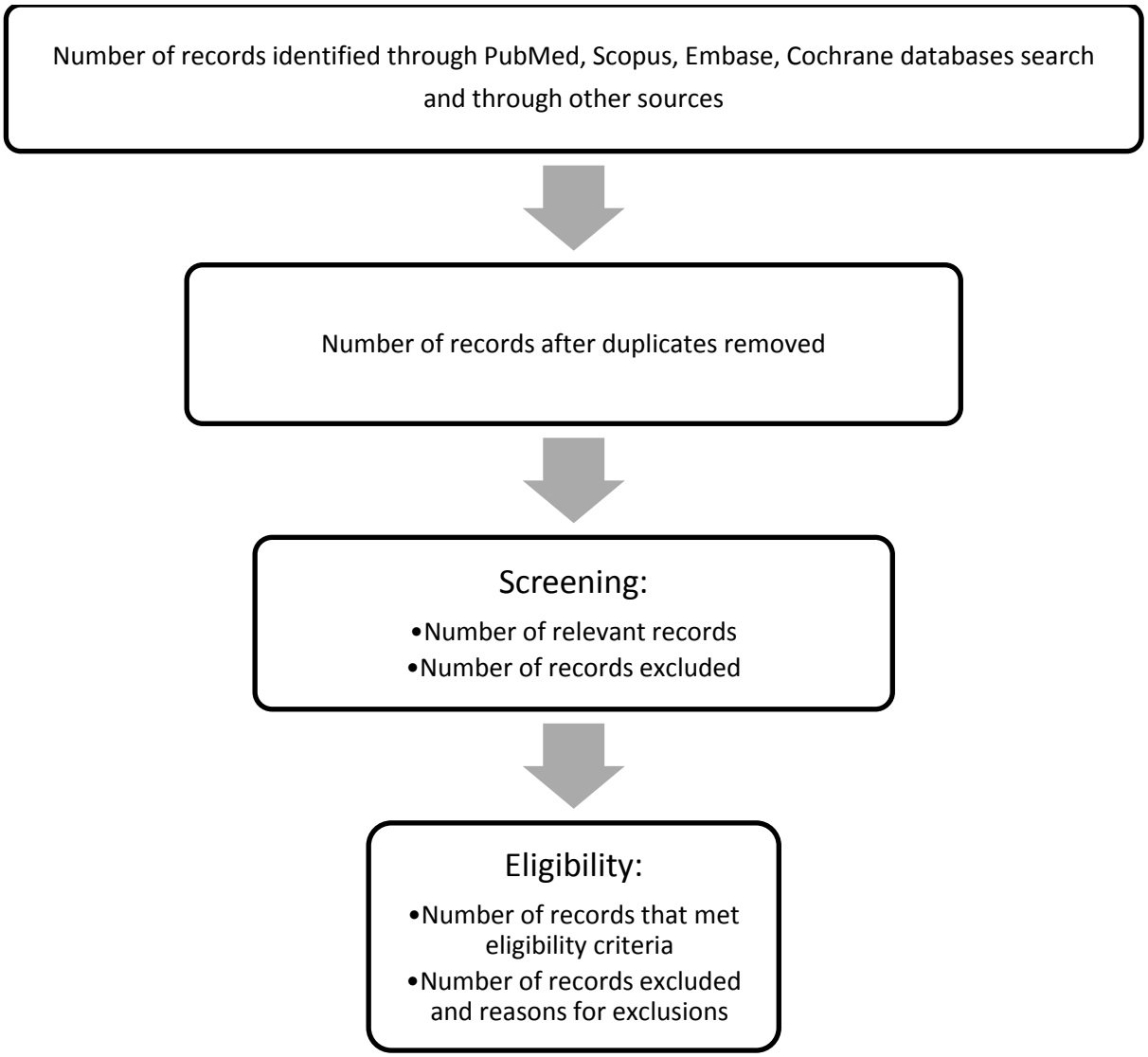


Figure 1. Flowchart for Systematic review.

Inclusion and classification of studies:

Studies for primary analysis: The study contains either data of Pearson's correlation(s) between E/e' and reference standard(s) or the study contains data sufficient to create 2x2 diagnostic tables (true positive, false positive, false negative, true negative) for E/e' cutoff(s) recommended by ASE to identify elevated/ normal LVFP and LVDD/HFpEF. Such data is available for the participants with LVEF $\geq$ 50%.

Studies for supplemental analysis: 1) the study contains data required for the primary analysis but such data is available for the participants with LVEF $\geq$ 40%; 2) the study does not contain data sufficient to create 2x2 table for recommended by ASE E/e' cutoffs but contains other valuable diagnostic data (ROC AUC value and/ or optimal E/e' cutoff value).

Data extraction:

Data will be extracted from selected studies according to a data collection form. Disagreements will be solved by consensus. Extracted information about evaluated studies and digital data will be input in the MS Word and Excel tables.

The following study information/digital data (what is available) will be collected:

1. PMID number (if available).
2. Year of publication.
3. Number of patients with preserved LVEF.
4. Mean age, mean LVEF or LVEF cutoff.
5. Number of males/females.
6. Number of patients with HFpEF, coronary artery disease, systemic hypertension, diabetes mellitus in study cohort.
7. Clinical indications for catheterization.
8. Index test(s).
9. Reference test(s).
10. Correlation size between echocardiographic index test values and invasive reference test values.
11. True positive, false positive, true negative, and false negative data for specific index and reference test cutoff.
12. ROC AUC values for specific reference test cutoff.

If data of interest not fully provided, additional calculations will be made to extract data of interest from graphical presentations and/or tables where available.

Assessment of methodological quality of evaluated studies:

Assessment of methodological quality of evaluated studies will be performed by a modified QUADAS-2 (see Appendix S3). Risk of bias will be tested for four domains which are patient selection, index test, reference test, and flow and timing; Applicability was tested for patient selection, index and reference test domains. This questionnaire is expanded to incorporate the findings from the study of Naaktgeboren et al, 2013 [13] to include the risks of differential verification on index test accuracy in clinical study.

Statistical analysis and data synthesis:

Statistical methodology would be based on approaches described in Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy. [2] Forest plots of sensitivity, specificity with 95% confidence intervals will be computed in OneMetaAnalyst.[14] Heterogeneity amongst the studies will be estimated by I^2 statistic. The correlation will be classified as negligible when r is between 0 – 0.3, low when r is 0.3 – 0.5, moderate when r is 0.5 – 0.7 and high when r is 0.7 – 0.9. [15] To obtain summary points taking into account within-study variability and between-study variability (heterogeneity), we will perform hierarchical summary receiver operating characteristic (HSROC) analysis. The Rutter and Gatsonis HSROC model [16] will be constructed in OneMetaAnalyst [14] for each category of diagnostic analysis. The summary sensitivity and specificity values will be also utilized to calculate the relationship of positive predictive value (diagnostic precision) with prevalence for elevated or normal LVFP ranging from 5% to 95%. The latter relationships will be compiled and graphed using Matlab R2013b. Additional statistical methodologies may be required based on discussion with experts in this field. We will also explore heterogeneity by using the different sources of heterogeneity as covariate(s) in HSROC analysis. Emphasis will be placed on evaluating the robustness of evidence and its clinical applicability taking into account expected heterogeneity in the studies.

Sensitivity analysis:

We will perform secondary analyses including forest plots, HSROC analysis and summary estimates of sensitivity and specificity for the subgroups of studies if a sufficient number of studies are present for identified subgroups.

References:

1. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ*. 2009;339:b2535.

2. Macaskill P, Gatsonis C, Deeks J, Harbord R, Takwoingi Y. Chapter 10: Analysing and Presenting Results. In: Deeks J, Bossuyt P, Gatsonis C, editors. Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy Version 1. The Cochrane Collaboration; 2010.

3. Redfield MM, Jacobsen SJ, Burnett JC, Mahoney DW, Bailey KR, Rodeheffer RJ. Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. *JAMA*. 2003;289:194–202.

4. Kane GC, Karon BL, Mahoney DW, Redfield MM, Roger VL, Burnett JC, Jacobsen SJ, Rodeheffer RJ. Progression of left ventricular diastolic dysfunction and risk of heart failure. *JAMA*. 2011;306:856–63.

5. Bursi F, Weston SA, Redfield MM, Jacobsen SJ, Pakhomov S, Nkomo VT, Meverden RA, Roger VL. Systolic and diastolic heart failure in the community. *JAMA*. 2006;296:2209–16.

6. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. *N Engl J Med*. 2006;355:251–9.

7. Nagueh SF, Appleton CP, Gillebert TC, Marino PN, Oh JK, Smiseth OA, Waggoner AD, Flachskampf FA, Pellikka PA, Evangelista A. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. *J Am Soc Echocardiogr*. 2009;22:107–33.

8. McMurray JJ V, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, Falk V, Filippatos G, Fonseca C, Gomez-Sanchez MA, Jaarsma T, Køber L, Lip GYH, Maggioni A Pietro, Parkhomenko A, Pieske BM, Popescu BA, Rønnevik PK, Rutten FH, Schwitter J, Seferovic P, Stepinska J, Trindade PT, Voors AA, Zannad F, Zeiher A. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart. *Eur Heart J*. 2012;33:1787–847.

9. European Study Group on Diastolic Heart. How to diagnose diastolic heart failure. *Eur Heart J*. 1998;19:990–1003.

10. Edelmann F, Wachter R, Schmidt AG, Kraigher-Krainer E, Colantonio C, Kamke W, Duvinage A, Stahrenberg R, Durstewitz K, Löffler M, Düngen H-D, Tschöpe C, Herrmann-Lingen C, Halle M, Hasenfuss G, Gelbrich G, Pieske B. Effect of spironolactone on diastolic function and exercise capacity in patients with heart failure with preserved ejection fraction: the Aldo-DHF randomized controlled trial. *JAMA*. 2013;309:781–91.

11. Kim Y-H, Kim SH, Lim SY, Cho G-Y, Baik I-K, Lim H-E, Na JO, Han SW, Ko Y-H, Shin C. Relationship between depression and subclinical left ventricular changes in the general population. *Heart*. 2012;98:1378–83.

12. Ohtani T, Mohammed SF, Yamamoto K, Dunlay SM, Weston SA, Sakata Y, Rodeheffer RJ, Roger VL, Redfield MM. Diastolic stiffness as assessed by diastolic wall strain is associated with adverse remodelling and poor outcomes in heart failure with preserved ejection fraction. *Eur Heart J*. 2012;33:1742–9.

13. Naaktgeboren CA, de Groot JAH, van Smeden M, Moons KGM, Reitsma JB. Evaluating diagnostic accuracy in the face of multiple reference standards. *Ann Intern Med*. 2013;159:195–202.

14. Wallace B, Dahabreh I, Trikalinos T, Lau J, Trow P, CH S. Closing the Gap between Methodologists and End-Users: R as a Computational Back-End. *J Stat Softw*. 2012;49:1–15.

15. Hinkle DE, Wiersma W, Urs SG. Applied Statistics for the Behavioral Sciences. 5th Ed. Boston, MA: Houghton Mifflin; 2003.

16. Rutter CM, Gatsonis CA. A hierarchical regression approach to meta-analysis of diagnostic test accuracy evaluations. *Stat Med*. 2001;20:2865–84.

APPENDIX 2

Data sources and search strategy

PubMed (total of 18791 original citations)	
Search 1	diastol* AND (echo* OR Doppl* OR ultrasound* OR acous*). Limits: English, Journal Article, Humans. Time range: 1/1/1980 - 11/14/2013 (identified **12733** document citations).
Search 2	diastol* AND catheter* AND Doppler* AND pressure. Limits: English, Journal Article, Humans. Time range: 1/1/1970 - 04/28/2014 (identified 738 document citations [**551** new and 187 duplicates])
Search 3	echocardiography AND tissue doppler AND catheterization. Limits: English. Time range: not specified - 02/06/2015 (identified 503 document citations [**291** new and 212 duplicates])
Search 4	((ventric* pressure*) OR "ventricular pressure"[MeSH Terms] OR "ventricular dysfunction"[MeSH Terms]) AND (Doppler* OR E/e* OR "echocardiography, doppler"[MeSH Terms]). Limits: English. Time range: not specified - 02/16/2015 (identified 9776 document citations [**5216** new and 4560 duplicates]). *All studies of our interest, which were selected from the results of Searches 1, 2, and 3 in PubMed, were also identified in the document* citations *of the Search 4*.
Scopus (total of 1580 original citations)	
Search 1	(TITLE-ABS-KEY (echocardiography) OR TITLE-ABS-KEY (tissue Doppler) AND TITLE-ABS-KEY (catheterization) AND DOCTYPE ("ar") AND SUBJAREA (mult OR agri OR bioc OR immu OR phar OR mult OR medi OR nurs OR vete OR dent OR heal) AND (LIMIT-TO (LANGUAGE , "English"). Time range: not specified - 02/06/2015 (identified 512 document citations [**167** new and 345 PubMed duplicates])
Search 2	(TITLE-ABS-KEY (ventric* pressure*) OR TITLE-ABS-KEY (ventricular dysfunction) AND TITLE-ABS-KEY (doppler*) OR TITLE-ABS-KEY (e/e*) OR TITLE-ABS-KEY (echocardiography,doppler)) AND SUBJAREA (mult OR medi OR nurs OR vete OR dent OR heal) AND NOT INDEX (medline) , AND (LIMIT-TO (LANGUAGE , "English")) AND (LIMIT-TO (SUBJAREA , "MEDI")) AND (LIMIT-TO (DOCTYPE , "ar") OR LIMIT-TO (DOCTYPE , "cp")). Time range: not specified - 02/16/2015 (identified **1413** document citations, as not indexed in Medline)
Embase (total of 594 original citations)	
Search 1	(ventric* near/2 pressure or ventric* near/3 'diastolic pressure' or ventric* near/3 'filling pressure' or 'ventricular pressure'/exp or 'ventricular pressure' or 'ventricular dysfunction'/exp or 'ventricular dysfunction' or 'diastolic heart failure'/exp or 'diastolic heart failure' or 'heart failure with normal' or 'heart failure with preserved' and ('doppler' or 'e/e' or 'echocardiography doppler'/exp or 'echocardiography doppler') and ([article]/lim or [article in press]/lim or [conference paper]/lim or [letter]/lim) and [english]/lim and [embase]/lim) and [embase]/lim not [medline]/lim. Time range: not specified - 03/05/2015 (identified **594** document citations, as not indexed in Medline)
Cochrane Library (March 2015) (total of 48 original citations (conference abstracts))	
Search 1	"filling pressure" AND "Doppler" (gives 78 citations [**5** new and 73 duplicates])
Search 2	"filling pressure" AND "E/e" (gives 42 citations [**6** new and 36 duplicates])
Search 3	"diastolic dysfunction" AND "e/e" (gives 46 citations [**10** new and 36 duplicates])
Search 4	"diastolic dysfunction" AND "tissue Doppler" (gives 70 citations [**26** new and 44 duplicates])
Search 5	"diagnostic accuracy" AND "diastolic dysfunction" (gives 3 citations [**0** new and 3 duplicates])
Search 6	"diagnostic accuracy" AND " diastolic heart failure" (gives 0 citations [**0** new and 0 duplicates])
Search 7	"diagnostic accuracy" AND "tissue doppler" (gives 6 citations [**1** new and 5 duplicates])
Search 8	"diagnostic accuracy" AND "E/e" (gives 2 citations [**0** new and 2 duplicates])

APPENDIX 3

TOOL FOR ASSESSMENT OF RISK OF BIAS AND APPLICABILITY

(Modified from QUADAS-2 publications listed in the end)

PMID:
Title:
Reviewer:
Date:
Group **Primary/Supplemental**

Note: Intent is to evaluate the paper to assess application for our study question (and not to critique the paper)

DOMAIN 1: PATIENT SELECTION

A. Risk of Bias

Description:

Study Design:	Case-Control Cross-Sectional Cohort Randomized Control Trial
Data Collection	Prospective Retrospective Unknown
Setting of patient selection	Clinic/ Cath lab/Echo/ ER/ ICU/ In-hospital/ Out-patient/ Community/ Others
Clinical characterization	complete data sheet (appendix A)

Signaling Questions:

Was a consecutive sample of patients enrolled? Yes/No/Unclear
Was a case-control design avoided? Yes/No/Unclear
Did the study avoid inappropriate exclusions? (confirmed cases of diastolic dysfunction) Yes/No/Unclear
Did the study avoid inappropriate inclusions (valvular heart disease, HCM, RCM, Afib)? Yes/No/Unclear

Could the selection of patients have introduced bias? RISK: LOW /HIGH/UNCLEAR

Comments: specify why bias

B. Concerns regarding applicability

Consider prior testing, presentation, intended use of index test and setting, severity of the target condition, demographic features, co-morbidities, preserved LVEF patients mixed with depressed LVEF patients

Is there concern that the included patients do not match our study question? CONCERN: LOW /HIGH/UNCLEAR

Comments: specify why bias

DOMAIN 2: INDEX TEST: E/e' lateral/septal/mean

A. Risk of Bias

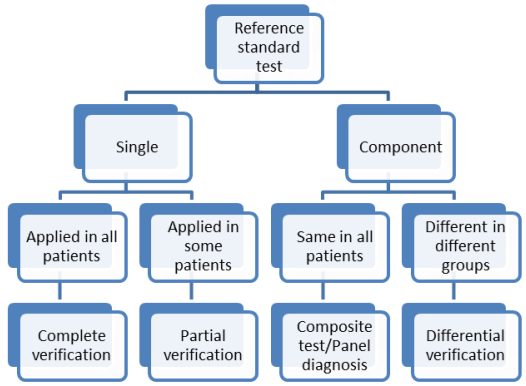
Were the index test results interpreted without knowledge of the results of the reference standard? Yes/No/Unclear
(Yes only if specific mention of blinding/averaging of several measurements)
If a threshold was used, was it pre-specified? Yes/No/Unclear/ Not applicable
Could the conduct or interpretation of the index test have introduced bias? RISK: LOW/ HIGH/UNCLEAR
Comments: specify why bias

B. Concerns regarding applicability:

Was Inter-observer Variation tested? Yes/No/Unclear
If tested, was Inter-observer Variation present? Yes/No/Unclear
Was Intra-observer Variation tested? Yes/No/Unclear
If tested, was Intra-observer Variation present? Yes/No/Unclear
Were there concerns regarding Test technology? Yes/No/Unclear
Were there concerns regarding Test execution? Yes/No/Unclear
Is there concern that the index test, its conduct, or interpretation differ from our study question? CONCERN: LOW /HIGH/UNCLEAR
Comments: specify why bias

DOMAIN 3: REFERENCE STANDARD

Circle where the study falls in the flow diagram



Select Reference Tests used:

LVEDP,
LVMDP,
LV Pre-A DP,
PCWP
Tau
Beta-stiffness
Clinical LVDD/HFpEF

A. Risk of Bias

Is the reference standard likely to correctly classify the target condition? Yes/No/Unclear
Were the reference standard results interpreted without knowledge of the results of the index test? Yes/No/Unclear
If 2, was there a partial verification bias? Yes/No/Unclear/ Not applicable
Was the use of reference standard only dependent on the results of the index test? Yes/No/Unclear
Was reference standard not applied to a large percentage of the participants? Yes/No/Unclear
If 3, was composite reference standard/panel diagnosis used? Yes/No/ Not applicable
If 4, was there Differential Verification bias? Yes/No/ Unclear/ Not applicable
Was the choice of reference standard completely dependent on the results of the index test? Yes/No/Unclear
If the answer to the first question is no, how accurate is the inferior reference standard? Yes/No/Unclear
Was large percentage of the participants diagnosed by use of the inferior reference standard? Yes/No/Unclear
If follow-up is used as the inferior reference standard, does it identify almost all hidden cases present at the time of the index test but very few new cases that develop afterward? Does follow-up detect the same type of cases as the preferred reference standard? Yes/No/Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias regarding our study question? RISK: LOW /HIGH/UNCLEAR
Comments: specify why bias

B. Concerns regarding applicability:

Was consistent Definition of Target Condition used? Yes/No/Unclear
Were there concerns regarding Test technology? Yes/No/Unclear
Were there concerns regarding Test execution? Yes/No/Unclear
Is there concern that the target condition as defined by the reference standard does not match the review question? CONCERN: LOW /HIGH/UNCLEAR
Comments: specify why bias

DOMAIN 4: FLOW AND TIMING

A. Risk of Bias

Was there an appropriate interval between index test(s) and reference standard? Yes/No/Unclear
Did all patients receive a reference standard? Yes/No/Unclear
Did patients receive the same reference standard? Yes/No/Unclear
Were all patients included in the analysis? Yes/No/Unclear
Could the patient flow have introduced bias related to our study question? RISK: LOW /HIGH/UNCLEAR
Comments: specify why bias

Appendix A: Data sheet

Sample Size: Overall

Sample Size for Preserved EF

What was LVEF criterion for preserved EF:

Clinical characteristics of Preserved LVEF:

Variable	Yes		No	Not Quantified	Comments
	Number	(%)			
Dyspnea					
NYHA class					
6 MWD					
Chest Pain					
Exercise stress test					
Left Ventricular Hypertrophy					
Heart Failure					
BNP					
Ethnicity/ Race					
Gender					
Age					
Body Habitus (weight, BSA, BMI)					
Habits (smoking, Etoh, Drugs)					
Co morbidities					
Hypertension					
Diabetes					
CAD					
CKD					
Sleep Apnea					
COPD					
Obesity					
Medications					
Socio Economic Status (education, salary etc)					

References

1. Whiting PF et at Quadas 2 Annals of Internal Medicine2011, 155: 529
2. Whiting PF et al J of clinical Epidemiology2013, 66; 1093
3. Naaktgeboren et al Annals of Internal Medicine 2013: 159: 195
4. Groot et al. BMJ 2011;343:d4770

APPENDIX 4

Full-text studies excluded with the reasons

Studies are identified with PMID (if available)

TEE approach:

1. 8078825
2. 9052288
3. 12356384
4. 23190400

LVEF not specified

5. 1905874
6. 1985353
7. 1987211
8. 2214134
9. 2278168
10. 2360494
11. 2498005
12. 2683699
13. 2782257
14. 2871286
15. 2958532
16. 3177175
17. 3209254
18. 7730680
19. 7771173
20. 7817903
21. 8319326
22. 8496538
23. 8606285
24. 8933237
25. 9046493
26. 9237029
27. 9247521
28. 10149211
29. 10969625
30. 11368862
31. 11593199
32. 11884251
33. 12487633
34. 16195393
35. 18325734
36. 24319341

Data available only for mixed LVEF group (extraction of data for LVpEF patients not possible)

37. 1827808
38. 7780619
39. 8736006
40. 1607511
41. 3392336
42. 8245357
43. 8557907
44. 9015003
45. 10913476
46. 10913478
47. 11279327
48. 11391284
49. 11560356
50. 11770447
51. 11926970
52. 14563593
53. 14652601
54. 15653227
55. 15891754
56. 16128376
57. 16500488
58. 16516591
59. 16682317
60. 20197576
61. 23103948
62. 18986412
63. 19168324
64. 19560662
65. 18612440
66. 18635276
67. 18771556
68. 16716013
69. 17069599
70. 17196474
71. 17451867
72. 17484986
73. 17541761
74. 17652894
75. 17658724
76. 17884382
77. 18514937
78. 18538465
79. 16682317
80. 17560894
81. 21245360
82. 22567531
83. Moladoust H. et al, Echocardiography: A Jrnl. of CV Ultrasound & Allied Tech. (2009) 26 (4), 403-411
84. Said K. et al, The Egyptian Heart Journal (2012) 64, 69-74
85. 11944011
86. 19602775

Data available only for low LVEF group

87. 2816770
88. 7193403
89. 7960266
90. 8890820
91. 12221410
92. 17079190
93. 17484987
94. 18406665
95. 18440343
96. 20117802
97. 22494067
98. 24174962

No results of our interest:

99. 1760176
100. 1800031
101. 1918702
102. 2629864
103. 2816706
104. 3153793
105. 3532754
106. 3903704
107. 6777405
108. 7561012
109. 7640020
110. 7673761
111. 7802299
112. 8001095
113. 8037096
114. 8184840
115. 8252682
116. 8261053
117. 8771303
118. 8891860
119. 8904686

120. 9043850
121. 9104907
122. 9137220
123. 9203493
124. 9424066
125. 9950969
126. 10230946
127. 10441218
128. 10980082
129. 11158951
130. 11407738
131. 11408426
132. 11433812
133. 11433813
134. 11433824
135. 11482709
136. 11490324
137. 11550110
138. 11585994
139. 11593203
140. 11696830
141. 11796872
142. 11809440
143. 11917193
144. 12094170
145. 12707119
146. 12714167
147. 12766750
148. 12804750
149. 12848693
150. 12940700
151. 14640103
152. 14641374
153. 14652600
154. 14670073
155. 14672750
156. 14717717
157. 14752488
158. 15172419
159. 15309696
160. 15476639
161. 15488086
162. 15781734
163. 15948097
164. 16014646
165. 16223980
166. 16284230
167. 16344121
168. 16434758
169. 16575023
170. 16949491
171. 17207727
172. 17313636
173. 17390199
174. 17394966
175. 17488411
176. 18198205
177. 18471459
178. 18597919
179. 19203992
180. 20058507
181. 20553318
182. 20625213
183. 20682947
184. 20970305
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208. 11175032
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225. Cong T. et al, Experimental & Clinical Cardiology (2014) 20 (1), 2479-2490
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Patients with comorbidities (excluded from our analysis)

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268. 23940422
269. 24626519
270. 24995376
271. 25414078
272. Wang W. et al, Acta Cardiol Sin (2012), 28, 206-215
273. Ahn J. et al, e-Herz (2013), DOI 10.1007/s00059-013-4010-0
274. 21718351

Repetitive data

275. 20813283

APPENDIX 5

Secondary analysis of E/e' correlation with LVFP

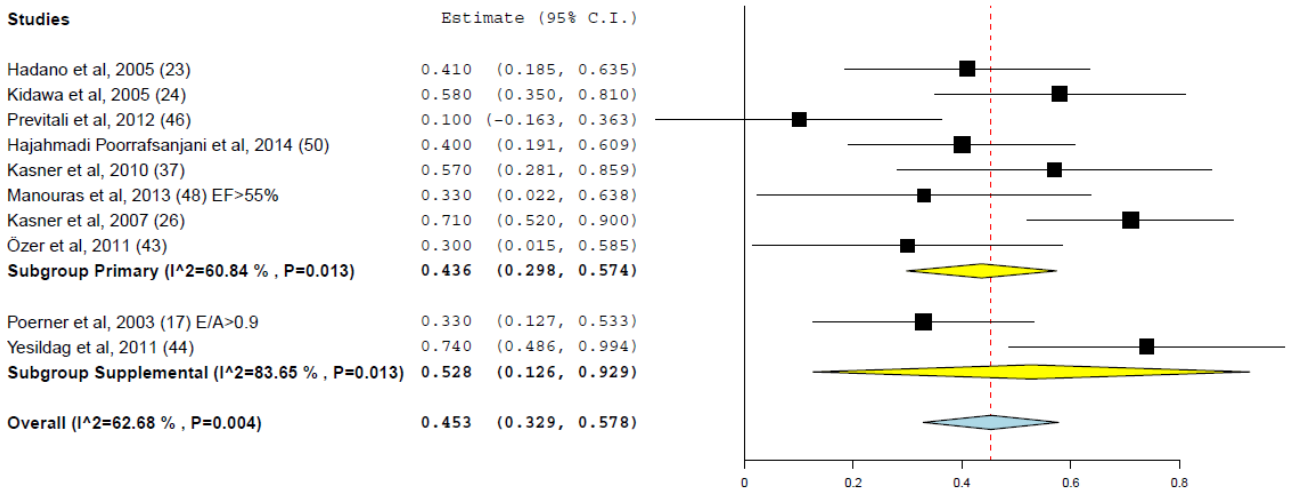
5.1. Subgroup analysis for $E/e'_{lateral}$ and LVFP

$E/e'_{lateral}$: Dataset for subgroup analysis (see also Tables 1 and 2)

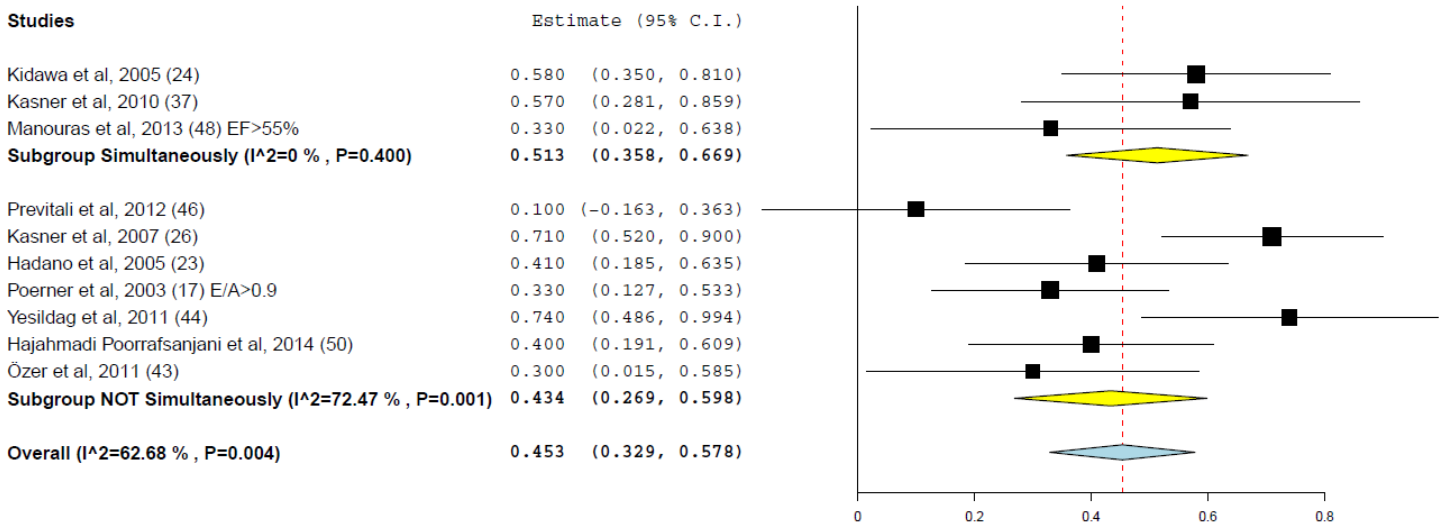
LVFP	*r*	se	Data	Timing	% HFpEF	% CAD	% HTN	% DM	Indication for cath
LVEDP									
LVEDP Kidawa et al, 2005 (24)	0.58	0.118	Primary	Simultaneously	unclear	unclear	unclear	unclear	angiography
LVEDP Manouras et al, 2013 (48) EF>55%	0.33	0.157	Primary	Simultaneously	unclear	no CAD	unclear	unclear	angiography
LVEDP Kasner et al, 2010 (37)	0.57	0.148	Primary	Simultaneously	~60% HF	no CAD	~60% HTN	~10% DM	dyspnea/angio
LVEDP Previtali et al, 2012 (46)	0.1	0.134	Primary	NOT Simultan.	no HF	unclear	unclear	unclear	unclear
LVEDP Hadano et al, 2005 (23)	0.41	0.115	Primary	NOT Simultan.	unclear	some CAD	unclear	unclear	unclear
LVEDP Kasner et al, 2007 (26)	0.71	0.097	Primary	NOT Simultan.	~80% HF	no CAD	~60% HTN	~10% DM	dyspnea/angio
LVEDP Özer et al, 2011 (43)	0.3	0.145	Primary	NOT Simultan.	unclear	all CAD	~60% HTN	~40% DM	angiography
LVEDP Hajahmadi Poorrafsanjani et al, 2014 (50)	0.4	0.107	Primary	NOT Simultan.	unclear	unclear	unclear	unclear	angiography
LVEDP Poerner et al, 2003 (17) E/A>0.9	0.33	0.104	Supplement	NOT Simultan.	unclear	unclear	unclear	unclear	angiography
LVEDP Yesildag et al, 2011 (44)	0.74	0.129	Supplement	NOT Simultan.	unclear	unclear	unclear	unclear	unclear
PCWP									
PCWP Rivas-Gotz et al, 2003 (18)	0.7	0.098	Primary	Simultaneously	unclear	unclear	unclear	unclear	ICU/Cath
PCWP Maeder et al, 2011 (42)	-0.04	0.171	Primary	NOT Simultan.	~40% HF	unclear	unclear	unclear	HF/PAH/volunteers
PCWP Gonzalez-Vilchez et al, 2002 (16)	0.54	0.154	Primary	NOT Simultan.	unclear	unclear	unclear	unclear	unclear
PCWP Hadano et al, 2005 (23)	0.54	0.106	Primary	NOT Simultan.	unclear	some CAD	unclear	unclear	unclear
PCWP Nagueh et al, 1998 (14) EF>45% Sinus Tachycardia >100bpm	0.72	0.101	Supplement	Simultaneously	unclear	unclear	unclear	unclear	ICU/Cath lab
Pre-A									
Pre-A Manouras et al, 2013 (48) EF>55%	0.4	0.106	Primary	Simultaneously	unclear	no CAD	unclear	unclear	angiography
Pre-A Mansencal et al, 2004 (20)	0.18	0.232	Primary	NOT Simultan.	~10% HF	all CAD	~10% HTN	unclear	unclear
Pre-A Previtali et al, 2012 (46)	0.11	0.134	Primary	NOT Simultan.	no HF	unclear	unclear	unclear	unclear
Pre-A Hsiao et al, 2011 (40)	0.23	0.098	Primary	NOT Simultan.	unclear	all CAD	~70% HTN	~50% DM	angiography
Pre-A Poerner et al, 2003 (17) E/A>0.9	0.49	0.096	Supplement	NOT Simultan.	unclear	unclear	unclear	unclear	unclear
LVMDP									
LVMDP Ommen et al, 2000 (15)	0.4	0.127	Primary	Simultaneously	unclear	unclear	unclear	unclear	unclear

LVFP=left ventricular filling pressure; LVEDP=left ventricular end diastolic pressure; LVMDP=left ventricular mean diastolic pressure; Pre-A DP=left ventricular pre–A wave diastolic pressure; PCWP=pulmonary capillary wedge pressure; CI=confidence interval; HFpEF=heart failure with preserved Ejection Fraction; CAD=coronary artery disease; HTN=hypertension; DM=diabetes mellitus; ICU=intensive care unit. Studies are identified by the first author, year of publication, and reference number (in brackets) as cited in the main text.

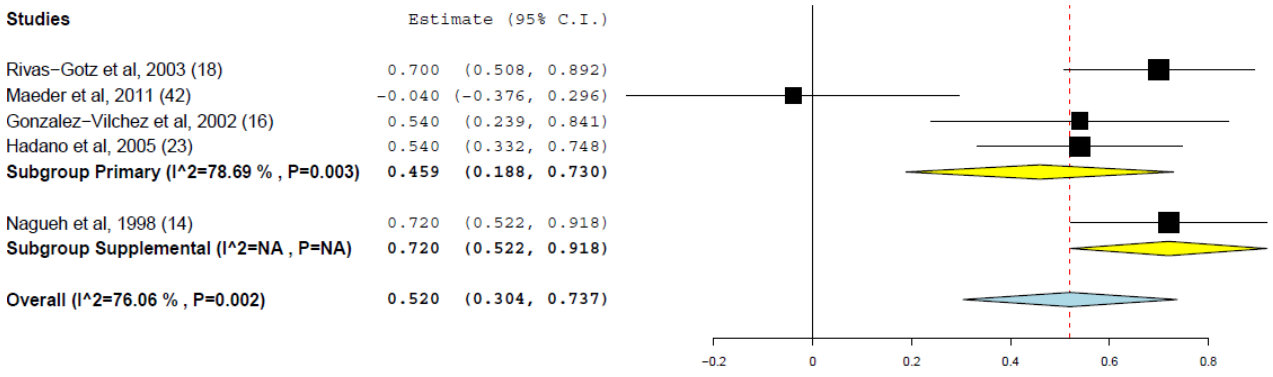
A. LVEDP (primary and supplemental data)



B. LVEDP (simultaneous and NOT simultaneous)

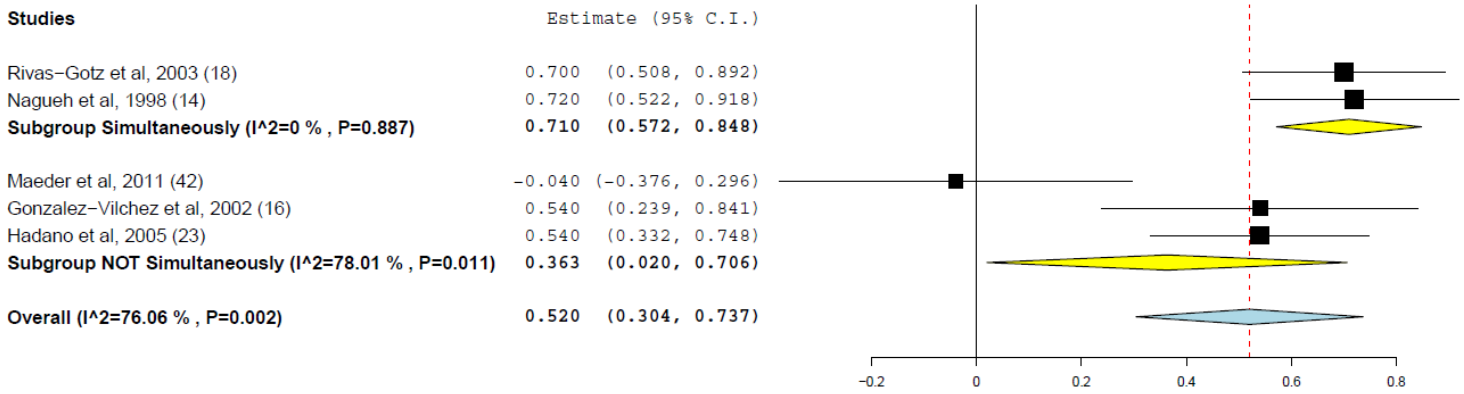


C. PCWP (primary and supplemental data)

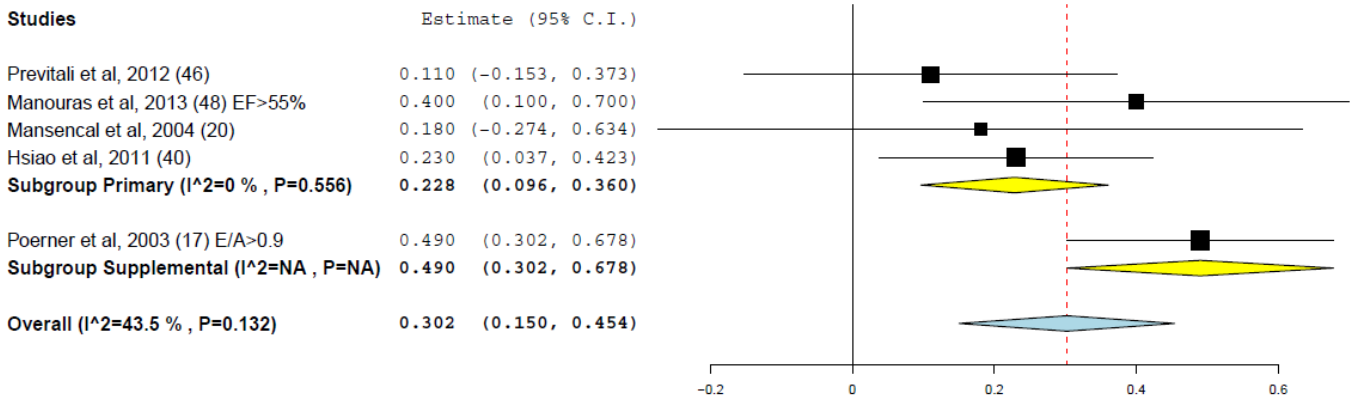


Heterogeneity amongst the studies was estimated by I2 statistic. Studies are identified by the first author, year of publication, and reference number (in brackets) as cited in the main text. OpenMetaAnalyst software (12) for Windows (64-bit version) was used for statistical analysis including graphical presentations of forest plots.

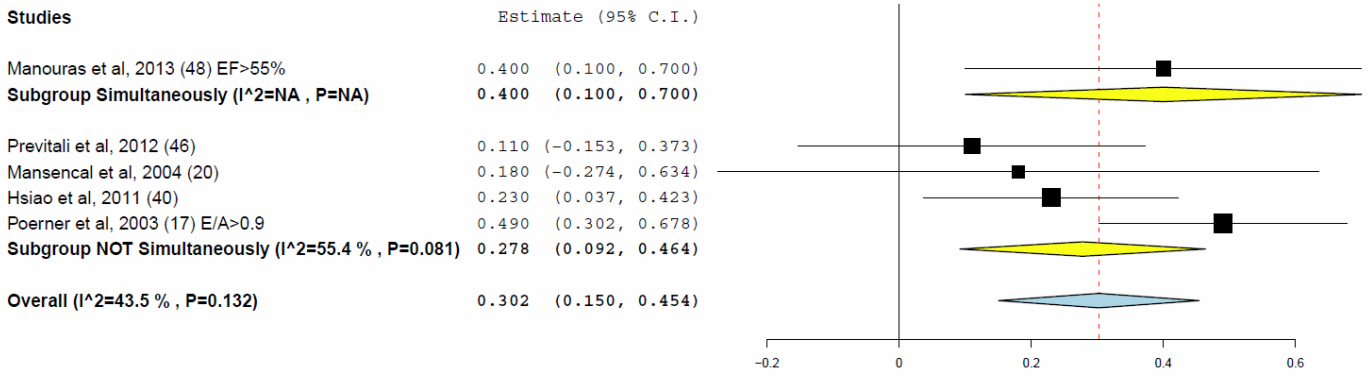
D. PCWP (simultaneous and NOT simultaneous)



E. Pre-A (primary and supplemental data)



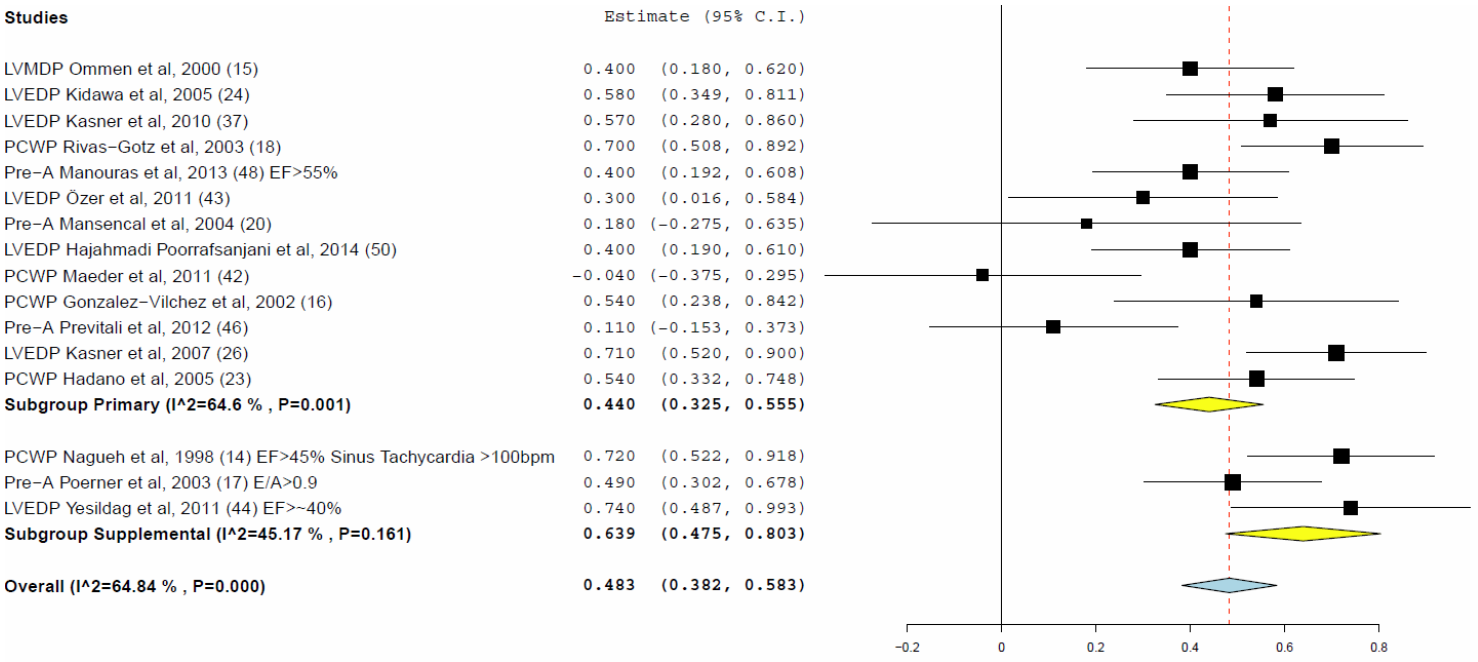
F. Pre-A (simultaneous and NOT simultaneous



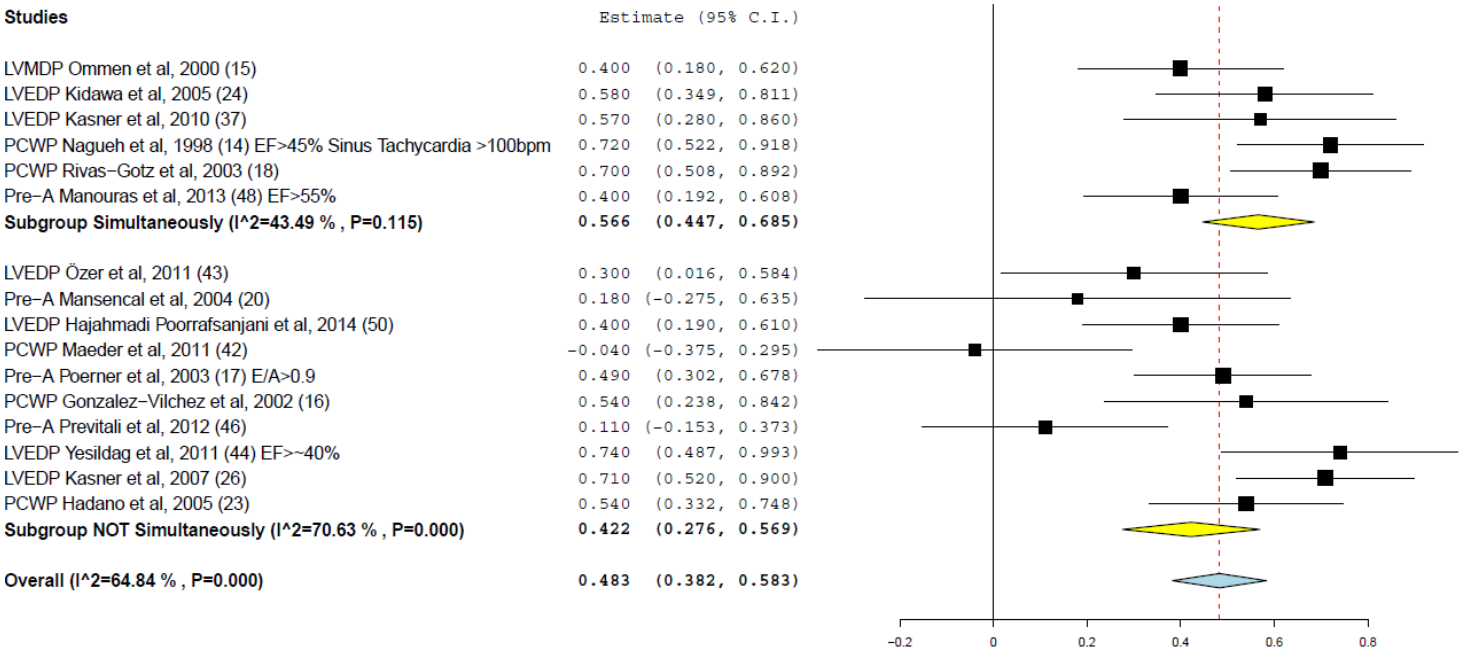
SUBGPOUP ANALYSIS for COMBINED LVFP and E/e'$_{lateral}$

For combined LVFP analysis, if the study measured two LVFP parameters we chose one that had the highest correlation coefficient.

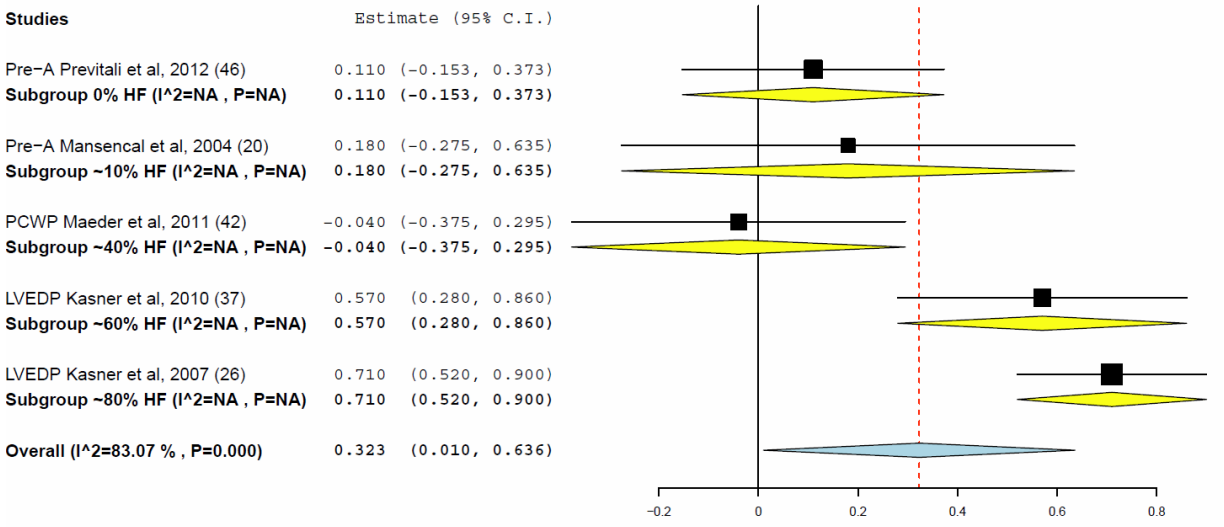
G. E/e'$_{lateral}$: combined LVFP – (primary and supplemental data)



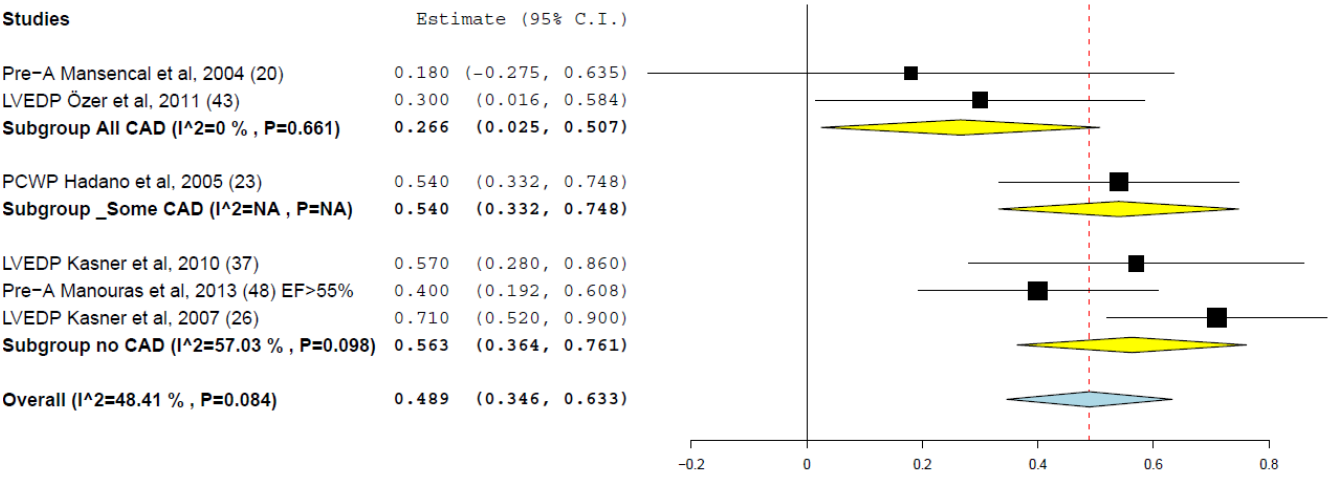
H. E/e'$_{lateral}$: combined LVFP – (simultaneous and NOT simultaneous)



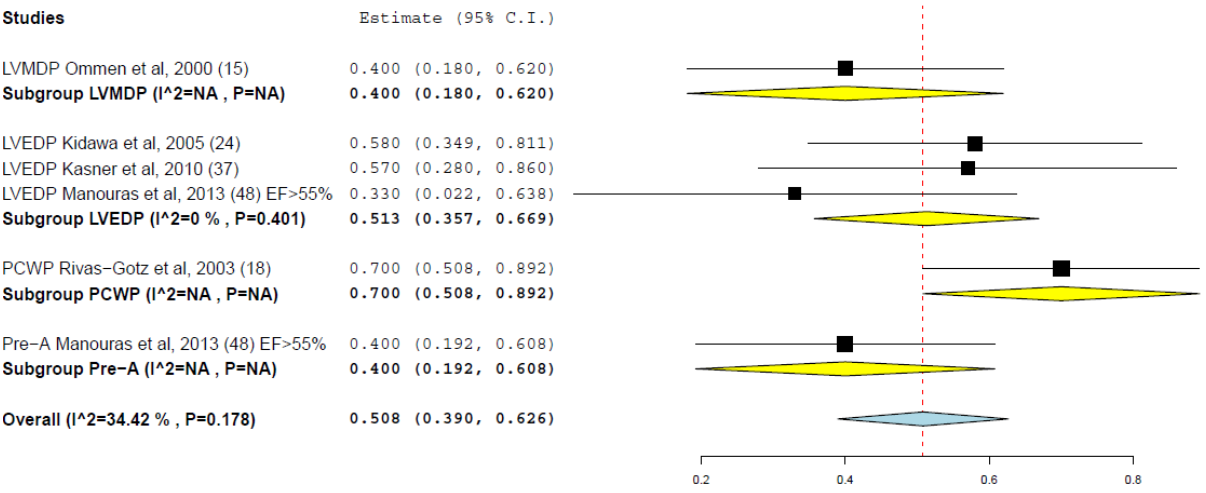
I. E/e'$_{lateral}$: combined LVFP – (HFpEF prevalence)



J. E/e'$_{lateral}$: combined LVFP – (CAD prevalence)



K. E/e'$_{lateral}$: Primary data variables measured simultaneously (shown as table 4B in the main text)



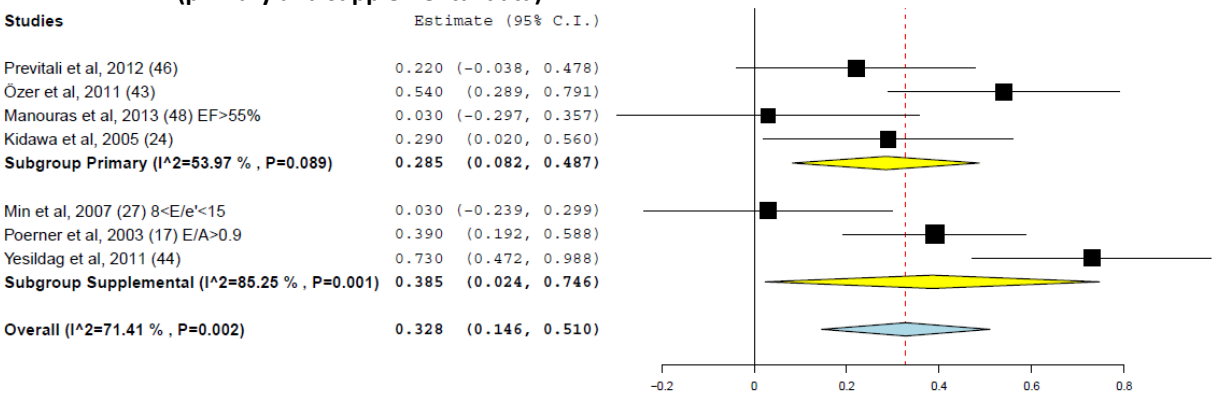
5.2. Subgroup analysis for E/e'_{septal} and LVFP

E/e'_{septal}: Dataset for subgroup analysis (see also Tables 1 and 2)

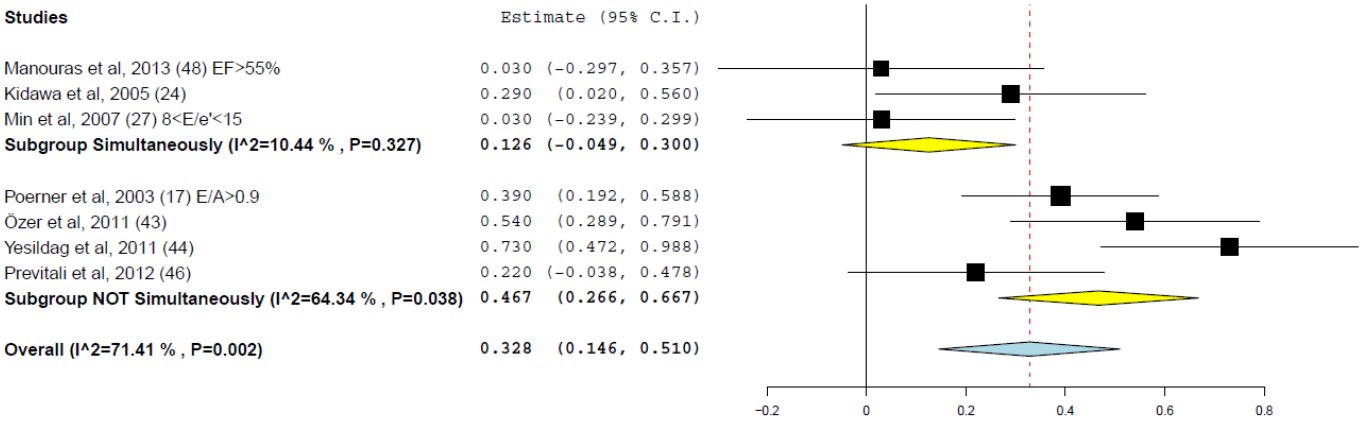
LVFP	*r*	se	Data	Timing	% HFpEF	% CAD	% HTN	% DM	Indication for cath
LVEDP									
LVEDP Manouras et al, 2013 (48) EF>55%	0.03	0.167	Primary	Simultaneously	unclear	no CAD	unclear	unclear	angiography
LVEDP Kidawa et al, 2005 (24)	0.29	0.138	Primary	Simultaneously	unclear	unclear	unclear	unclear	angiography
LVEDP Previtali et al, 2012 (46)	0.22	0.132	Primary	NOT Simultan.	no HF	unclear	unclear	unclear	unclear
LVEDP Özer et al, 2011 (43)	0.54	0.128	Primary	NOT Simultan.	unclear	all CAD	~60% HTN	~40% DM	angiography
LVEDP Poerner et al, 2003 (17) E/A>0.9	0.39	0.101	Supplemer	NOT Simultan.	unclear	unclear	unclear	unclear	angiography
LVEDP Yesildag et al, 2011 (44) EF> ~40%	0.73	0.132	Supplemer	NOT Simultan.	unclear	unclear	unclear	unclear	unclear
LVEDP Min et al, 2007 (27) 8<E/e'<15	0.03	0.137	Supplemer	Simultaneously	unclear	some CAD	~50% HTN	~30% DM	unclear
PCWP									
PCWP Rivas-Gotz et al, 2003 (18)	0.55	0.115	Primary	Simultaneously	unclear	unclear	unclear	unclear	ICU/Cath lab
PCWP Maeder et al, 2011 (42)	0.23	0.167	Primary	NOT Simultan.	~40% HF	unclear	unclear	unclear	HF/PAH/volunteers
PCWP Tatsumi et al, 2014 (51)	0.64	0.172	Primary	NOT Simultan.	unclear	unclear	unclear	unclear	unclear
Pre-A									
Pre-A Manouras et al, 2013 (48) EF>55%	0.02	0.161	Primary	Simultaneously	unclear	no CAD	unclear	unclear	angiography
Pre-A Previtali et al, 2012 (46)	0.28	0.129	Primary	NOT Simultan.	no HF	unclear	unclear	unclear	unclear
Pre-A Hsiao et al, 2011 (40)	0.31	0.096	Primary	NOT Simultan.	unclear	all CAD	~70% HTN	~50% DM	angiography
Pre-A Poerner et al, 2003 (17) E/A>0.9	0.4	0.101	Supplemer	NOT Simultan.	unclear	unclear	unclear	unclear	unclear
LVMDP									
LVMDP Ommen et al, 2000 (15)	0.47	0.112	Primary	Simultaneously	unclear	unclear	unclear	unclear	unclear
LVMDP Rudko et al, 2008 (32)	0.47	0.145	Primary	Simultaneously	~20% HF	~80% CAD	~50% HTN	unclear	unclear

LVFP=left ventricular filling pressure; LVEDP=left ventricular end diastolic pressure; LVMDP=left ventricular mean diastolic pressure; Pre-A DP=left ventricular pre–A wave diastolic pressure; PCWP=pulmonary capillary wedge pressure; CI=confidence interval; HFpEF=heart failure with preserved Ejection Fraction; CAD=coronary artery disease; HTN=hypertension; DM=diabetes mellitus; ICU=intensive care unit. Studies are identified by the first author, year of publication, and reference number (in brackets) as cited in the main text.

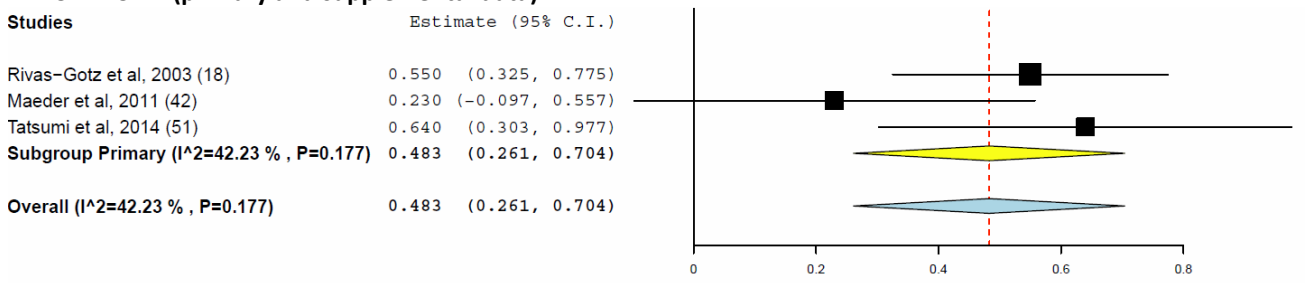
A. LVEDP (primary and supplemental data)



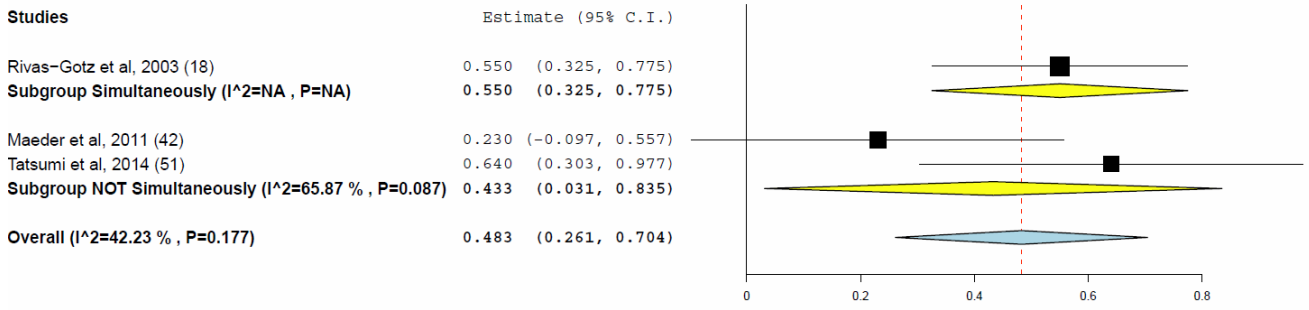
B. LVEDP (simultaneous and NOT Simultaneous)



C. PCWP (primary and supplemental data)

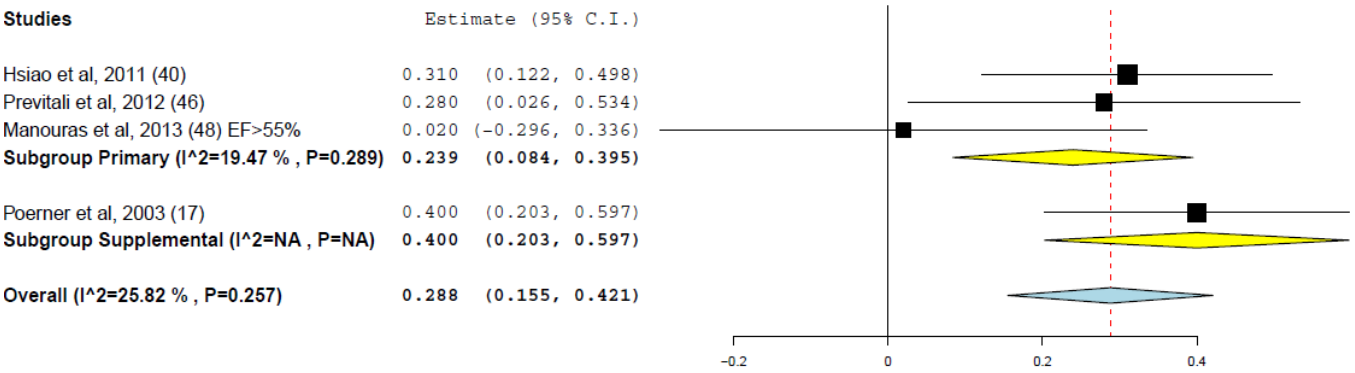


D. PCWP (simultaneous and NOT simultaneous)

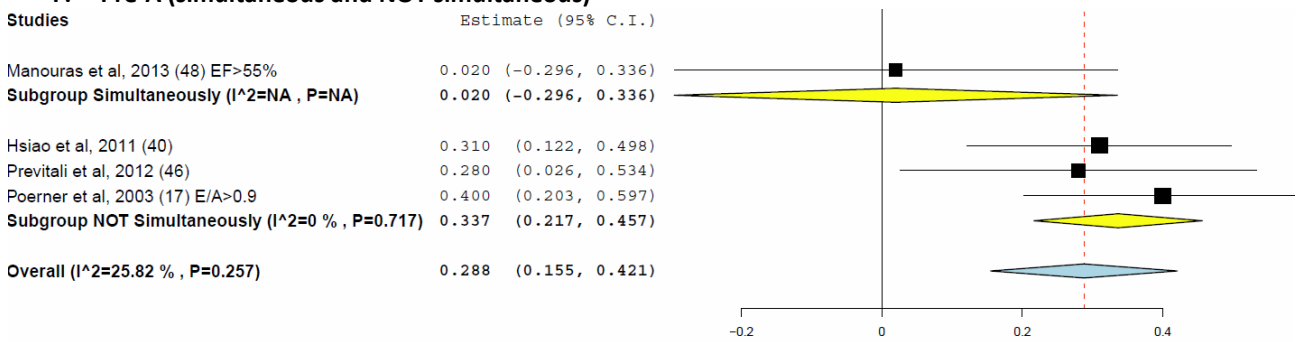


Heterogeneity amongst the studies was estimated by I2 statistic. Studies are identified by the first author, year of publication, and reference number (in brackets) as cited in the main text. OpenMetaAnalyst software (12) for Windows (64-bit version) was used for statistical analysis including graphical presentations of forest plots.

E. Pre-A (primary and supplemental data)



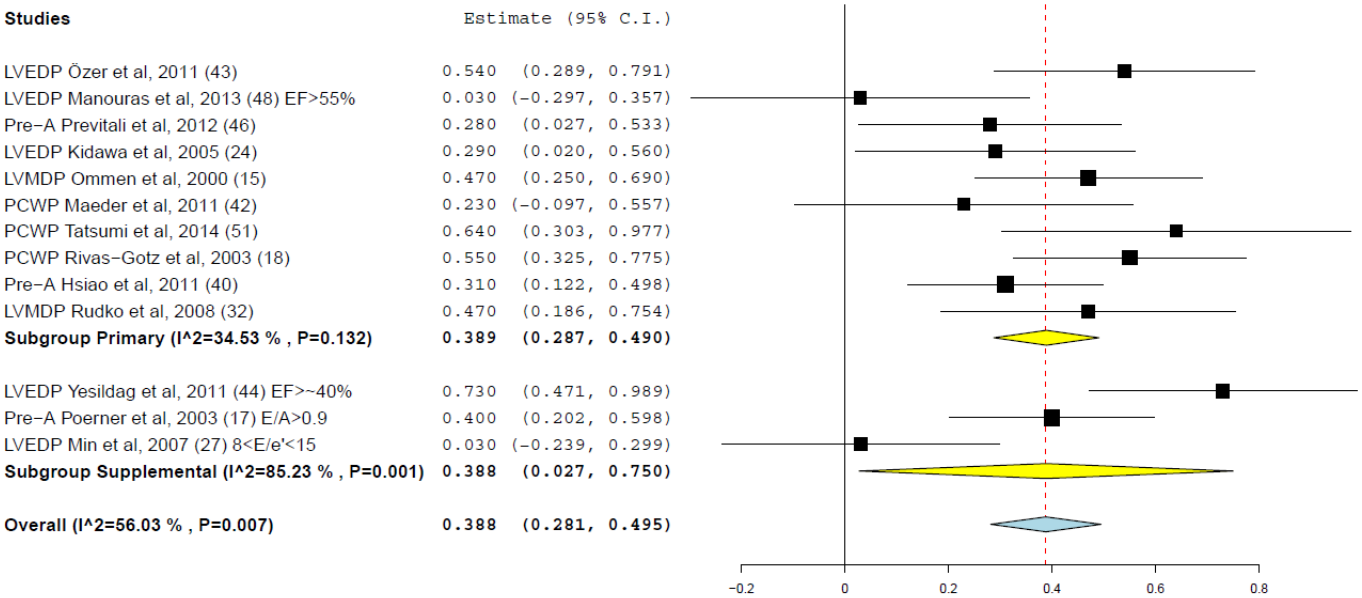
F. Pre-A (simultaneous and NOT simultaneous)



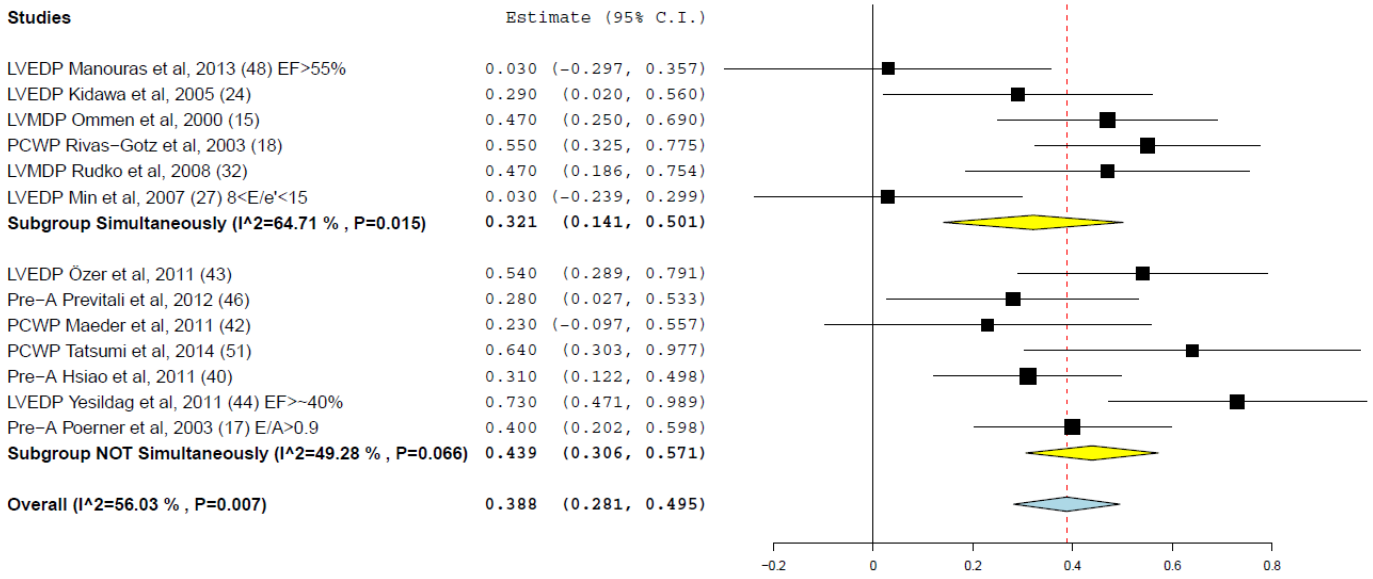
SUBGPOUP ANALYSIS for COMBINED LVFP and E/e'$_{septal}$

For combined LVFP analysis, if the study measured two LVFP parameters we chose that had the highest correlation coefficient.

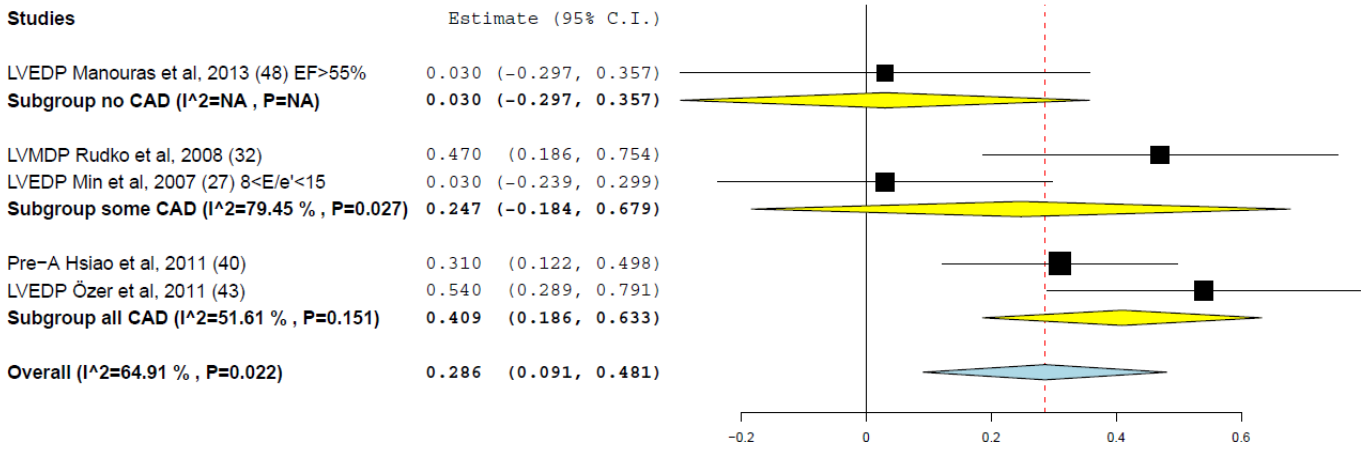
G. E/e'$_{septal}$: combined LVFP (primary and supplemental data)



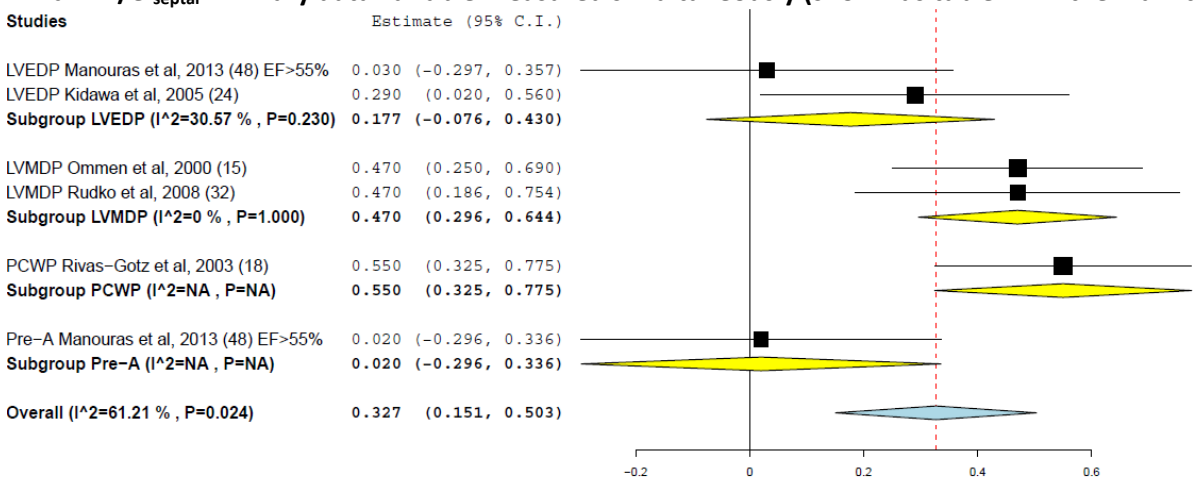
H. E/e'$_{septal}$: combined LVFP (simultaneous and NOT simultaneous)



I. E/e'$_{septal}$: combined LVFP (CAD prevalence)



J. E/e'$_{septal}$: Primary data variable measured simultaneously (shown as table 4B in the main text)



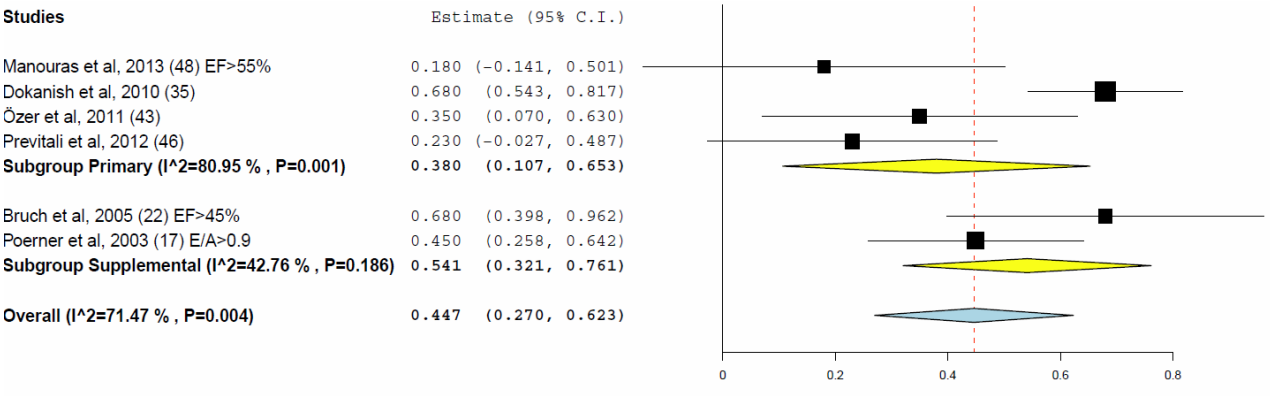
5.3. Subgroup analysis for E/e'_{mean} and LVFP

E/e'_{mean}: Dataset for subgroup analysis (see also Tables 1 and 2)

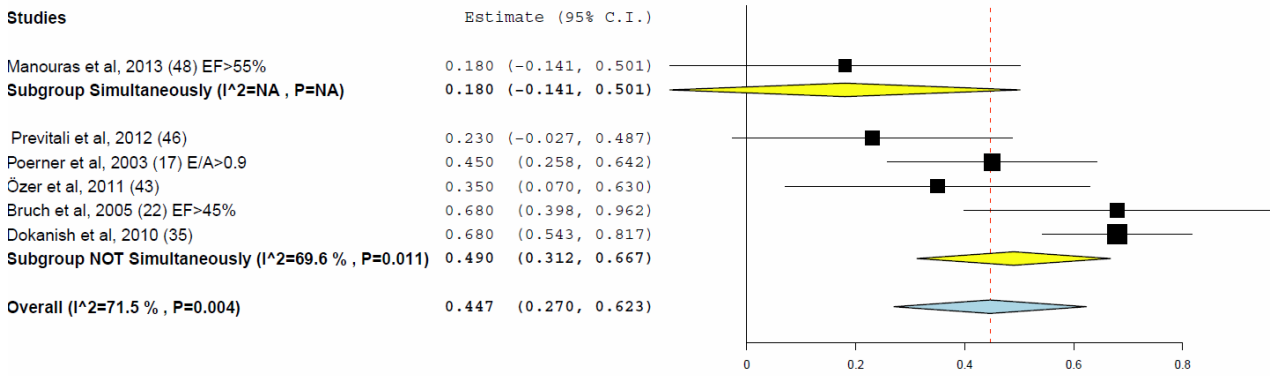
LVFP	*r*	se	Data	Timing	% HFpEF	% CAD	% HTN	% DM	Indication for cath
LVEDP									
LVEDP Manouras et al, 2013 (48) EF>55%	0.18	0.164	Primary	Simultaneously	unclear	no CAD	unclear	unclear	angiography
LVEDP Dokanish et al, 2010 (35)	0.68	0.07	Primary	NOT Simultan.	unclear	some CAD	~90% HTN	~40% DM	angiography
LVEDP Özer et al, 2011 (43)	0.35	0.143	Primary	NOT Simultan.	unclear	all CAD	~60% HTN	~40% DM	angiography
LVEDP Previtali et al, 2012 (46)	0.23	0.131	Primary	NOT Simultan.	0% HF	unclear	unclear	unclear	unclear
LVEDP Bruch et al, 2005 (22) EF>45%	0.68	0.144	Supplemer	NOT Simultan.	all HF	some CAD	~80% HTN%	unclear	dyspnea
LVEDP Poerner et al, 2003 (17) E/A>0.9	0.45	0.098	Supplemer	NOT Simultan.	unclear	unclear	unclear	unclear	angiography
PCWP									
PCWP Rivas-Gotz et al, 2003 (18)	0.57	0.113	Primary	Simultaneously	unclear	unclear	unclear	unclear	ICU/Cath lab
PCWP Wang et al, 2007 (29)	0.65	0.179	Primary	Simultaneously	unclear	unclear	unclear	unclear	ICU/Cath lab
PCWP Bhella et al, 2011 (39)	0.65	0.253	Primary	Simultaneously	all HF	no CAD	all HTN	~60% DM	research
PCWP Maeder et al, 2011 (42)	0.13	0.17	Primary	NOT Simultan.	~40% HF	unclear	unclear	unclear	HF/PAH/volunteers
PCWP Bruch et al, 2005 (22) EF>45%	0.56	0.162	Supplemer	NOT Simultan.	all HF	some CAD	~80% HTN	unclear	dyspnea
Pre-A									
Pre-A Manouras et al, 2013 (48) EF>55%	0.21	0.163	Primary	Simultaneously	unclear	no CAD	unclear	unclear	angiography
Pre-A Hsiao et al, 2011 (40)	0.25	0.098	Primary	NOT Simultan.	unclear	all CAD	~70% HTN	~50% DM	angiography
Pre-A Previtali et al, 2012 (46)	0.02	0.135	Primary	NOT Simultan.	0% HF	unclear	unclear	unclear	unclear
Pre-A Dokanish et al, 2008 (30)	0.39	0.168	Primary	NOT Simultan.	unclear	unclear	unclear	unclear	dyspnea
Pre-A Dokanish et al, 2010 (34)	0.63	0.071	Primary	NOT Simultan.	unclear	some CAD	~90% HTN	~60% DM	angiography
Pre-A Poerner et al, 2003 (17) E/A>0.9	0.57	0.09	Supplemer	NOT Simultan.	unclear	unclear	unclear	unclear	unclear
LVMDP									
LVMDP Ommen et al, 2000 (15)	0.45	0.121	Primary	Simultaneously	unclear	unclear	unclear	unclear	unclear

LVFP=left ventricular filling pressure; LVEDP=left ventricular end diastolic pressure; LVMDP=left ventricular mean diastolic pressure; Pre-A DP=left ventricular pre–A wave diastolic pressure; PCWP=pulmonary capillary wedge pressure; CI=confidence interval; HFpEF=heart failure with preserved Ejection Fraction; CAD=coronary artery disease; HTN=hypertension; DM=diabetes mellitus; ICU=intensive care unit. Studies are identified by the first author, year of publication, and reference number (in brackets) as cited in the main text.

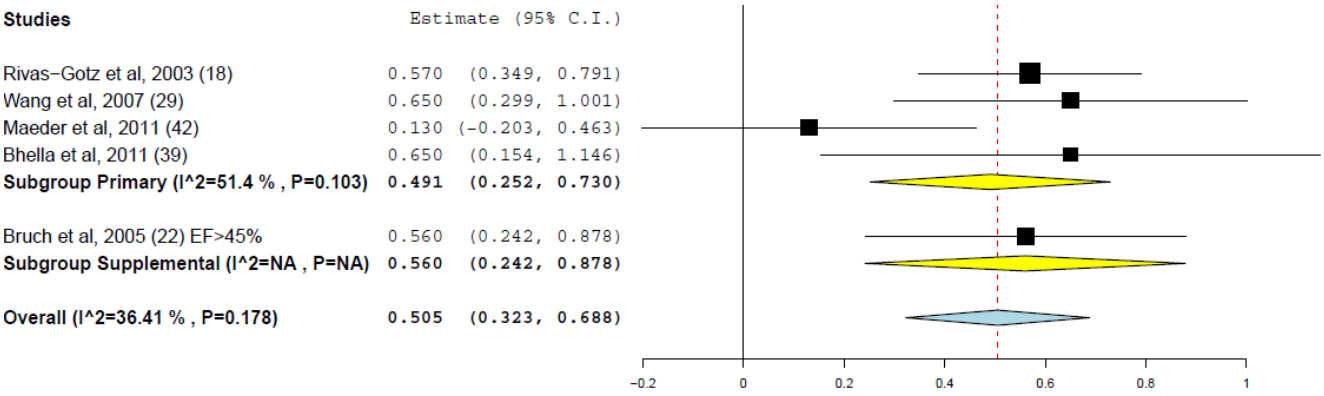
A. LVEDP (primary and supplemental data)



B. LVEDP (simultaneous and NOT simultaneous)

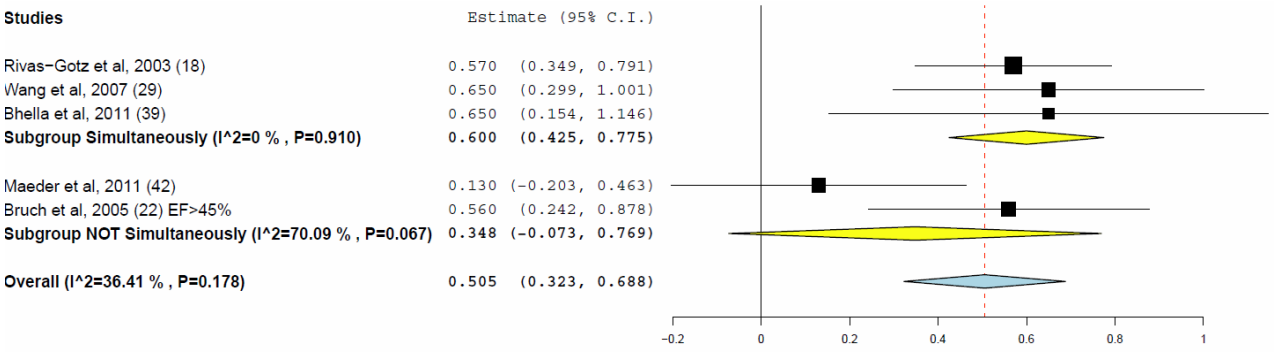


C. PCWP (primary and supplemental data)

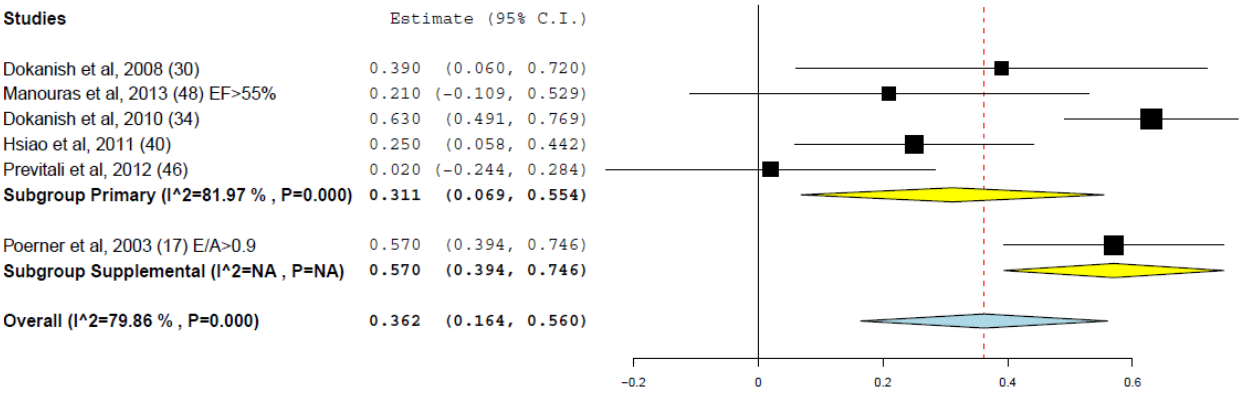


Heterogeneity amongst the studies was estimated by I2 statistic. Studies are identified by the first author, year of publication, and reference number (in brackets) as cited in the main text. OpenMetaAnalyst software (12) for Windows (64-bit version) was used for statistical analysis including graphical presentations of forest plots.

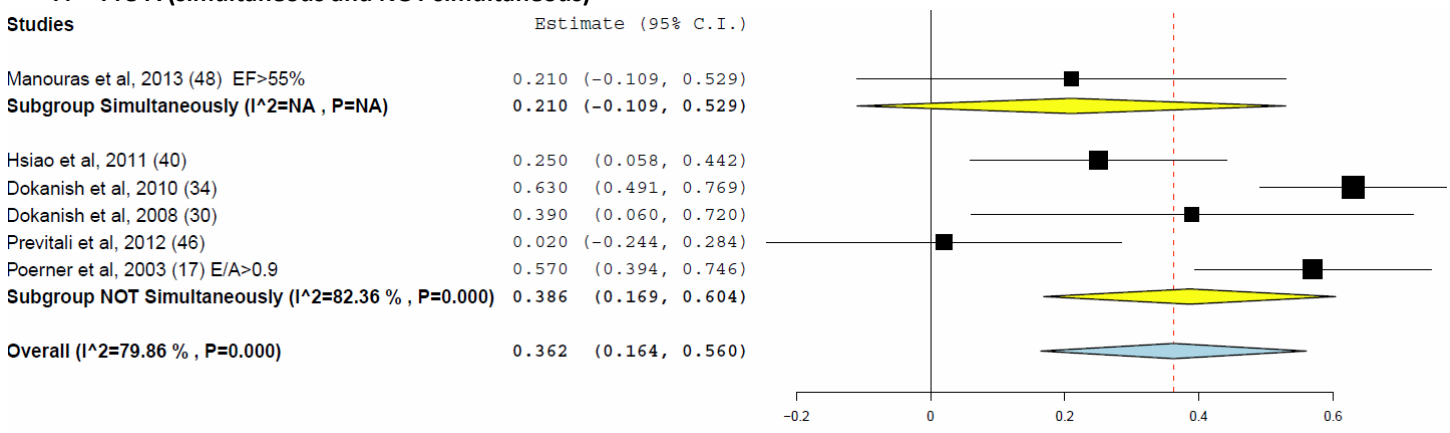
D. PCWP (simultaneous and NOT simultaneous)



E. Pre-A (primary and supplemental data)



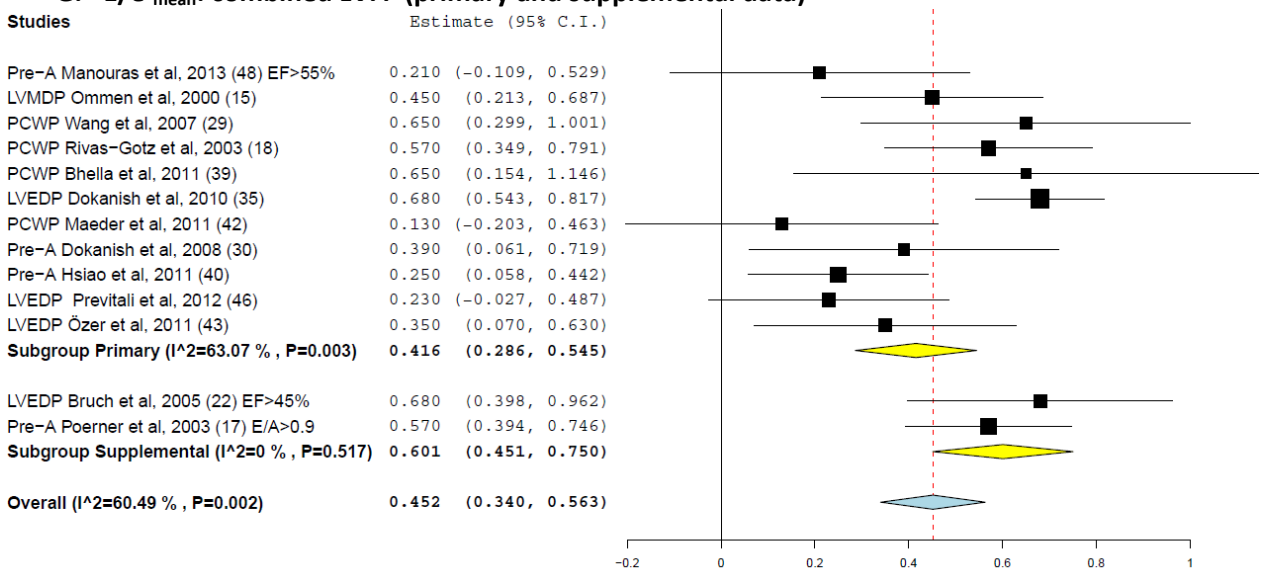
F. Pre-A (simultaneous and NOT simultaneous)



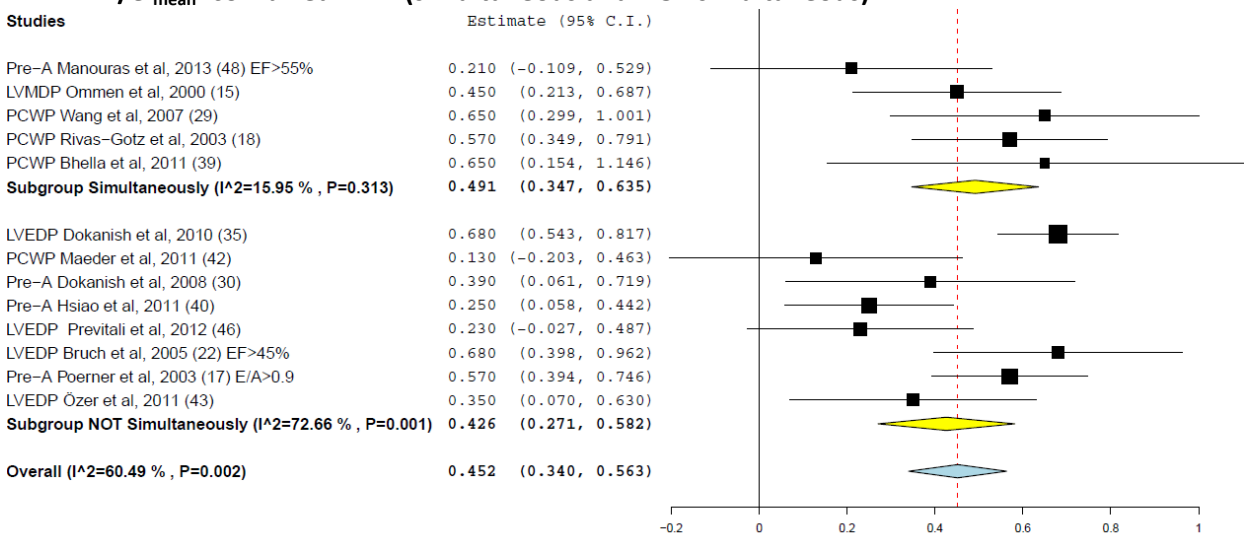
SUBGPOUP ANALYSIS for COMBINED LVFP and E/e'$_{mean}$

For combined LVFP analysis, if the study measured two LVFP parameters we chose that had the highest correlation coefficient.

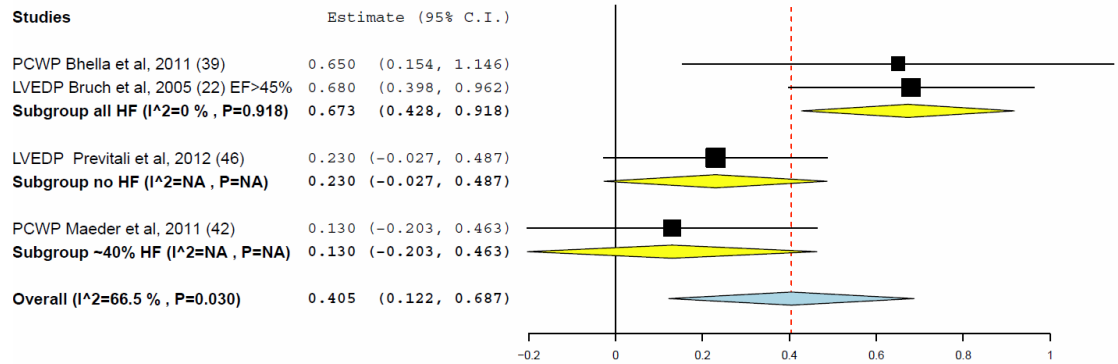
G. E/e'$_{mean}$: combined LVFP (primary and supplemental data)



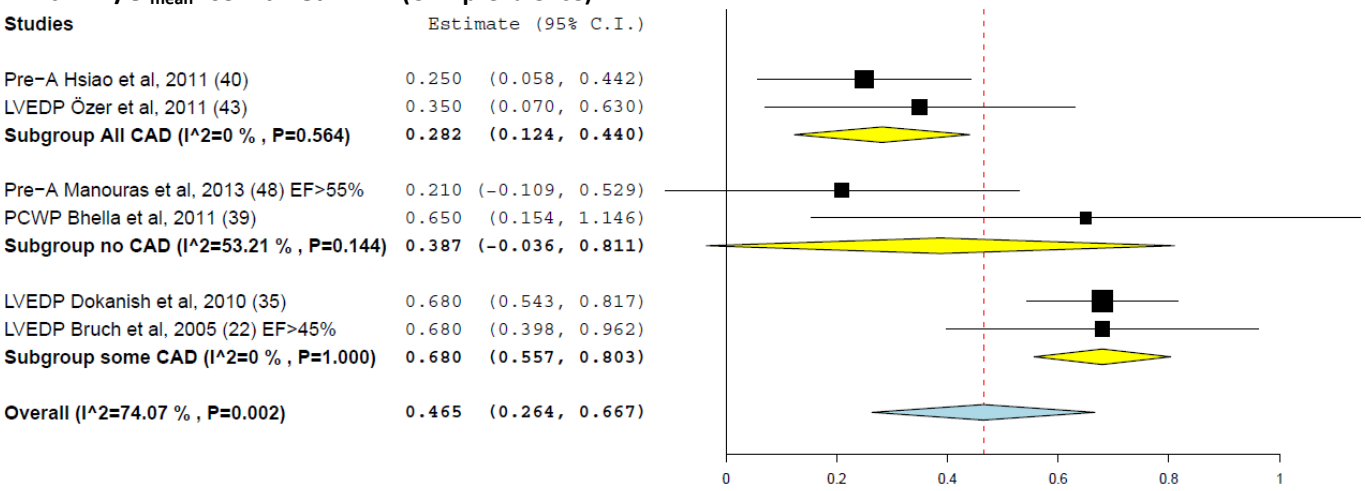
H. E/e'$_{mean}$: combined LVFP (simultaneous and NOT simultaneous)



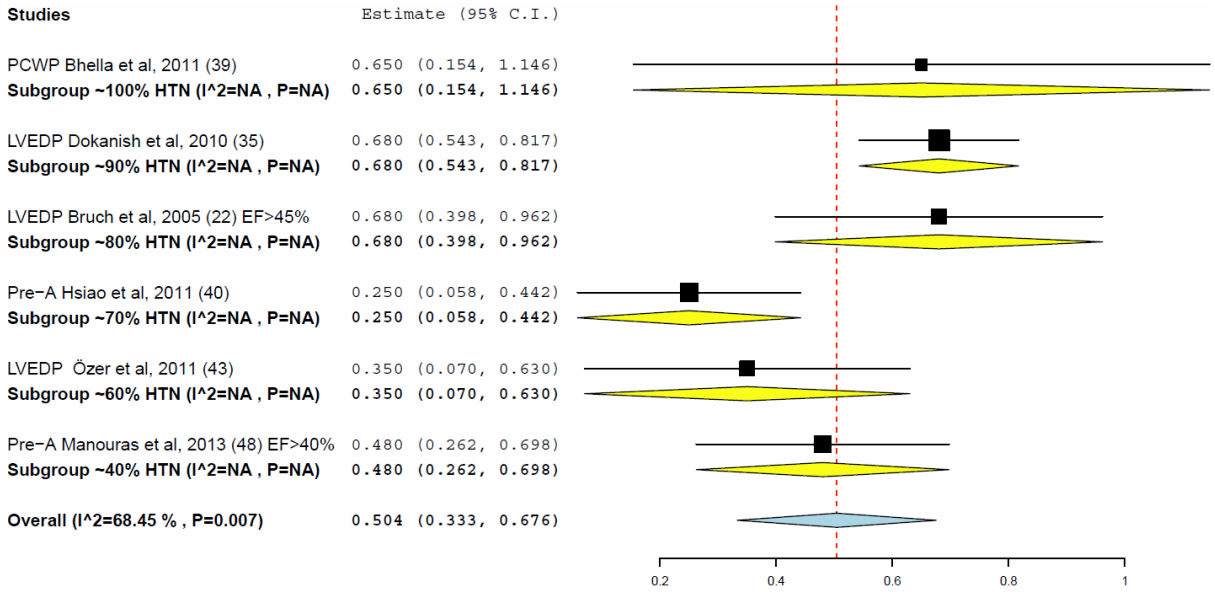
I. E/e'$_{mean}$: combined LVFP (HFpEF prevalence)



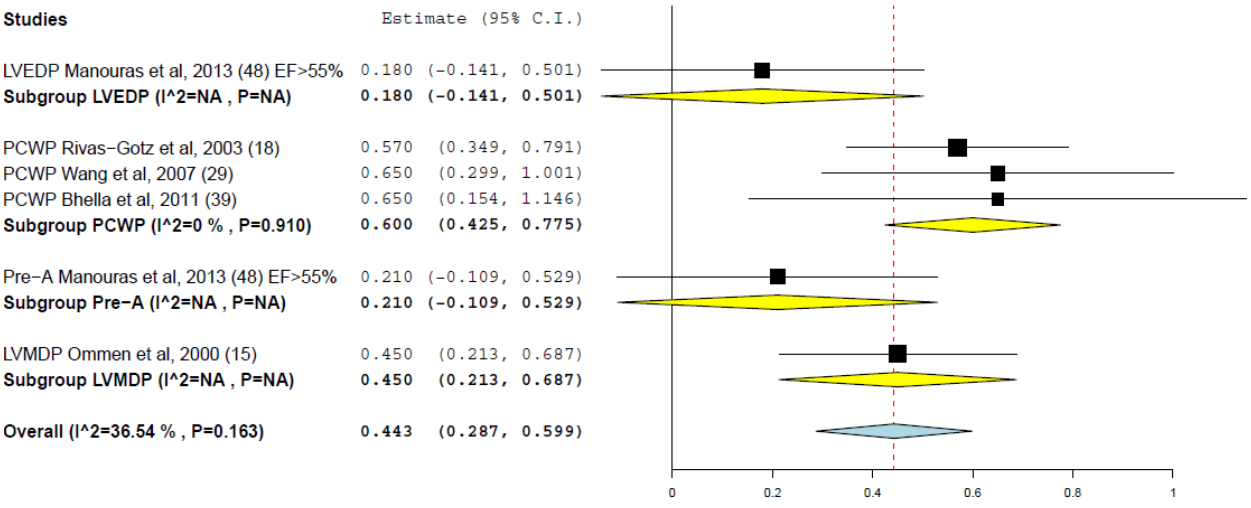
J. E/e'_{mean}: combined LVFP (CAD prevalence)



K. E/e'_{mean}: combined LVFP (HTN prevalence)



L. E/e'_{mean}: Primary data variables measured simultaneously (shown as table 4B in the main text)



APPENDIX 6

Secondary analysis of sensitivity/specificity of E/e' cutoffs to predict elevated LVFP

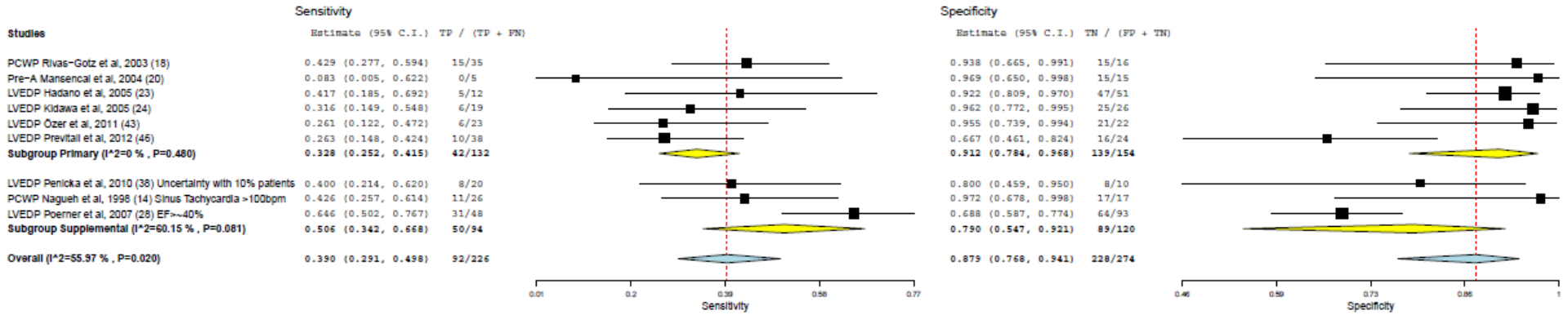
6.1. Subgroup analysis for $E/e'_{lateral}$ >12 to identify elevated LVFP

$E/e'_{lateral}$: Dataset for subgroup analysis (see also Tables 1 and 2)

study	TP	FN	FP	TN	SENS.	lower	upper	SPEC.	lower	upper	Data	Timing	% HFpEF	% CAD	% HTN	% DM	Indication for cath	LR+
LVEDP Kidawa et al, 2005 (24)	6	13	1	25	**0.316**	0.149	0.548	**0.962**	0.772	0.995	Primary	Simultaneously	unclear	unclear	unclear	unclear	angiography	8.3
PCWP Rivas-Gotz et al, 2003 (18)	15	20	1	15	**0.429**	0.277	0.594	**0.937**	0.665	0.991	Primary	Simultaneously	Unclear	Unclear	Unclear	Unclear	ICU/Cath lab	6.8
LVEDP Previtali et al, 2012 (46)	10	28	8	16	**0.263**	0.148	0.424	**0.667**	0.461	0.824	Primary	NOT simultaneou	0% HF	unclear	unclear	unclear	unclear	0.8
LVEDP Hadano et al, 2005 (23)	5	7	4	47	**0.417**	0.185	0.692	**0.922**	0.809	0.970	Primary	NOT simultaneou	unclear	some CAD	unclear	unclear	unclear	5.3
LVEDP Özer et al, 2011 (43)	6	17	1	21	**0.261**	0.122	0.472	**0.955**	0.739	0.994	Primary	NOT simultaneou	unclear	all CAD	~60% HTN	~40% DM	angiography	5.8
Pre-A Mansencal et al, 2004 (20)	0	5	0	15	**0.083**	0.005	0.622	**0.969**	0.650	0.998	Primary	NOT simultaneou	~5% HF	all CAD	~10% HTN	unclear	angiography	2.7
LVEDP Poerner et al, 2007 (28) EF>~40%	31	17	29	64	**0.646**	0.502	0.767	**0.688**	0.587	0.774	Suppleme	NOT simultaneou	Unclear	some CAD	~60% HTN	~30% DM	angiography	2.1
PCWP Nagueh et al, 1998 (14) EF>45% Sinus Tachycardia >100bpm	11	15	0	17	**0.426**	0.257	0.614	**0.972**	0.678	0.998	Suppleme	Simultaneously	Unclear	Unclear	Unclear	Unclear	ICU/Cath lab	15.2
LVEDP Penicka et al, 2010 (38) Uncertainty with 10% patients	8	12	2	8	**0.400**	0.214	0.620	**0.800**	0.459	0.950	Suppleme	Simultaneously	~70% HF	no CAD	~70% HTN	~30% DM	dyspnea	2.0

LVFP=left ventricular filling pressure; LVEDP=left ventricular end diastolic pressure; LVMDP=left ventricular mean diastolic pressure; Pre-A DP=left ventricular pre–A wave diastolic pressure; PCWP=pulmonary capillary wedge pressure; CI=confidence interval; HFpEF=heart failure with preserved Ejection Fraction; CAD=coronary artery disease; HTN=hypertension; DM=diabetes mellitus; ICU=intensive care unit; TP=true positive; FP= false positive; FN= false negative; TN=true negative; Sens.= sensitivity; Spec.=specificity; LR+=positive likelihood ratio. Studies are identified by the first author, year of publication, and reference number (in brackets) as cited in the main text.

A. Combined LVFP (primary and supplemental data)

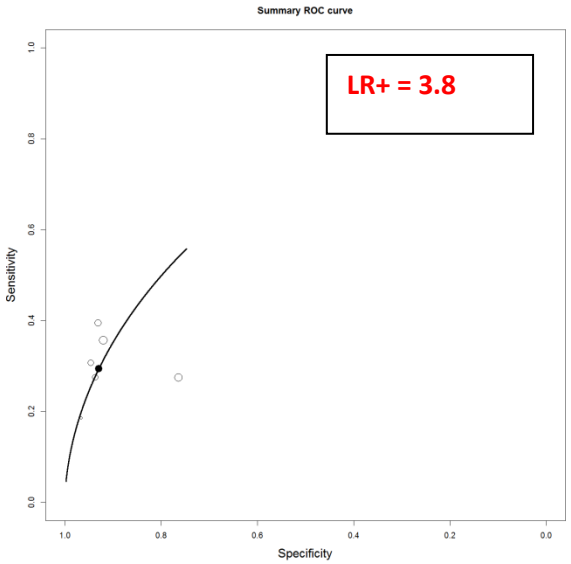


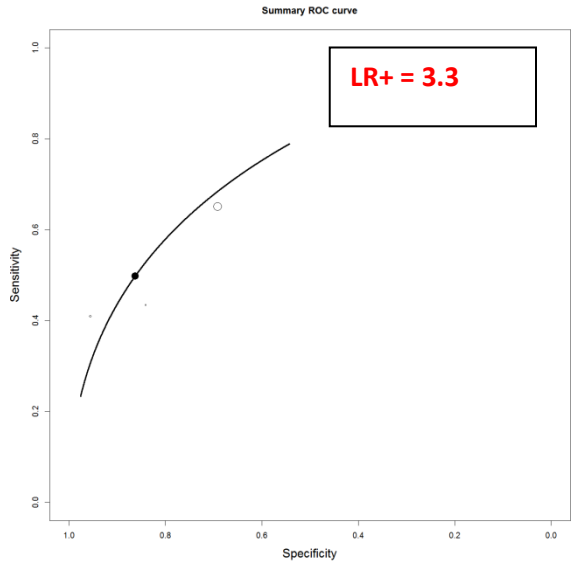
HSROC analysis

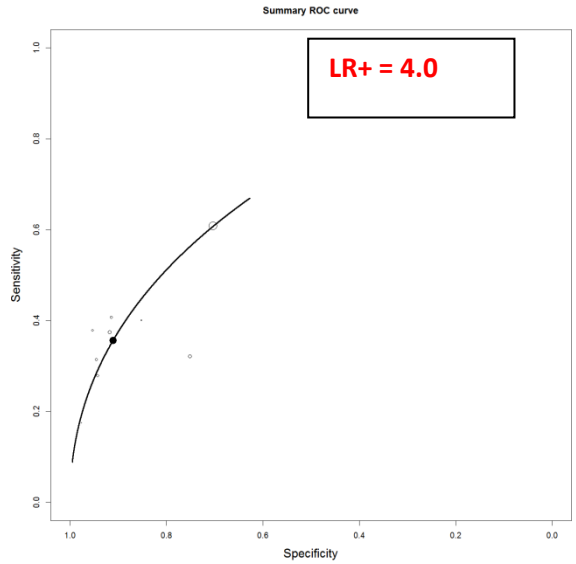
Primary studies combined (n=6, **as in Figure 3**)
Sensitivity (summary) 0.30 (0.09 - 0.48)
Specificity (summary) 0.92 (0.83 - 1.0)

Supplemental studies combined (n=3)
Sensitivity (summary) 0.50 (0.10 - 0.84)
Specificity (summary) 0.85 (0.50 – 1.0)

All studies combined (n=9)
Sensitivity (summary) 0.36 (0.18 - 0.51)
Specificity (summary) 0.91 (0.81- 0.99)

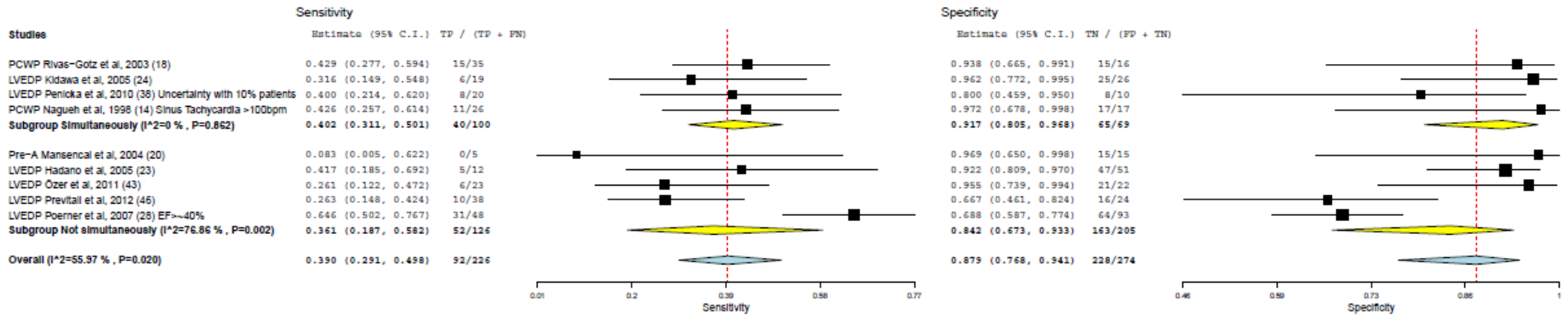






TP=true positive; FP= false positive; FN= false negative; TN=true negative; Sens.= sensitivity; Spec.=specificity; LR+=positive likelihood ratio; HSROC=hierarchical summary receiver operating characteristic. Heterogeneity amongst the studies was estimated by I2 statistic. Studies are identified by the first author, year of publication, and reference number (in brackets) as cited in the main text. OpenMetaAnalyst software (12) for Windows (64-bit version) was used for statistical analysis including graphical presentations of forest plots.

B. Combined LVFP (Simultaneous and not simultaneous measurements

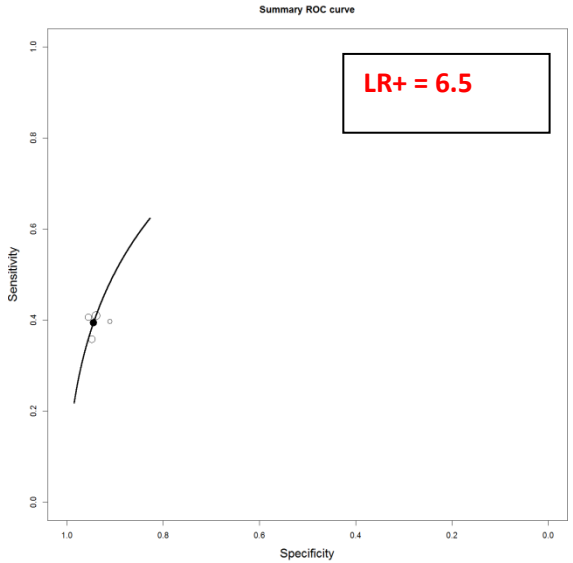


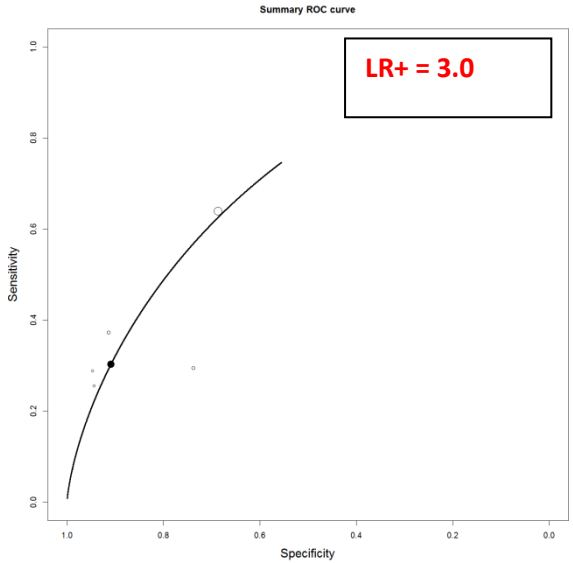
HSROC analysis

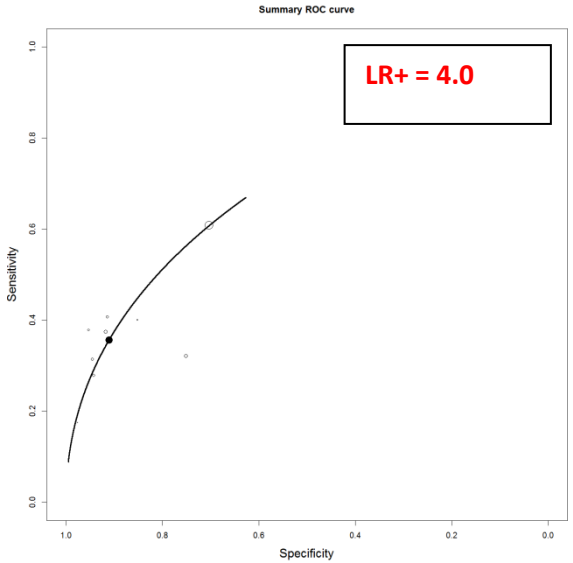
Simultaneous studies combined (n=4)
Sensitivity (summary) 0.39 (0.18 - 0.58)
Specificity (summary) 0.94 (0.40 - 1.0)

Not Simultaneous studies combined (n=5)
Sensitivity (summary) 0.30 (0.06 - 0.59)
Specificity (summary) 0.90 (0.76 – 1.0)

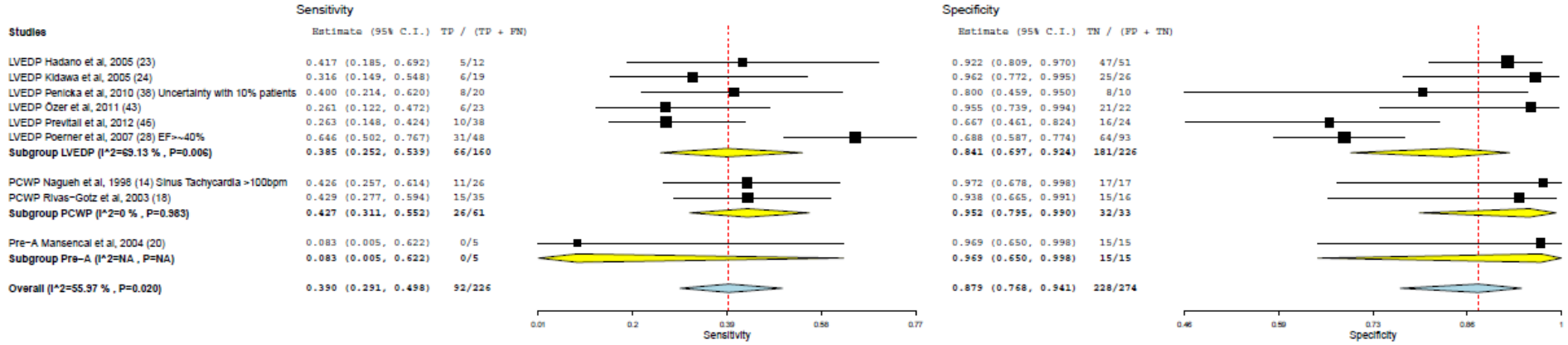
All studies combined (n=9)
Sensitivity (summary) 0.36 (0.18 - 0.51)
Specificity (summary) 0.91 (0.81- 0.99)







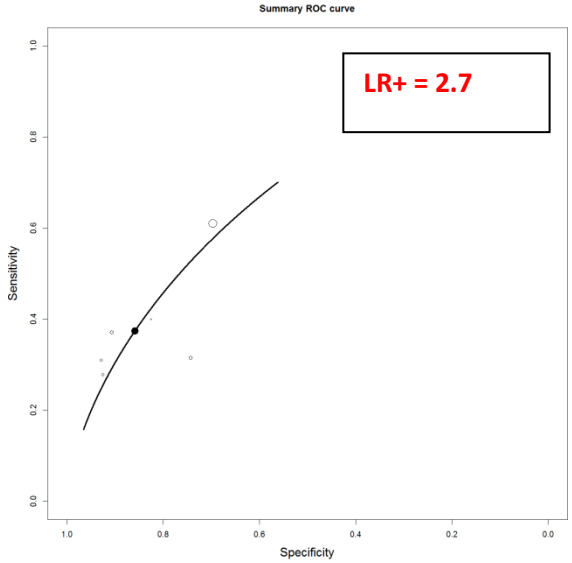
C. Separate analysis for LVFP measurements

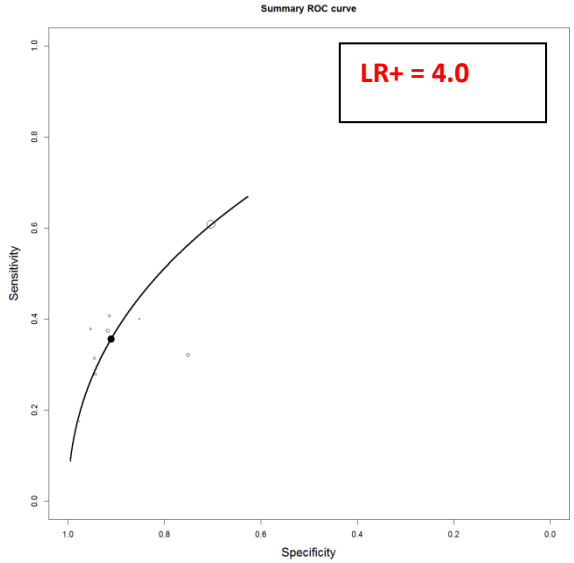


HSROC analysis

LVEDP studies combined (n=6)
Sensitivity (summary) 0.38 (0.17 - 0.59)
Specificity (summary) 0.86 (0.71 – 0.98)

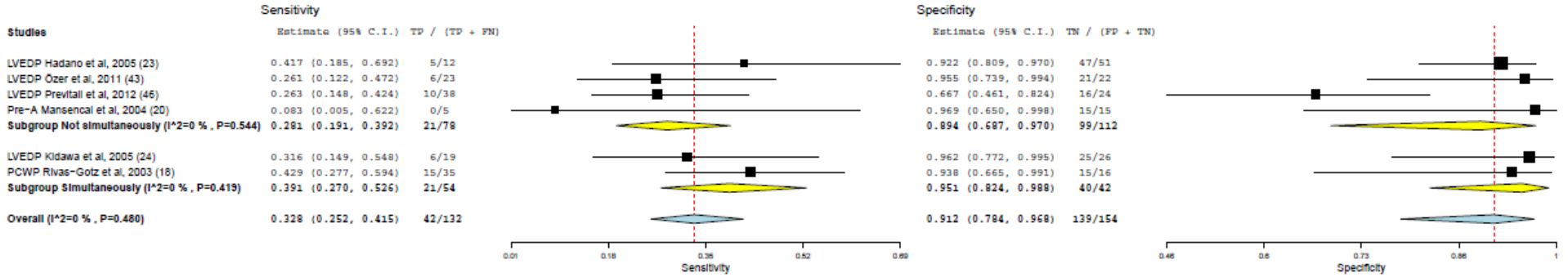
All studies combined (n=9)
Sensitivity (summary) 0.36 (0.18 - 0.51)
Specificity (summary) 0.91 (0.81- 0.99)





There are insufficient number of studies that measured PCWP (n=2) to perform a meaningful analysis.

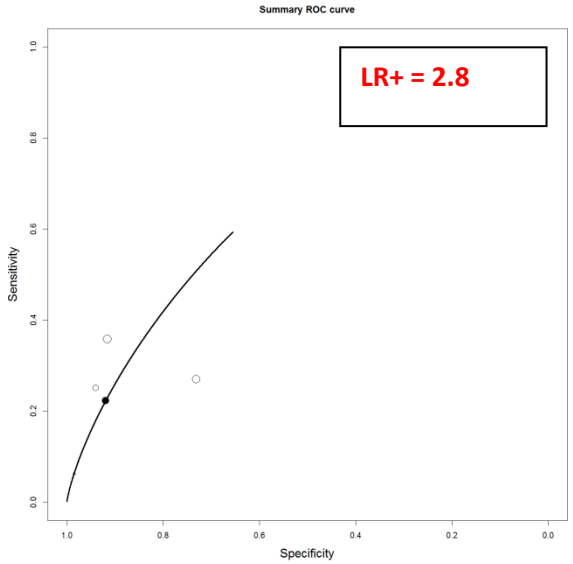
D. PRIMARY DATA SUMMARY - Primary studies only (Simultaneous and Not Simultaneous)

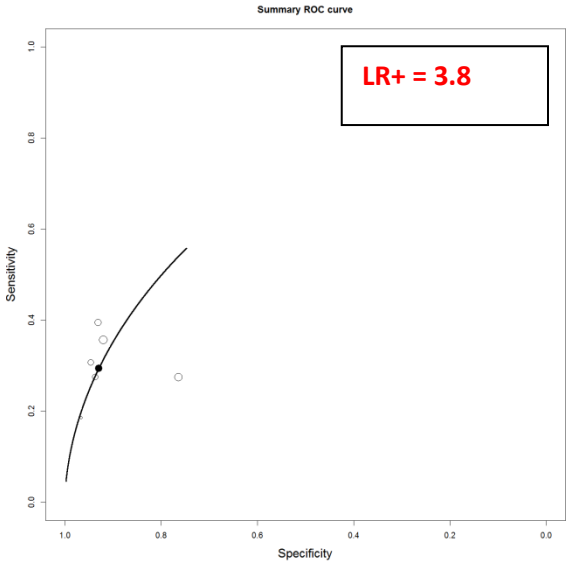


HSROC analysis

Primary Not Simultaneous studies (n=4)
Sensitivity (summary) 0.22 (0.01 - 0.53)
Specificity (summary) 0.92 (0.70 - 1.0)

All primary studies combined (n=6)
Sensitivity (summary) 0.36 (0.18 - 0.51)
Specificity (summary) 0.92 (0.83 - 1.0)





There are insufficient number of studies that performed simultaneous measurements (n=2) to perform a meaningful analysis.

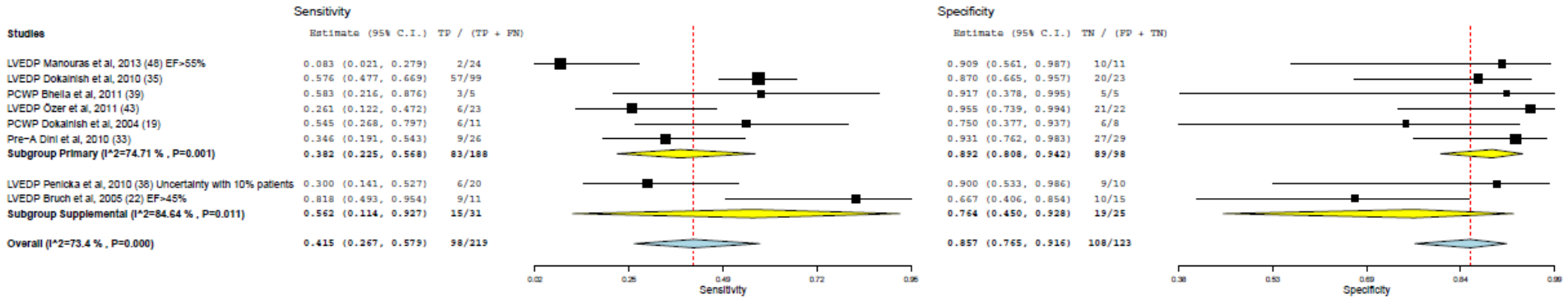
6.2. Subgroup analysis for E/e'_{mean} >13 to identify elevated LVFP

E/e'_{mean}: Dataset for subgroup analysis (see also Tables 1 and 2)

study	TP	FN	FP	TN	SENS.	lower	upper	SPEC.	lower	upper	Data	Timing	% HFpEF	% CAD	% HTN	% DM	Indication for cath	LR+
LVEDP Manouras et al, 2013 (48) EF>55%	2	22	1	10	**0.083**	0.021	0.279	**0.909**	0.561	0.987	Primary	Simultaneously	unclear	no CAD	unclear	unclear	angiography	0.9
PCWP Bhella et al, 2011 (39)	3	2	0	5	**0.583**	0.216	0.876	**0.917**	0.378	0.995	Primary	Simultaneously	100% HF	no CAD	100% HTN	~60% DM	research	7.0
PCWP Dokainish et al, 2004 (19)	6	5	2	6	**0.545**	0.268	0.797	**0.750**	0.377	0.937	Primary	Simultaneously	unclear	unclear	~60% HTN	~20% DM	ICU/CCU	2.2
LVEDP Dokainish et al, 2010 (35)	57	42	3	20	**0.576**	0.477	0.669	**0.870**	0.665	0.957	Primary	NOT simultaneou	unclear	some CAD	~90% HTN	~40% DM	angiography	4.4
LVEDP Özer et al, 2011 (43)	6	17	1	21	**0.261**	0.122	0.472	**0.955**	0.739	0.994	Primary	NOT simultaneou	unclear	all CAD	~60% HTN	~40% DM	angiography	5.8
Pre-A Dini et al, 2010 (33)	9	17	2	27	**0.346**	0.191	0.543	**0.931**	0.762	0.983	Primary	NOT simultaneou	100% HF	unclear	unclear	unclear	dyspnea	5.0
LVEDP Penicka et al, 2010 (38) Uncertainty with 10% patients	6	14	1	9	**0.300**	0.141	0.527	**0.900**	0.533	0.986	Suppleme	Simultaneously	~70% HF	no CAD	~70% HTN	~30% DM	dyspnea	3.0
LVEDP Bruch et al, 2005 (22) EF>45%	9	2	5	10	**0.818**	0.493	0.954	**0.667**	0.406	0.854	Suppleme	NOT simultaneou	100% HF	some CAD	~80% HTN	unclear	dyspnea	2.5

LVFP=left ventricular filling pressure; LVEDP=left ventricular end diastolic pressure; LVMDP=left ventricular mean diastolic pressure; Pre-A DP=left ventricular pre–A wave diastolic pressure; PCWP=pulmonary capillary wedge pressure; CI=confidence interval; HFpEF=heart failure with preserved Ejection Fraction; CAD=coronary artery disease; HTN=hypertension; DM=diabetes mellitus; ICU=intensive care unit; TP=true positive; FP= false positive; FN= false negative; TN=true negative; Sens.= sensitivity; Spec.=specificity; LR+=positive likelihood ratio. Studies are identified by the first author, year of publication, and reference number (in brackets) as cited in the main text.

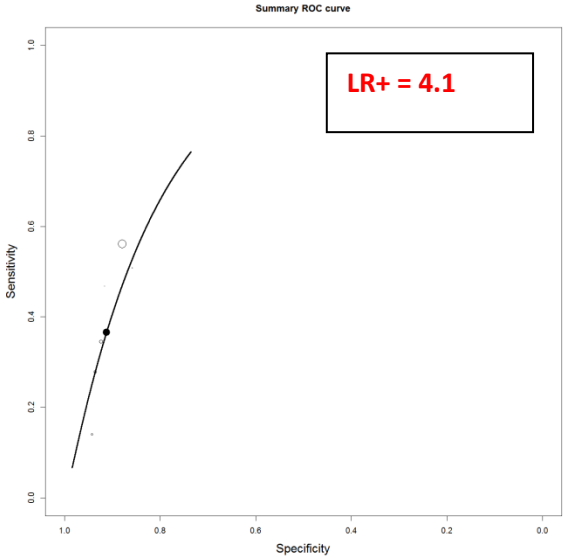
A. Combined LVFP (primary and supplemental data)

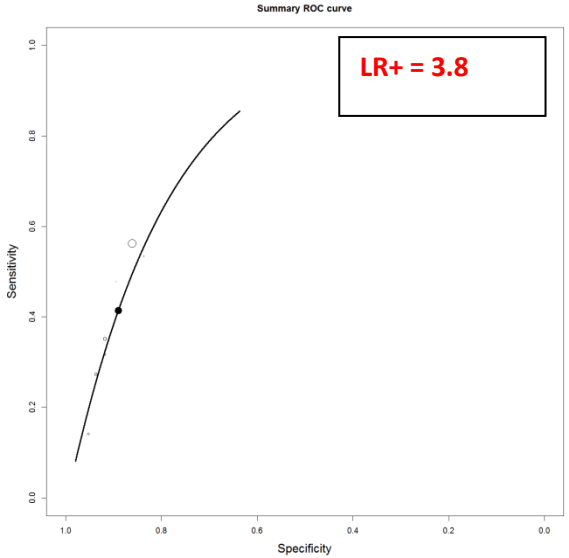


HSROC analysis

Primary studies combined (n=6, **as in Figure 3**)
Sensitivity (summary) 0.37 (0.13 - 0.61)
Specificity (summary) 0.91 (0.81 – 0.99)

All studies combined (n=8)
Sensitivity (summary) 0.42 (0.19 - 0.65)
Specificity (summary) 0.89 (0.77- 0.98)

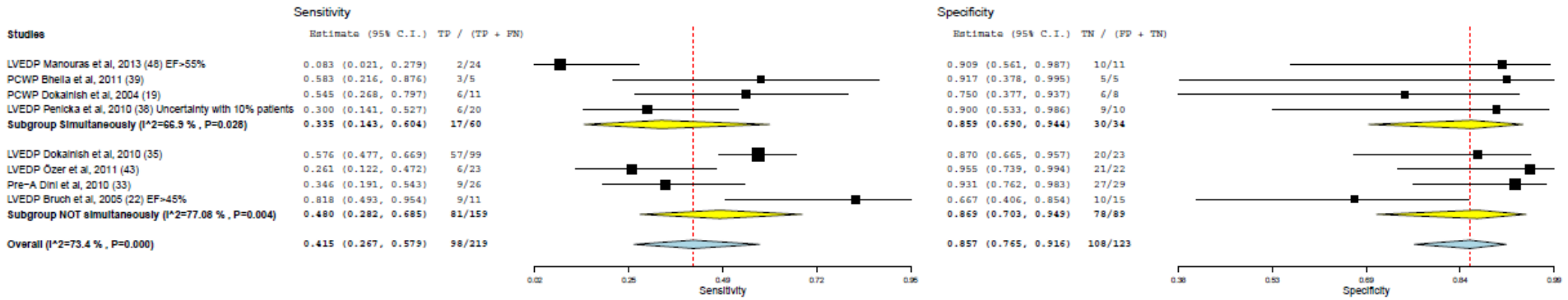




There are insufficient number of studies that provided supplemental data (n=2) to perform a meaningful analysis.

TP=true positive; FP= false positive; FN= false negative; TN=true negative; Sens.= sensitivity; Spec.=specificity; LR+=positive likelihood ratio; HSROC=hierarchical summary receiver operating characteristic. Heterogeneity amongst the studies was estimated by I2 statistic. Studies are identified by the first author, year of publication, and reference number (in brackets) as cited in the main text. OpenMetaAnalyst software (12) for Windows (64-bit version) was used for statistical analysis including graphical presentations of forest plots.

B. Combined LVFP (Simultaneous and not simultaneous measurements)

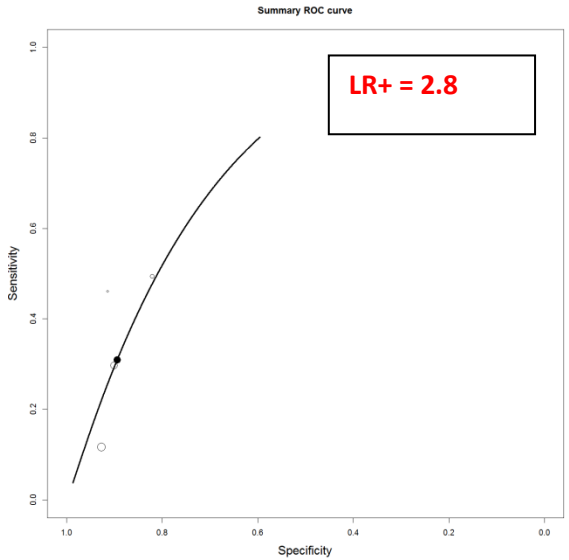


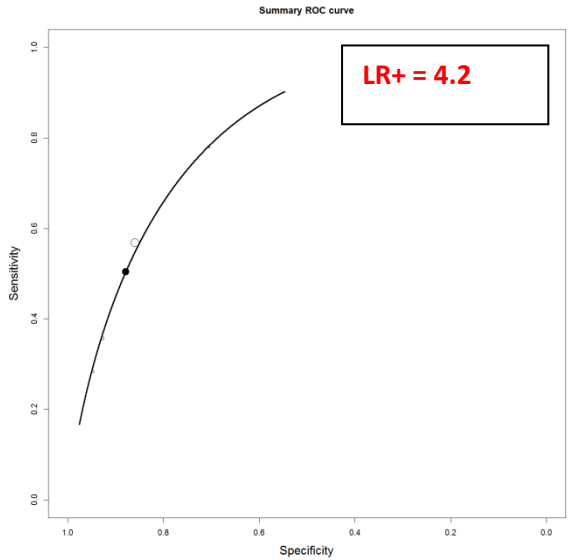
HSROC analysis

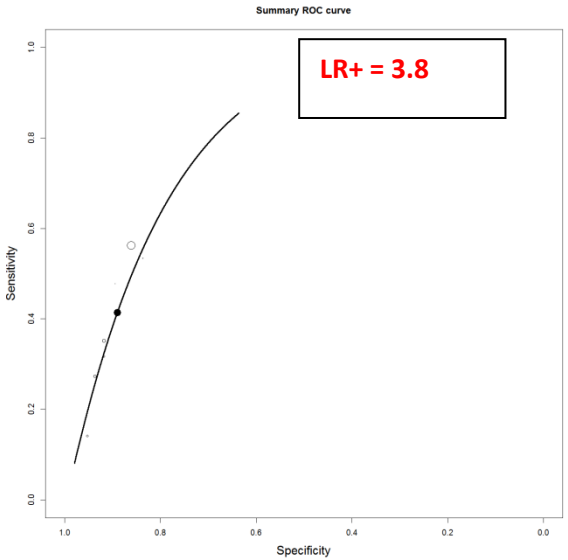
Simultaneous studies combined (n=4)
Sensitivity (summary) 0.31 (0.04 - 0.67)
Specificity (summary) 0.89 (0.67 – 1.0)

NOT Simultaneous studies combined (n=4)
Sensitivity (summary) 0.50 (0.11 – 0.84)
Specificity (summary) 0.88 (0.65 – 1.0)

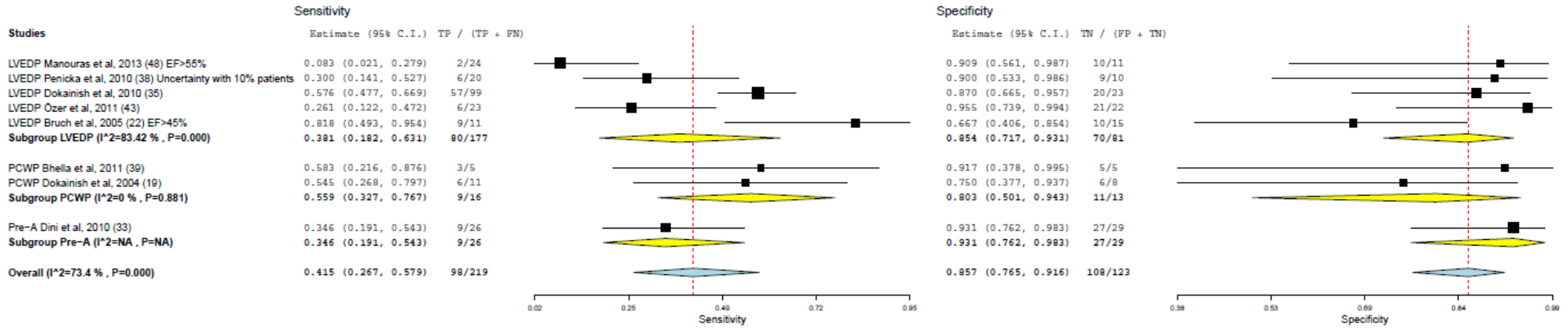
All studies combined (n=8)
Sensitivity (summary) 0.42 (0.19 - 0.65)
Specificity (summary) 0.89 (0.77- 0.98)







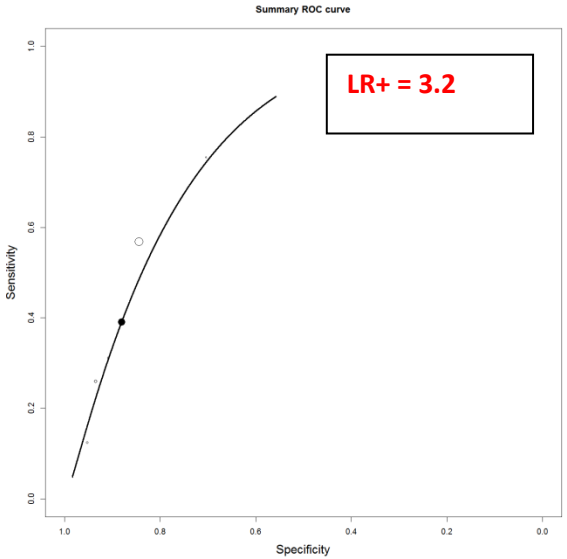
C. Separate analysis for LVFP measurements

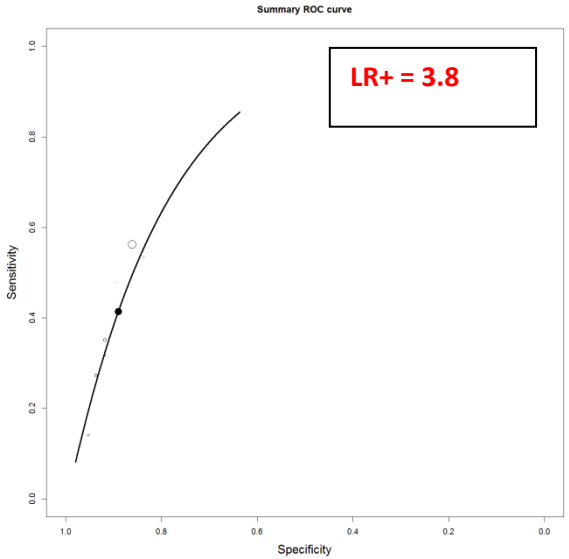


HSROC analysis

LVEDP studies (n=4)
Sensitivity (summary) 0.39 (0.07 - 073)
Specificity (summary) 0.88 (0.69 – 0.99)

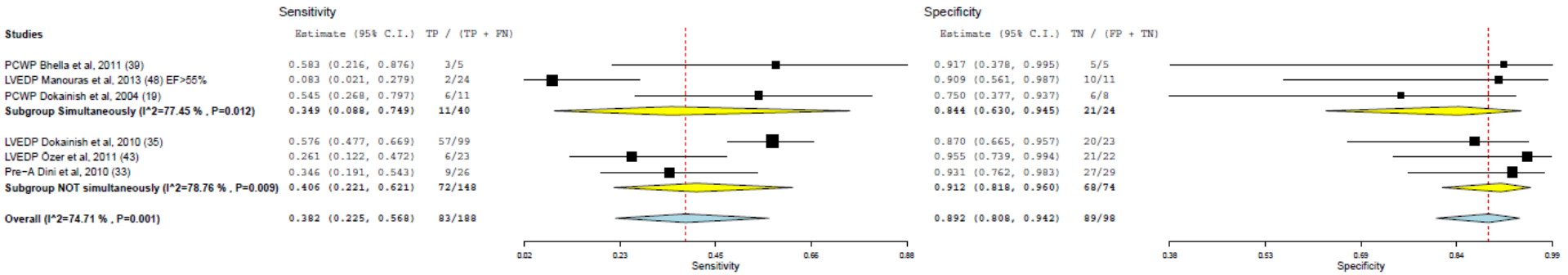
All studies combined (n=8)
Sensitivity (summary) 0.42 (0.19 - 0.65)
Specificity (summary) 0.89 (0.77- 0.98)





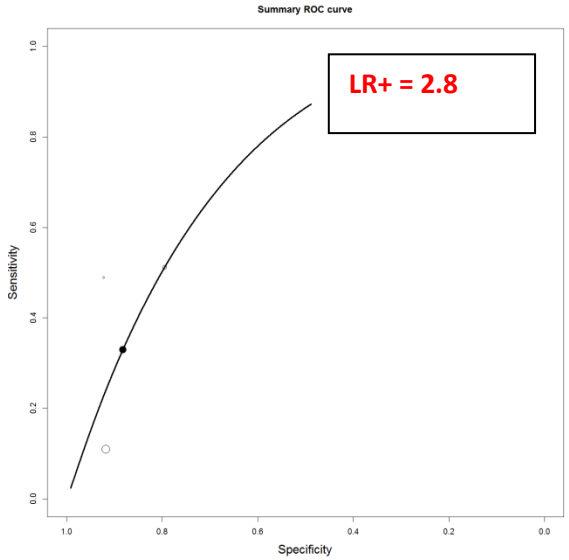
There are insufficient number of studies that measured PCWP (n=2) to perform a meaningful analysis.

D. PRIMARY DATA SUMMARY - Primary studies only (Simultaneous and Not Simultaneous)

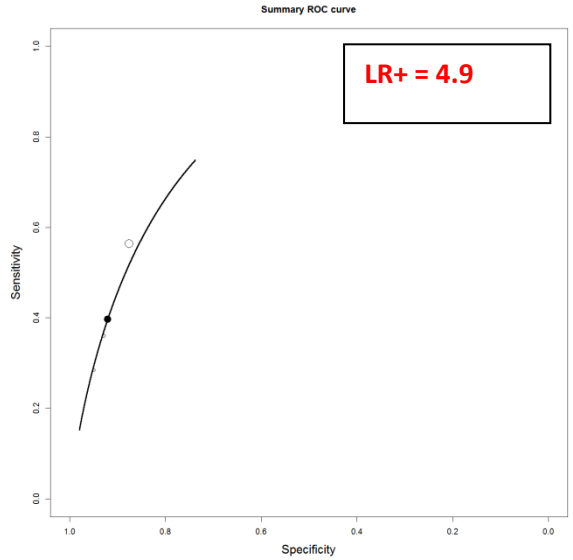


HSROC analysis

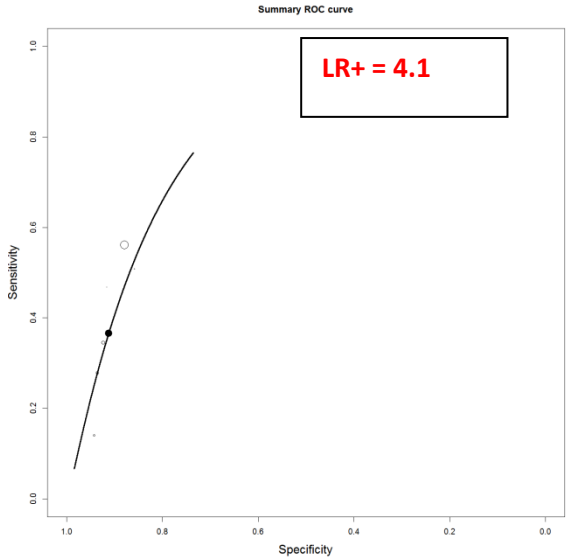
Primary Simultaneous studies (n=3)
Sensitivity (summary) 0.33 (0.03 – 0.77)
Specificity (summary) 0.88 (0.53 – 1.0)



Primary NOT Simultaneous studies (n=3)
Sensitivity (summary) 0.39 (0.07 – 0.73)
Specificity (summary) 0.92 (0.71 – 1.0)



All Primary studies (n=6)
Sensitivity (summary) 0.37 (0.13 - 0.61)
Specificity (summary) 0.91 (0.81 – 0.99)



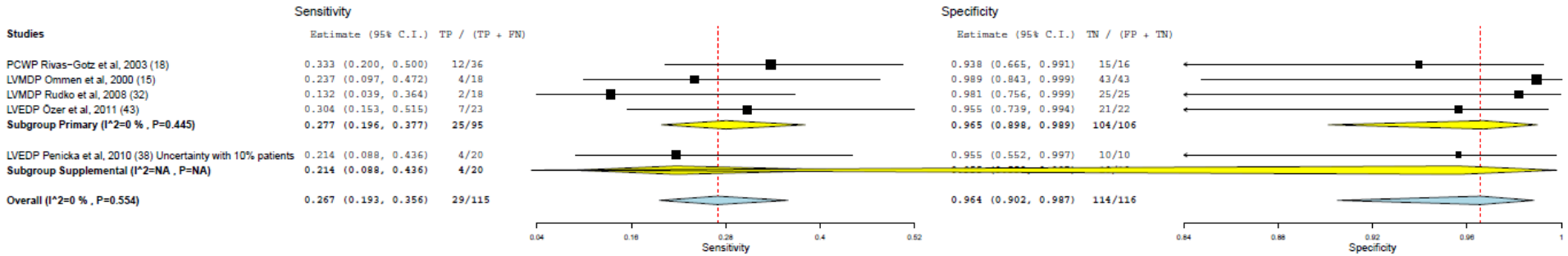
6.3. Subgroup analysis for E/e'_{septal} >15 to identify elevated LVFP

E/e'_{septal}: Dataset for subgroup analysis (see also Tables 1 and 2)

study	TP	FN	FP	TN	SENS.	lower	upper	SPEC.	lower	upper	Data	Timing	% HFpEF	% CAD	% HTN	% DM	Indication for cath	LR+
PCWP Rivas-Gotz et al, 2003 (18)	12	24	1	15	**0.333**	0.200	0.500	**0.937**	0.665	0.99	Primary	Simultaneously	Unclear	Unclear	Unclear	Unclear	ICU/Cath lab	5.3
LVMDP Ommen et al, 2000 (15)	4	14	0	43	**0.237**	0.097	0.472	**0.989**	0.843	1.00	Primary	Simultaneously	Unclear	Unclear	Unclear	Unclear	Unclear	21.5
LVMDP Rudko et al, 2008 (32)	2	16	0	25	**0.132**	0.039	0.364	**0.981**	0.756	1.00	Primary	Simultaneously	~20% HF	~80% CAD	~50% HTN	Unclear	Unclear	6.9
LVEDP Özer et al, 2011 (43)	7	16	1	21	**0.304**	0.153	0.515	**0.955**	0.739	0.99	Primary	NOT simultaneou	unclear	all CAD	~60% HTN	~40% DM	angiography	6.8
LVEDP Penicka et al, 2010 (38) Uncertainty with 10% patients	4	16	0	10	**0.214**	0.088	0.436	**0.955**	0.552	1.00	Supplemen	Simultaneously	~70% HF	no CAD	~70% HTN	~30% DM	dyspnea	4.8

LVFP=left ventricular filling pressure; LVEDP=left ventricular end diastolic pressure; LVMDP=left ventricular mean diastolic pressure; Pre-A DP=left ventricular pre–A wave diastolic pressure; PCWP=pulmonary capillary wedge pressure; CI=confidence interval; HFpEF=heart failure with preserved Ejection Fraction; CAD=coronary artery disease; HTN=hypertension; DM=diabetes mellitus; ICU=intensive care unit; TP=true positive; FP= false positive; FN= false negative; TN=true negative; Sens.= sensitivity; Spec.=specificity; LR+=positive likelihood ratio. Studies are identified by the first author, year of publication, and reference number (in brackets) as cited in the main text.

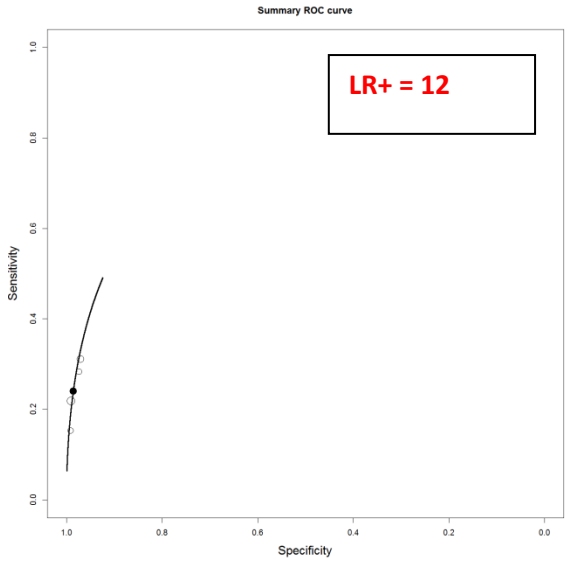
A. Combined LVFP (primary and supplemental data)

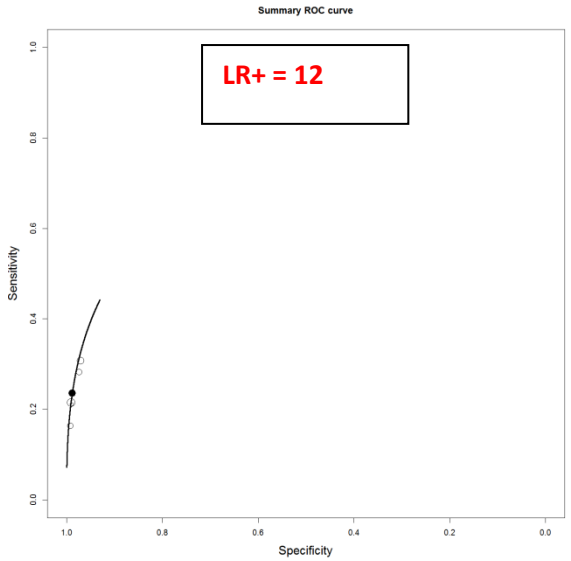


HSROC analysis

Primary studies (n=4)
Sensitivity (summary) 0.24 (0.06 – 0.46)
Specificity (summary) 0.98 (0.92 – 1.0)

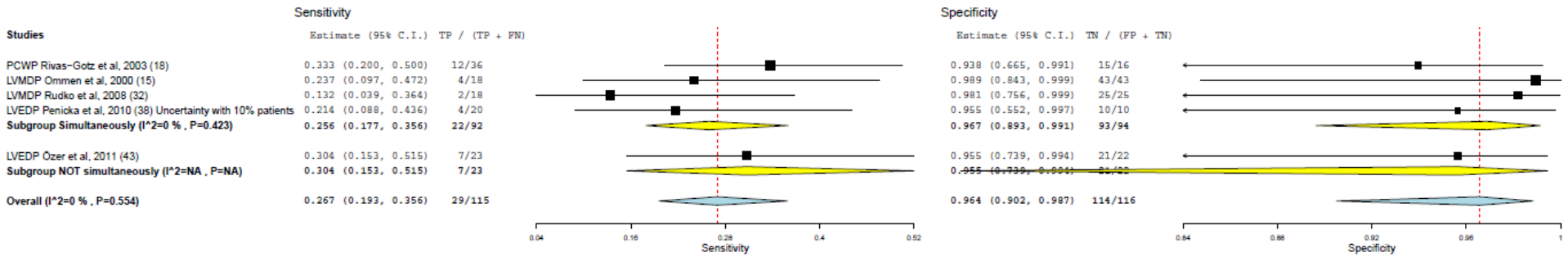
All studies (n=5)
Sensitivity (summary) 0.23 (0.10 - 0.39)
Specificity (summary) 0.98 (0.94 – 1.0)





TP=true positive; FP= false positive; FN= false negative; TN=true negative; Sens.= sensitivity; Spec.=specificity; LR+=positive likelihood ratio; HSROC=hierarchical summary receiver operating characteristic. Heterogeneity amongst the studies was estimated by I2 statistic. Studies are identified by the first author, year of publication, and reference number (in brackets) as cited in the main text. OpenMetaAnalyst software (12) for Windows (64-bit version) was used for statistical analysis including graphical presentations of forest plots.

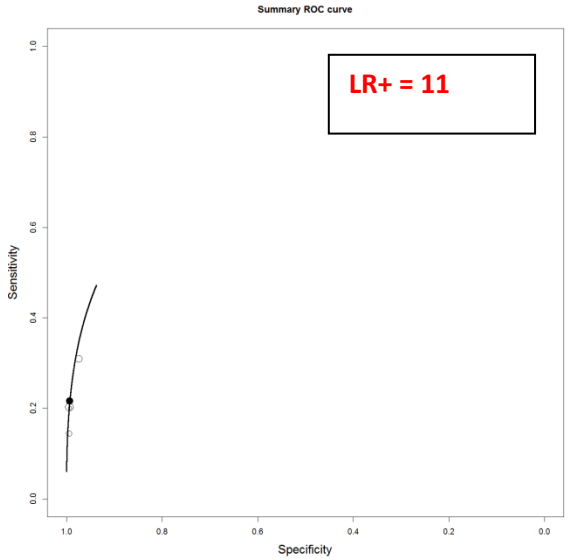
B. Combined LVFP (Simultaneous and not simultaneous measurements)

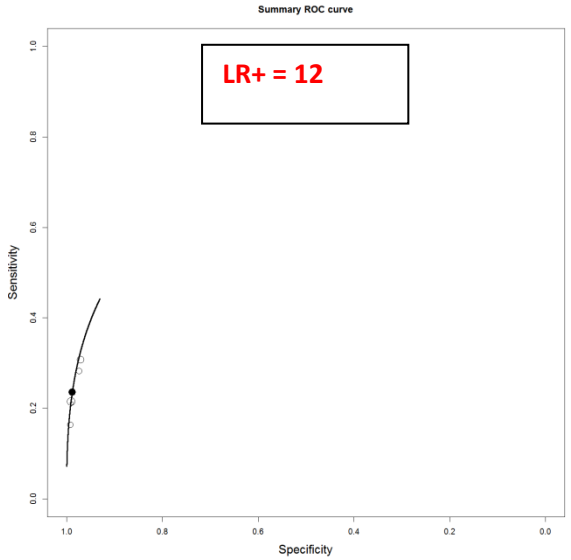


HSROC analysis

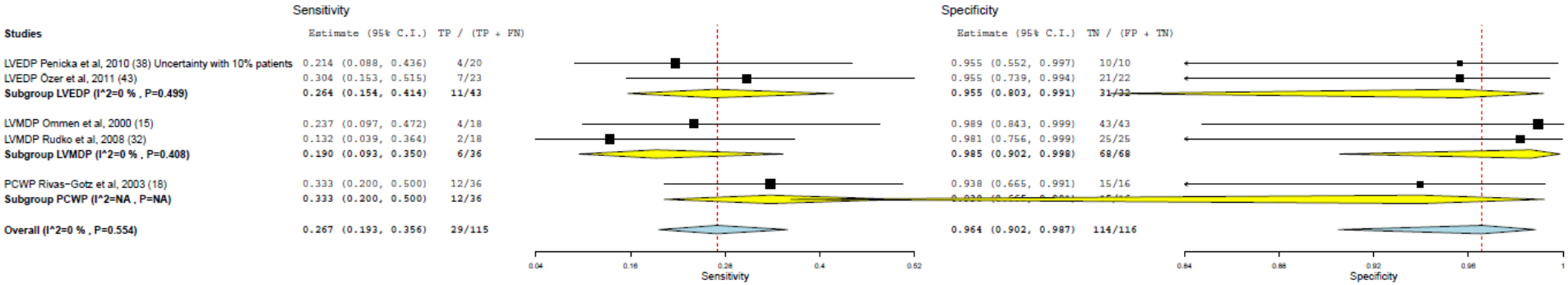
Simultaneous studies (n=4)
Sensitivity (summary) 0.22 (0.08 – 0.44)
Specificity (summary) 0.98 (0.93 – 1.0)

All studies (n=5)
Sensitivity (summary) 0.23 (0.10 - 0.39)
Specificity (summary) 0.98 (0.94 – 1.0)





C. Separate analysis for LVFP measurements

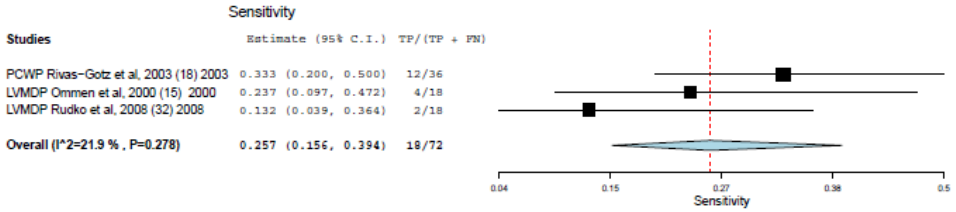


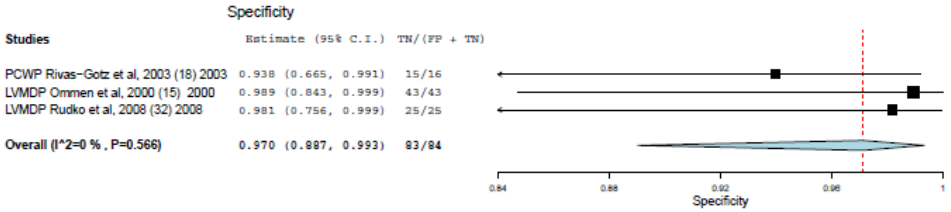
HSROC analysis

There are insufficient number of studies that measured LVEDP (n=2) or LVDP (n=2) to perform a meaningful analysis.

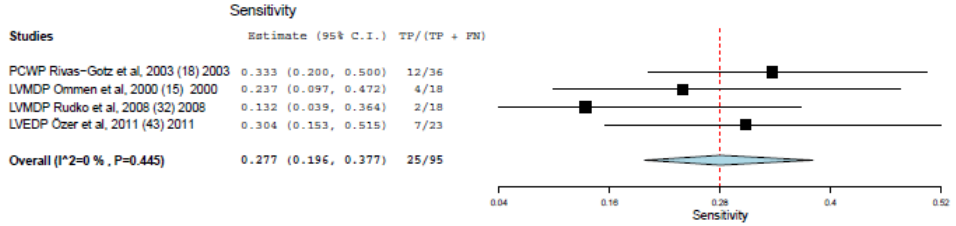
D. PRIMARY DATA SUMMARY - Primary studies only (Simultaneous and Not Simultaneous)

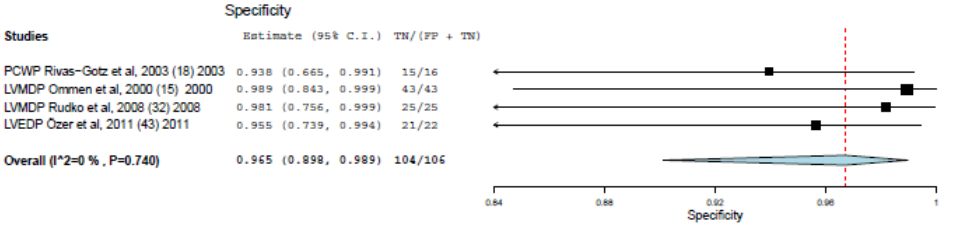
Simultaneous studies





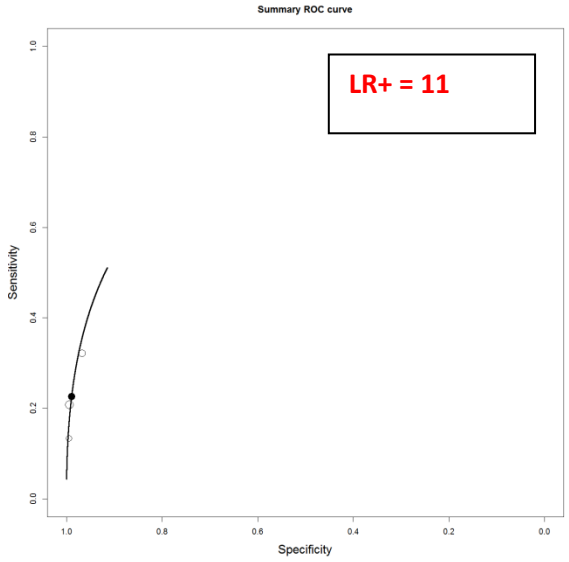
All studies



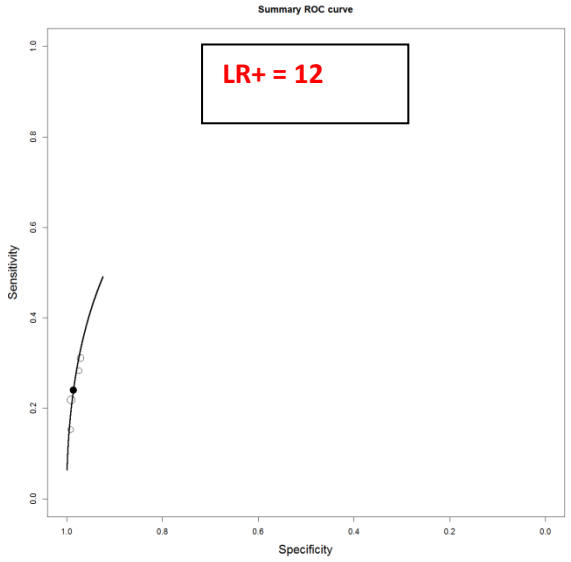


HSROC analysis

Primary Simultaneous studies (n=3)
Sensitivity (summary) 0.22 (0.04 – 0.54)
Specificity (summary) 0.98 (0.87 – 1.0)



All Primary studies (n=4)
Sensitivity (summary) 0.24 (0.06 – 0.46)
Specificity (summary) 0.98 (0.92 – 1.0)



APPENDIX 7

Optimal cutoffs and AUC for elevated LVFP

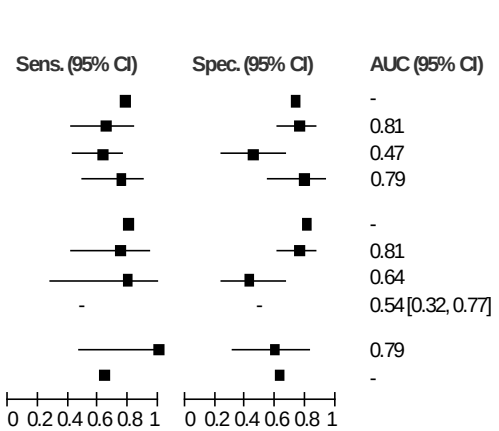
7.1. Identification of elevated LVFP based on 'optimal' E/e'$_{mean}$ cutoffs from ROC analysis

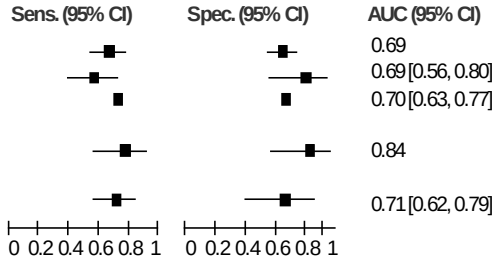
LVEF≥50%

Study	N	LVFP cutoff	E/e' cutoff	Prev. (%)	TP	FP	FN	TN	Sens. (95% CI)	Spec. (95% CI)	AUC (95% CI)
Kidawa, 2005 (24)	50	LVEDP ≥15	**>8**	54	-	-	-	-	0.76	0.76	-
Hadano, 2005* (23)	63/65	LVEDP >16	**>9**	19	10	11	5	37	0.67 [0.41, 0.85]	0.77 [0.63, 0.87]	0.81
Previtali, 2012* (46)	62/57	LVEDP>16	**>9**	61	24	13	14	11	0.63 [0.46, 0.78]	0.46 [0.26, 0.67]	0.47
Arques 2013 (47)	36	LVEDP>16	**>6.6**	58	15	3	6	12	0.71 [0.49, 0.87]	0.80 [0.53, 0.93]	0.79
Rivas-Gotz, 2003 (18)	55	PCWP >15	**>10**	-	-	-	-	-	0.79	0.80	-
Hadano, 2005* (23)	63/65	PCWP >12	**>9**	19	9	12	3	39	0.75 [0.43, 0.95]	0.76 [0.63, 0.87]	0.81
Nagueh, 1997* (E/A<1) (13)	23/26	PCWP >12	**>8**	22	4	10	1	8	0.80 [0.29, 0.99]	0.44 [0.22, 0.69]	0.64
Maeder, 2011 (42)	36	PCWP >12	**-**	25	-	-	-	-	-	-	0.54 [0.32, 0.77]
Mansencal, 2004* (20)	20/20	Pre-A >15	**>6**	25	5	6	0	9	1.00 [0.48, 1.00]	0.60 [0.32, 0.84]	0.79
Hsiao, 2011 (40)	100	Pre-A >15	**>9.7**	-	-	-	-	-	64	63	-

LVEF≥40%

Study	N	LVFP cutoff	E/e' cutoff	Prev. (%)	TP	FP	FN	TN	Sens. (95% CI)	Spec. (95% CI)	AUC (95% CI)
Poerner, 2007 (28)	176	LVEDP>16	**>10**	41	48	37	24	67	0.67 [0.55, 0.77]	0.64 [0.54, 0.74]	0.69
Jaubert, 2010 (36)	59	LVEDP>16	**>6.7**	66	22	4	17	16	0.56 [0.40, 0.72]	0.80 [0.56, 0.94]	0.69 [0.56, 0.80]
Manouras, 2013 (48)	65	LVEDP >16	**>8**	72	-	-	-	-	0.73	0.65	0.70 [0.63, 0.77]
Nagueh, 1998* (14)	43/49	PCWP >12	**>9**	60	20	3	6	14	0.77 [0.56, 0.91]	0.82 [0.57, 0.96]	0.84
Manouras, 2013 (48)	65	Pre-A >12	**>8**	68	33	7	11	14	0.74 [0.60, 0.85]	0.67 [0.45, 0.83]	0.71 [0.62, 0.79]





LVFP=left ventricular filling pressure; LVEDP=left ventricular end diastolic pressure; LVMDP=left ventricular mean diastolic pressure; Pre-A DP=left ventricular pre–A wave diastolic pressure; PCWP=pulmonary capillary wedge pressure; Prev.=Prevalence of patients with elevated LVFP; TP=true positive; FP=false positive; FN=false negative; TN=true negative; Sens.=Sensitivity; Spec.=Specificity; AUC=area under receiver operating characteristic (ROC) curve; CI=confidence interval. Empty cells are due to no data available.

*=TP, FP, FN, TN values were extracted from the graphical data representation of LVFP vs. E/e' in study results; for such study, column presenting patient number (N) include 2 numbers: first number is actual counted patients in the plot, and second number is total patients in the study group.

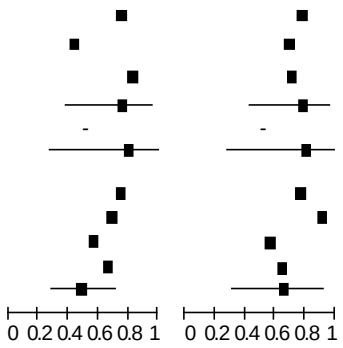
In studies that did not provide the optimal cutoff, we created ROC curve and identified the optimal cutoff as the point on the ROC curve closest to (0, 1 on x-y coordinate).

Studies are identified by the first author, year of publication, and reference number (in brackets) as cited in the main text.

7.2. Identification of elevated LVFP based on 'optimal' E/e'_{mean} cutoffs from ROC analysis

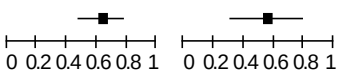
LVEF≥50%

Study	N	LVFP cutoff	E/e' cutoff	Prev. (%)	TP	FP	FN	TN	Sens. (95% CI)	Spec. (95% CI)	AUC (95% CI)
Dokainish , 2010 (35)	122	LVEDP≥20	**>12**	56	-	-	-	-	0.75	0.78	0.79
Previtali, 2012 (46)	57	LVEDP>15	**>12.08**	72	-	-	-	-	0.44	0.71	0.52
Rivas-Gotz, 2003 (18)	55	PCWP >15	**>10**	-		-			0.82	0.72	-
Dokainish, 2004* (19)	19	PCWP >15	**>11**	47	7	2	2	8	0.78 [0.40, 0.97]	0.80 [0.44, 0.97]	-
Maeder, 2011 (42)	36	PCWP >12	**-**	25		-			-	-	0.62 [0.39, 0.85]
Bhella et al, 2011* (39)	10/10	PCWP >12	**>10**	50	4	1	1	4	0.80 [0.28, 0.99]	0.80 [0.28, 0.99]	0.78
Dokainish , 2008 (30)	32	Pre-A >15	**>15**	-		-			73	77	-
Dokainish , 2010 (34)	122	Pre-A ≥15	**>13**	56	-	-	-	-	0.70	0.93	0.82
Hsiao, 2011 (40)	100	Pre-A >15	**>11**	-		-			60	60	-
Hsiao, 2012 (12)	376	Pre-A >15	**>11**	-		-			66	64	0.72 [0.67, 0.77]
Manouras, 2013* (48)	35/38	Pre-A >12	**>8**	69	12	4	12	7	0.50 [0.31, 0.69]	0.64 [0.34, 0.86]	0.55



LVEF≥40%

Study	N	LVFP cutoff	E/e' cutoff	Prev. (%)	TP	FP	FN	TN	Sens. (95% CI)	Spec. (95% CI)	AUC (95% CI)
Bruch , 2005 (22)	28	LVEDP≥15	**>11**	n/a		-			0.94	0.90	0.98 [0.96, 1.00]
Ng , 2008 (31)	20	LVEDP≥12	**-**	60		-			-	-	0.69
Manouras, 2013 (48)	65	LVEDP >16	**>9**	72		-			-	-	0.66 [0.58, 0.74]
Manouras, 2013* (48)	62/65	Pre-A >12	**>8**	71	28	8	16	10	0.64 [0.48, 0.78]	0.56 [0.31, 0.78]	0.70 [0.61, 0.79]



LVFP=left ventricular filling pressure; LVEDP=left ventricular end diastolic pressure; LVMDP=left ventricular mean diastolic pressure; Pre-A DP=left ventricular pre–A wave diastolic pressure; PCWP=pulmonary capillary wedge pressure; Prev.=Prevalence of patients with elevated LVFP; TP=true positive; FP=false positive; FN=false negative; TN=true negative; Sens.=Sensitivity; Spec.=Specificity; AUC=area under receiver operating characteristic (ROC) curve; CI=confidence interval. Empty cells are due to no data available.

*=TP, FP, FN, TN values were extracted from the graphical data representation of LVFP vs. E/e' in study results; for such study, column presenting patient number (N) include 2 numbers: first number is actual counted patients in the plot, and second number is total patients in the study group.

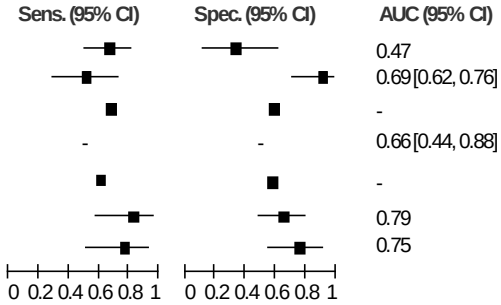
In studies that did not provide the optimal cutoff, we created ROC curve and identified the optimal cutoff as the point on the ROC curve closest to (0, 1 on x-y coordinate).

Studies are identified by the first author, year of publication, and reference number (in brackets) as cited in the main text.

7.3. Identification of elevated LVFP based on 'optimal' E/e'$_{septal}$ cutoffs from ROC analysis

LVEF≥50%

Study	N	LVFP cutoff	E/e' cutoff	Prev. (%)	TP	FP	FN	TN	Sens. (95% CI)	Spec. (95% CI)	AUC (95% CI)
Min, 2007* (8<E/e'<15) (27)	55/55	LVEDP >16	**>10**	73	27	10	13	5	0.68 [0.51, 0.81]	0.33 [0.12, 0.62]	0.47
Ozer, 2011 (43)	45	LVEDP >16	**>9.62**	51	12	2	11	20	0.52 [0.31, 0.73]	0.91 [0.71, 0.99]	0.69 [0.62, 0.76]
Rivas-Gotz, 2003 (18)	55	PCWP >15	**>12**	-		-			0.70	0.60	-
Maeder, 2011 (42)	36	PCWP >12	**-**	25		-			-	-	0.66 [0.44, 0.88]
Hsiao, 2011 (40)	100	Pre-A >15	**>13.1**	-		-			64	61	-
Ommen, 2000* (15)	61/64	LVMDP >12	**>11**	30	15	15	3	28	0.83 [0.59, 0.96]	0.65 [0.49, 0.79]	0.79
Rudko, 2008* (32)	43/39	LVMDP >12	**>9**	42	14	6	4	19	0.78 [0.52, 0.94]	0.76 [0.55, 0.91]	0.75



LVFP=left ventricular filling pressure; LVEDP=left ventricular end diastolic pressure; LVMDP=left ventricular mean diastolic pressure; Pre-A DP=left ventricular pre–A wave diastolic pressure; PCWP=pulmonary capillary wedge pressure; Prev.=Prevalence of patients with elevated LVFP; TP=true positive; FP=false positive; FN=false negative; TN=true negative; Sens.=Sensitivity; Spec.=Specificity; AUC=area under receiver operating characteristic (ROC) curve; CI=confidence interval. Empty cells are due to no data available.

*=TP, FP, FN, TN values were extracted from the graphical data representation of LVFP vs. E/e' in study results; for such study, column presenting patient number (N) include 2 numbers: first number is actual counted patients in the plot, and second number is total patients in the study group.

In studies that did not provide the optimal cutoff, we created ROC curve and identified the optimal cutoff as the point on the ROC curve closest to (0, 1 on x-y coordinate).

Studies are identified by the first author, year of publication, and reference number (in brackets) as cited in the main text.

APPENDIX 8

Secondary analysis of sensitivity/specificity of E/e' cutoffs to predict normal LVFP

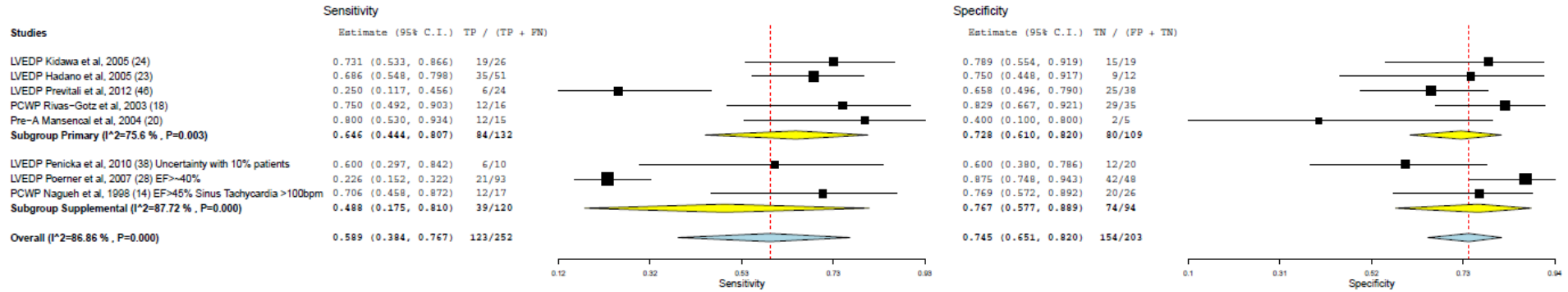
8.1. Subgroup analysis for $E/e'_{lateral}$ <8 to identify normal LVFP

$E/e'_{lateral}$: Dataset for subgroup analysis (see also Tables 1 and 2)

study	TP	FN	FP	TN	SENS.	lower	upper	SPEC.	lower	upper	Data	Timing	% HFpEF	% CAD	% HTN	% DM	Indication for cath	LR+
LVEDP Kidawa et al, 2005 (24)	19	7	4	15	**0.731**	0.533	0.866	**0.789**	0.554	0.919	Primary	Simultaneously	unclear	unclear	unclear	unclear	angiography	3.5
PCWP Rivas-Gotz et al, 2003 (18)	12	4	6	29	**0.750**	0.492	0.903	**0.829**	0.667	0.921	Primary	Simultaneously	unclear	unclear	unclear	unclear	ICU/Cath	4.4
LVEDP Hadano et al, 2005 (23)	35	16	3	9	**0.686**	0.548	0.798	**0.750**	0.448	0.917	Primary	NOT simultaneous	unclear	some CAD	unclear	unclear	unclear	2.7
LVEDP Previtali et al, 2012 (46)	6	18	13	25	**0.250**	0.117	0.456	**0.658**	0.496	0.790	Primary	NOT simultaneous	0% HF	unclear	unclear	unclear	unclear	0.7
Pre-A Mansencal et al, 2004 (20)	12	3	3	2	**0.800**	0.530	0.934	**0.400**	0.100	0.800	Primary	NOT simultaneous	~5% HF	all CAD	~10% HTN	unclear	angiography	1.3
LVEDP Penicka et al, 2010 (38) Uncertainty with 10% patients	6	4	8	12	**0.600**	0.297	0.842	**0.600**	0.380	0.786	Supplemer	Simultaneously	~70% HF	no CAD	~70% HTN	~30% DM	dyspnea	1.5
PCWP Nagueh et al, 1998 (14) EF>45% Sinus Tachycardia >100bpm	12	5	6	20	**0.706**	0.458	0.872	**0.769**	0.572	0.892	Supplemer	Simultaneously	unclear	unclear	unclear	unclear	ICU/Cath	3.1
LVEDP Poerner et al, 2007 (28) EF>~40%	21	72	6	42	**0.226**	0.152	0.322	**0.875**	0.748	0.943	Supplemer	NOT simultaneous	unclear	some CAD	~60% HTN	~30% DM	angiography	1.8

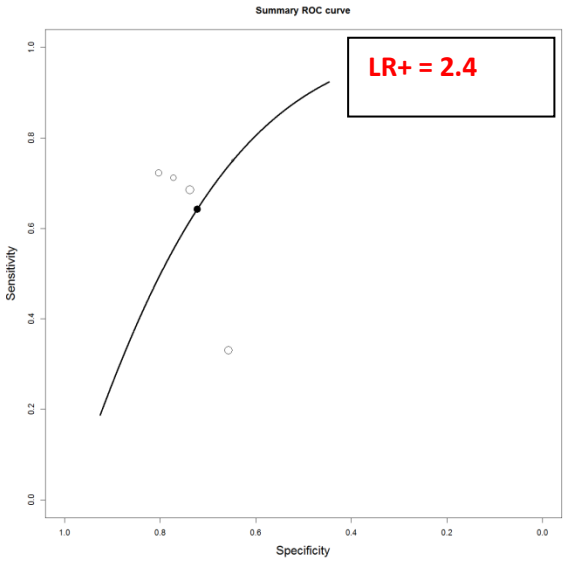
LVFP=left ventricular filling pressure; LVEDP=left ventricular end diastolic pressure; LVMDP=left ventricular mean diastolic pressure; Pre-A DP=left ventricular pre–A wave diastolic pressure; PCWP=pulmonary capillary wedge pressure; CI=confidence interval; HFpEF=heart failure with preserved Ejection Fraction; CAD=coronary artery disease; HTN=hypertension; DM=diabetes mellitus; ICU=intensive care unit; TP=true positive; FP= false positive; FN= false negative; TN=true negative; Sens.= sensitivity; Spec.=specificity; LR+=positive likelihood ratio. Studies are identified by the first author, year of publication, and reference number (in brackets) as cited in the main text.

A. Combined LVFP (primary and supplemental data)

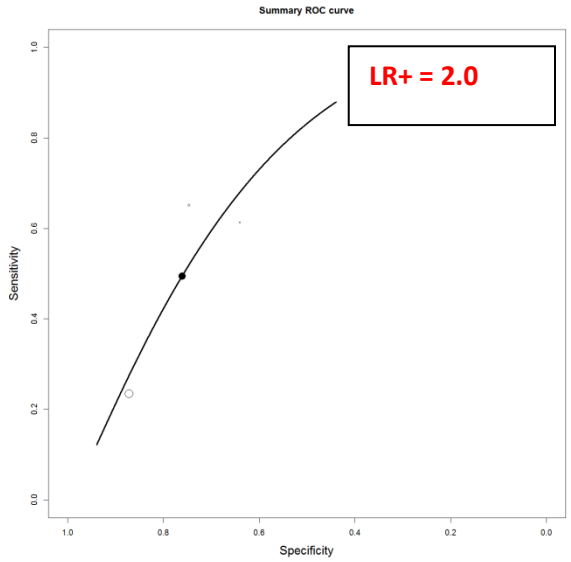


HSROC analysis

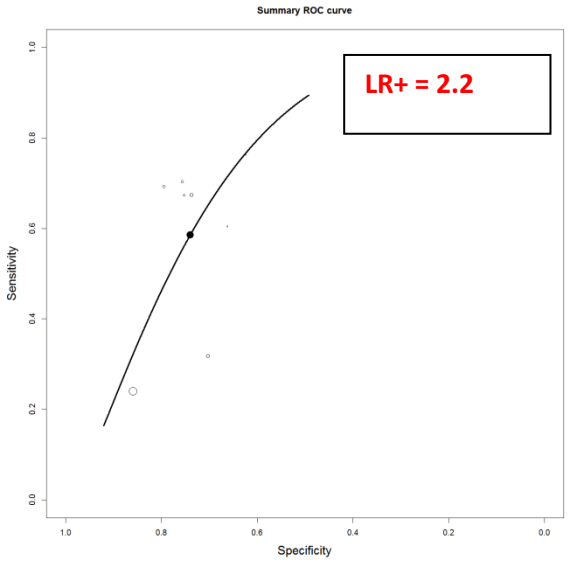
Primary studies combined (n=5, **as in Figure 4**)
Sensitivity (summary) 0.64 (0.37 - 0.87)
Specificity (summary) 0.73 (0.54 – 0.89)



Supplemental studies combined (n=3)
Sensitivity (summary) 0.49 (0.10 - 0.93)
Specificity (summary) 0.76 (0.41 – 1.0)

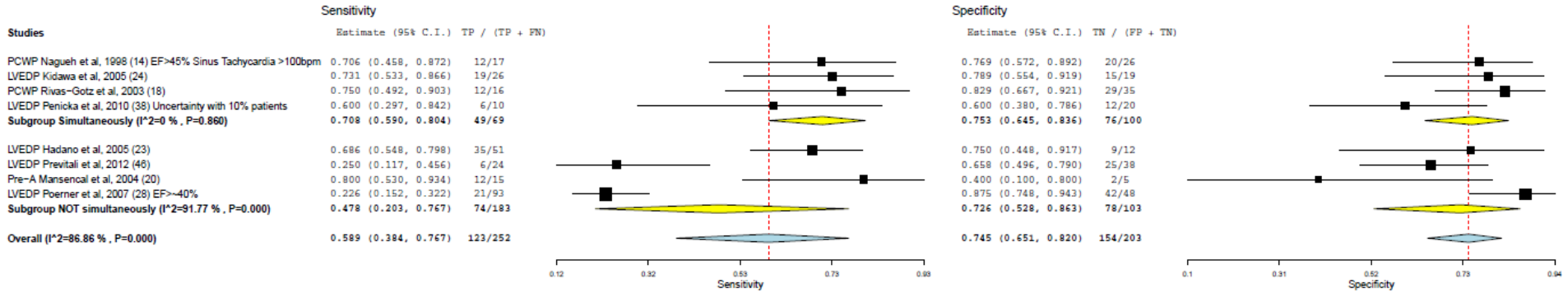


All studies combined (n=8)
Sensitivity (summary) 0.58 (0.38 - 0.78)
Specificity (summary) 0.74 (0.61- 0.87)



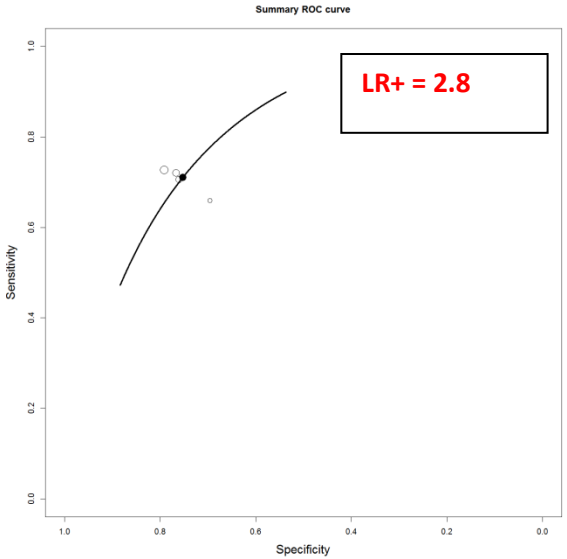
TP=true positive; FP= false positive; FN= false negative; TN=true negative; Sens.= sensitivity; Spec.=specificity; LR+=positive likelihood ratio; HSROC=hierarchical summary receiver operating characteristic. Heterogeneity amongst the studies was estimated by I2 statistic. Studies are identified by the first author, year of publication, and reference number (in brackets) as cited in the main text. OpenMetaAnalyst software (12) for Windows (64-bit version) was used for statistical analysis including graphical presentations of forest plots.

B. Combined LVFP (Simultaneous and not simultaneous measurements

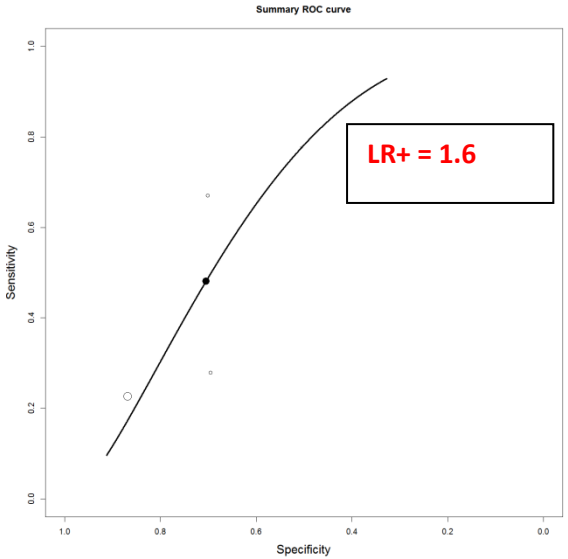


HSROC analysis

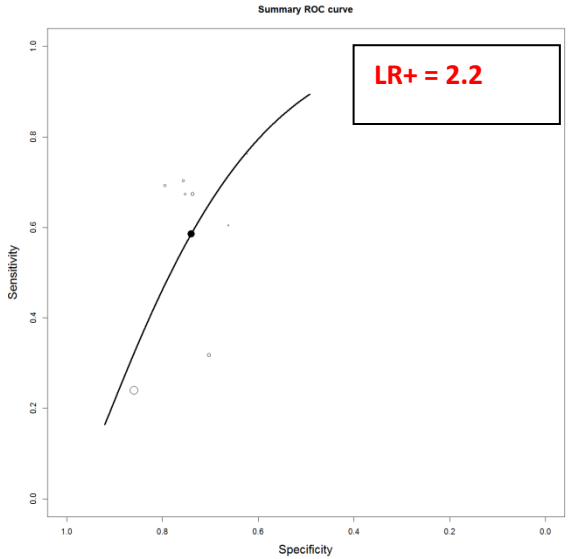
Simultaneous studies combined (n=4)
Sensitivity (summary) 0.70 (0.49 - 0.86)
Specificity (summary) 0.75 (0.58 – 0.88)



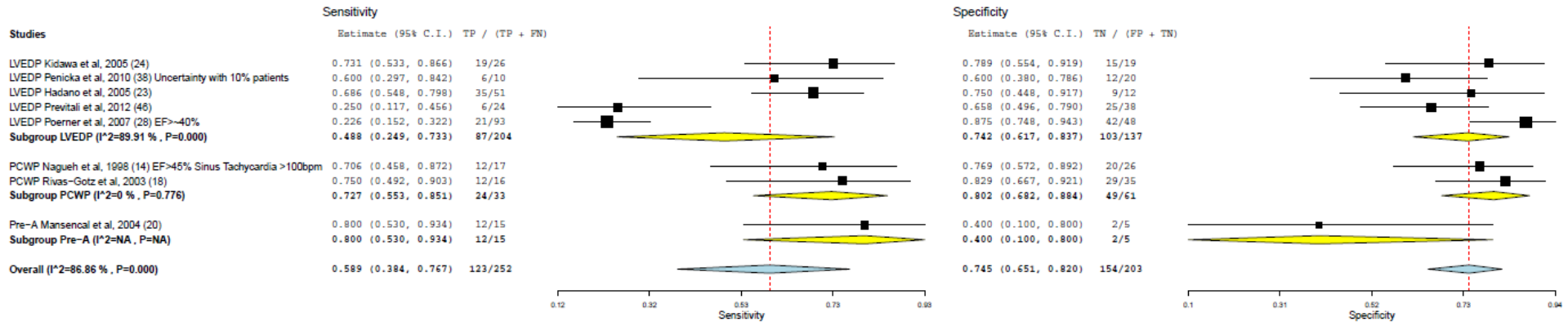
Not Simultaneous studies combined (n=4)
Sensitivity (summary) 0.48 (0.08 - 0.88)
Specificity (summary) 0.71 (0.39 – 0.97)



All studies combined (n=8)
Sensitivity (summary) 0.58 (0.38 - 0.78)
Specificity (summary) 0.74 (0.61- 0.87)

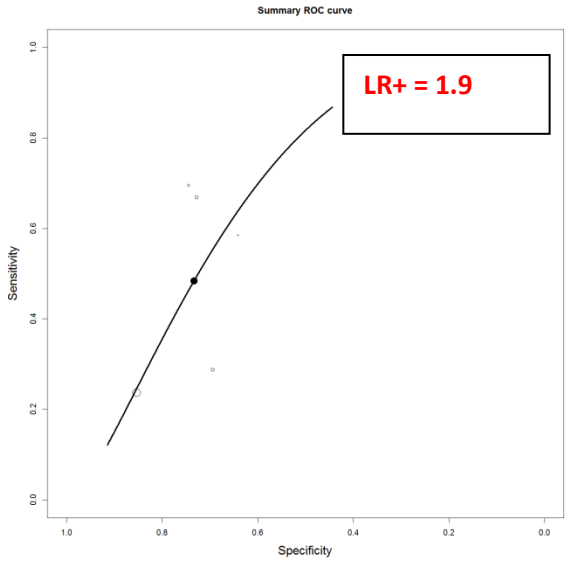


C. Separate analysis for LVFP measurements

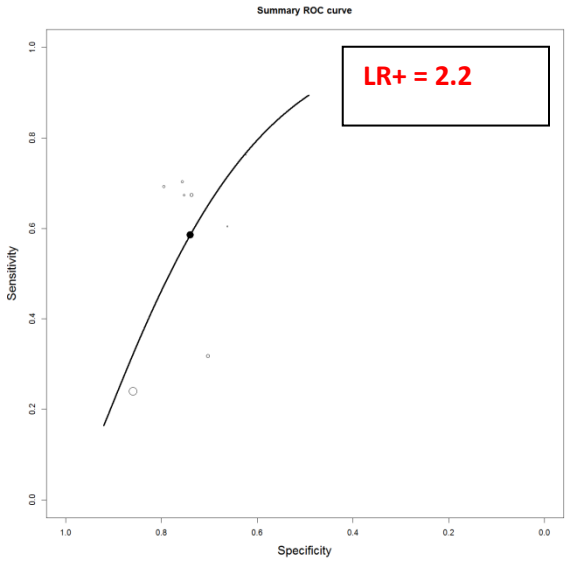


HSROC analysis

LVEDP studies combined (n=5)
Sensitivity (summary) 0.49 (0.19 - 0.80)
Specificity (summary) 0.74 (0.52 – 0.92)

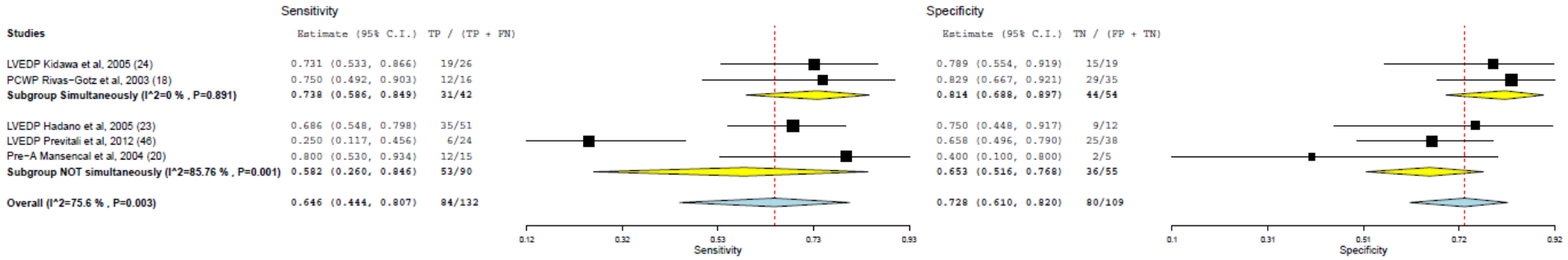


All studies combined (n=8)
Sensitivity (summary) 0.58 (0.38 - 0.78)
Specificity (summary) 0.74 (0.61- 0.87)



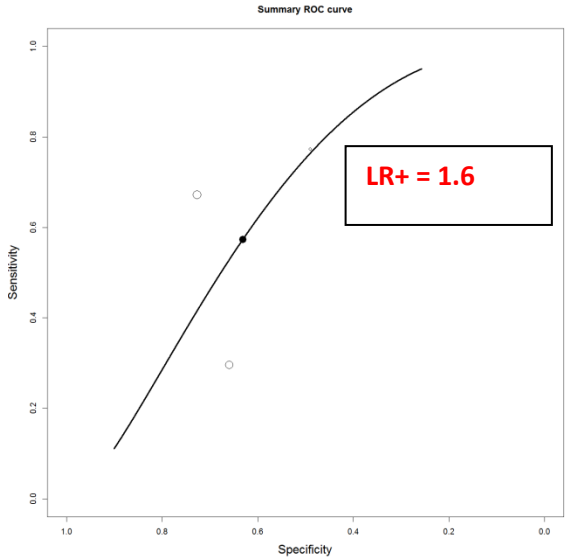
There are insufficient number of studies (n=2) that measured PCWP measurements to perform a meaningful analysis.

D. PRIMARY DATA SUMMARY - Primary studies only (Simultaneous and Not Simultaneous)

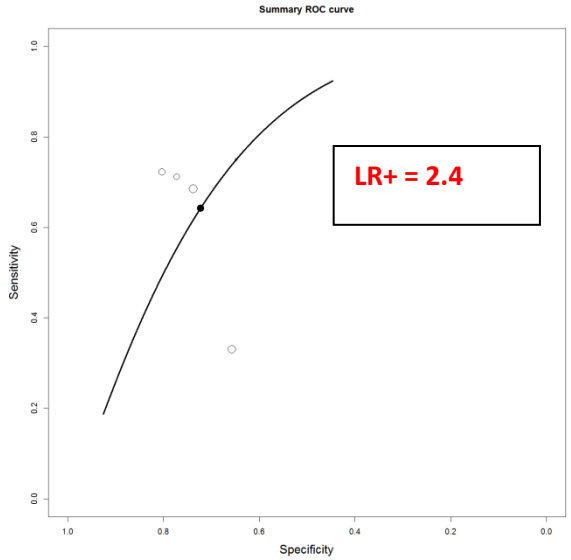


HSROC analysis

Primary Not Simultaneous studies (n=3)
Sensitivity (summary) 0.58 (0.18 - 0.99)
Specificity (summary) 0.63 (0.24 – 0.96)



All primary studies combined (n=5)
Sensitivity (summary) 0.64 (0.37 - 0.87)
Specificity (summary) 0.73 (0.54 – 0.89)



There are insufficient number of studies (n=2) with simultaneous measurements to perform a meaningful analysis.

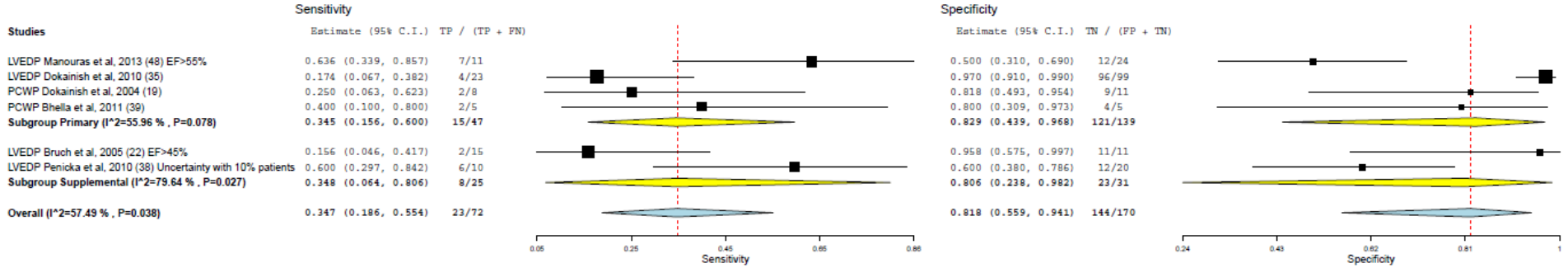
8.2. Subgroup analysis for E/e'_{mean} <8 to identify normal LVFP

E/e'_{mean}: Dataset for subgroup analysis (see also Tables 1 and 2)

study	TP	FN	FP	TN	SENS.	lower	upper	SPEC.	lower	upper	Data	Timing	% HFpEF	% CAD	% HTN	% DM	dication for ca	LR+
LVEDP Manouras et al, 2013 (48) EF>55%	7	4	12	12	**0.636**	0.339	0.857	**0.500**	0.310	0.690	Primary	Simultaneously	unclear	no CAD	unclear	unclear	angiography	1.3
PCWP Dokainish et al, 2004 (19)	2	6	2	9	**0.250**	0.063	0.623	**0.818**	0.493	0.954	Primary	Simultaneously	unclear	unclear	~60% HTN	~20% DM	ICU/CCU	1.4
PCWP Bhella et al, 2011 (39)	2	3	1	4	**0.400**	0.100	0.800	**0.800**	0.309	0.973	Primary	Simultaneously	100% HF	no CAD	100% HTN	~60% DM	research	2.0
LVEDP Dokainish et al, 2010 (35)	4	19	3	96	**0.174**	0.067	0.382	**0.970**	0.910	0.990	Primary	NOT simultaneou	unclear	some CAD	~90% HTN	~40% DM	angiography	5.8
LVEDP Bruch et al, 2005 (22) EF>45%	2	13	0	11	**0.156**	0.046	0.417	**0.958**	0.575	0.997	Supplemer	NOT simultaneou	100% HF	some CAD	~80% HTN	unclear	dyspnea	3.7
LVEDP Penicka et al, 2010 (38) Uncertainty with 10% patients	6	4	8	12	**0.600**	0.297	0.842	**0.600**	0.380	0.786	Supplemer	Simultaneously	~70% HF	no CAD	~70% HTN	~30% DM	dyspnea	1.5

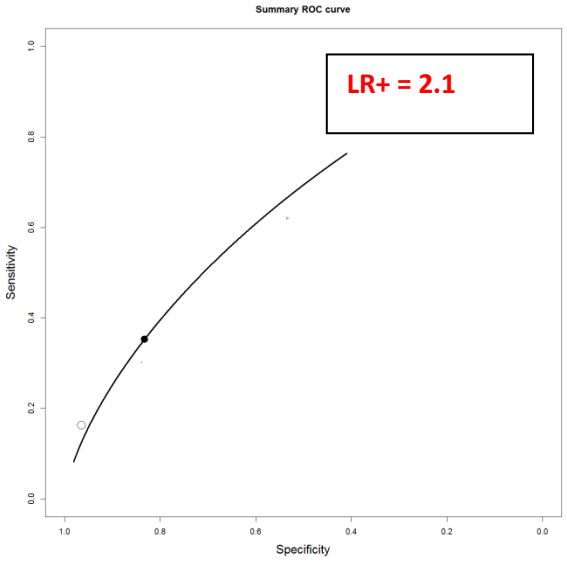
LVFP=left ventricular filling pressure; LVEDP=left ventricular end diastolic pressure; LVMDP=left ventricular mean diastolic pressure; Pre-A DP=left ventricular pre–A wave diastolic pressure; PCWP=pulmonary capillary wedge pressure; CI=confidence interval; HFpEF=heart failure with preserved Ejection Fraction; CAD=coronary artery disease; HTN=hypertension; DM=diabetes mellitus; ICU=intensive care unit; TP=true positive; FP= false positive; FN= false negative; TN=true negative; Sens.= sensitivity; Spec.=specificity; LR+=positive likelihood ratio. Studies are identified by the first author, year of publication, and reference number (in brackets) as cited in the main text.

A. Combined LVFP (primary and supplemental data)

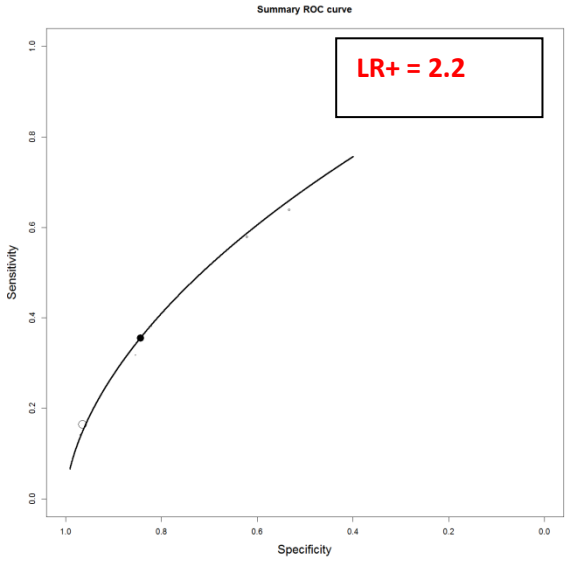


HSROC analysis

Primary studies combined (n=4, **as in Figure 4**)
Sensitivity (summary) 0.36 (0.03 - 0.74)
Specificity (summary) 0.83 (0.49 – 1.0)



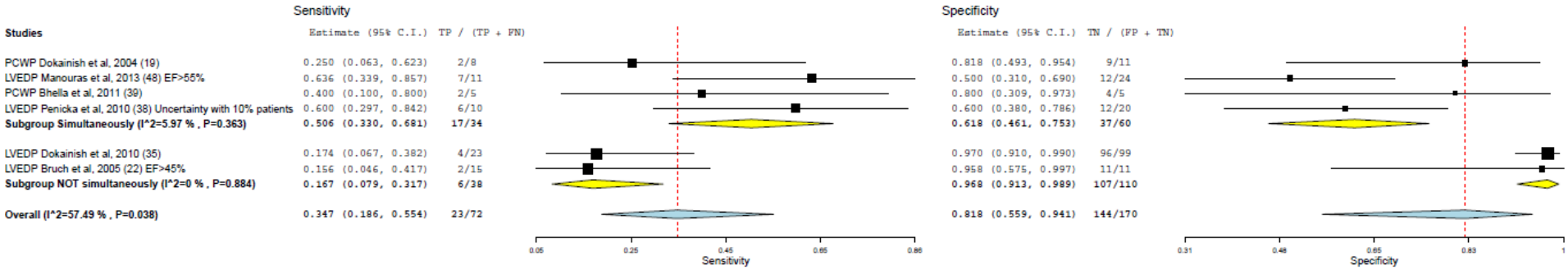
All studies combined (n=6)
Sensitivity (summary) 0.36 (0.10 - 0.65)
Specificity (summary) 0.84 (0.61- 1.0)



There are insufficient number of studies (n=2) with supplements data to perform a meaningful analysis.

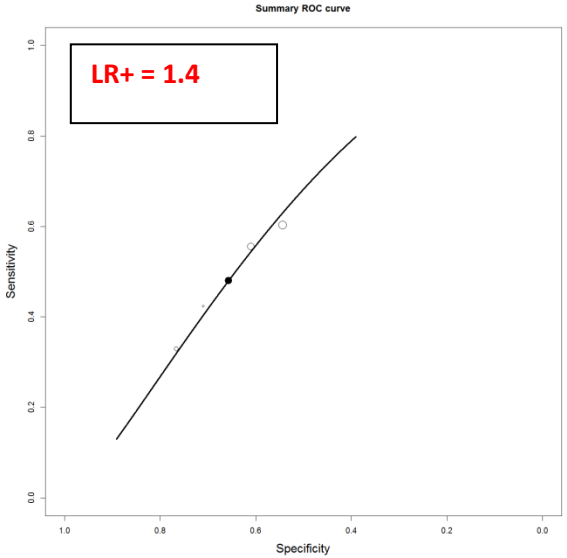
TP=true positive; FP= false positive; FN= false negative; TN=true negative; Sens.= sensitivity; Spec.=specificity; LR+=positive likelihood ratio; HSROC=hierarchical summary receiver operating characteristic. Heterogeneity amongst the studies was estimated by I2 statistic. Studies are identified by the first author, year of publication, and reference number (in brackets) as cited in the main text. OpenMetaAnalyst software (12) for Windows (64-bit version) was used for statistical analysis including graphical presentations of forest plots.

B. Combined LVFP (Simultaneous and not simultaneous measurements)

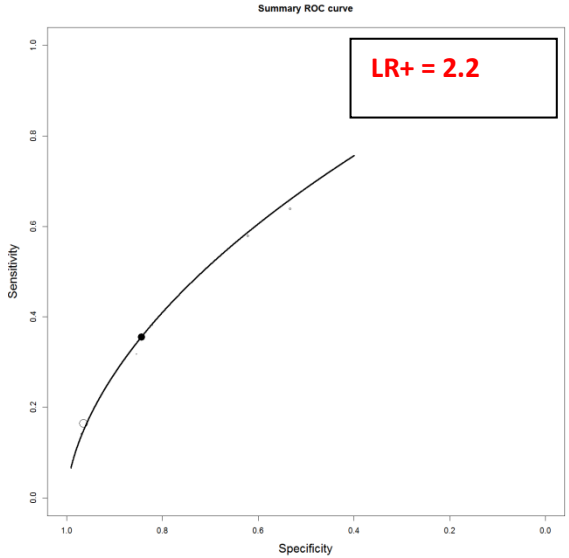


HSROC analysis

Simultaneous studies combined (n=4)
Sensitivity (summary) 0.48 (0.13 - 0.80)
Specificity (summary) 0.66 (0.38 – 0.91)

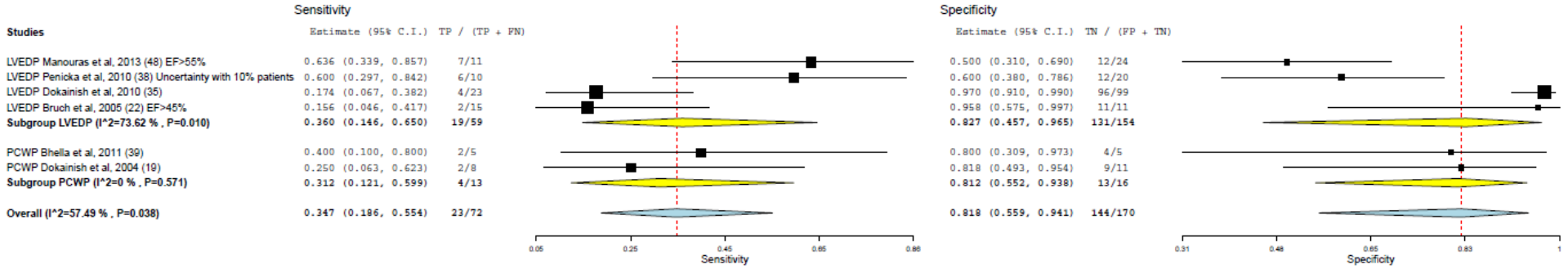


All studies combined (n=6)
Sensitivity (summary) 0.36 (0.10 - 0.65)
Specificity (summary) 0.84 (0.61- 1.0)



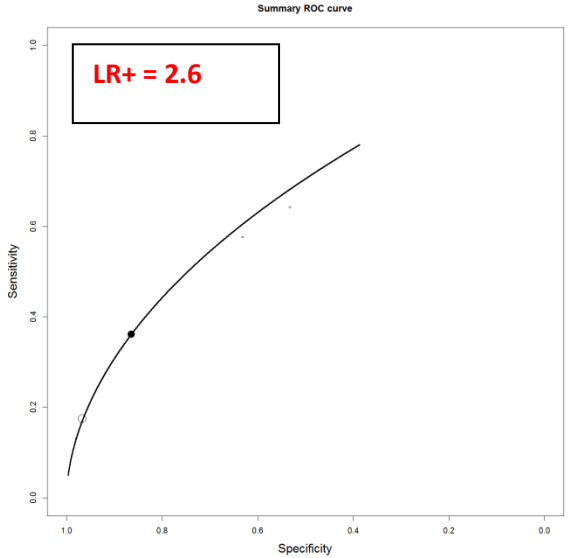
There are insufficient number of studies (n=2) with NOT simultaneous measurements to perform a meaningful analysis.

C. Separate analysis for LVFP measurements

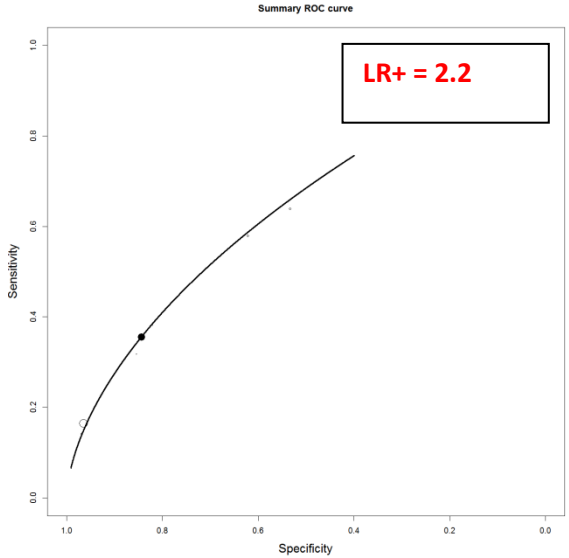


HSROC analysis

LVEDP studies (n=4)
Sensitivity (summary) 0.36 (0.05 – 1.0)
Specificity (summary) 0.86 (0.47 – 1.0)



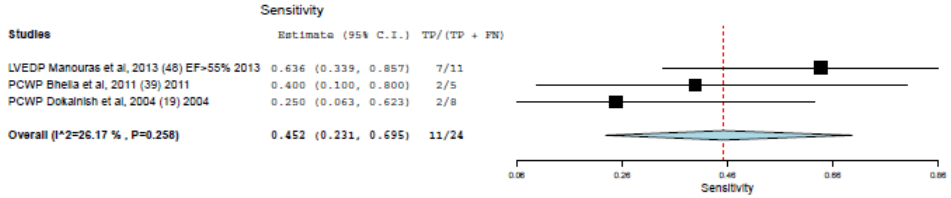
All studies combined (n=6)
Sensitivity (summary) 0.36 (0.10 - 0.65)
Specificity (summary) 0.84 (0.61- 1.0)

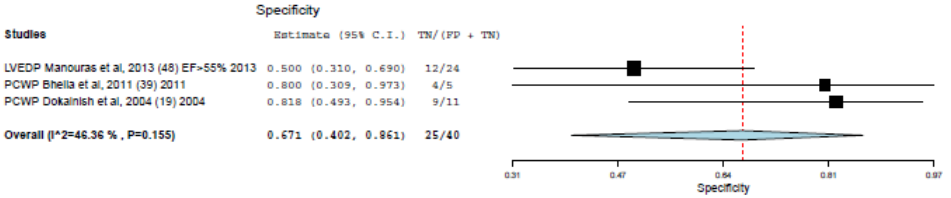


There are insufficient number of studies (n=2) that measured PCWP measurements) to perform a meaningful analysis.

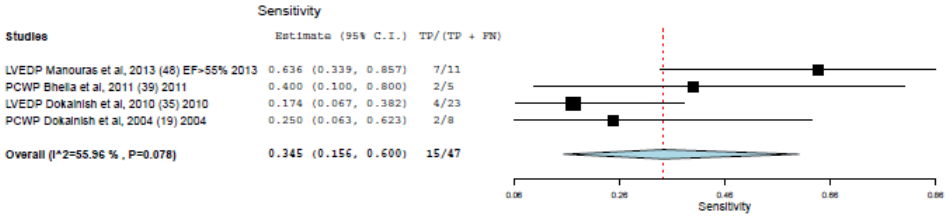
D. PRIMARY DATA SUMMARY - Primary studies only (Simultaneous and Not Simultaneous)

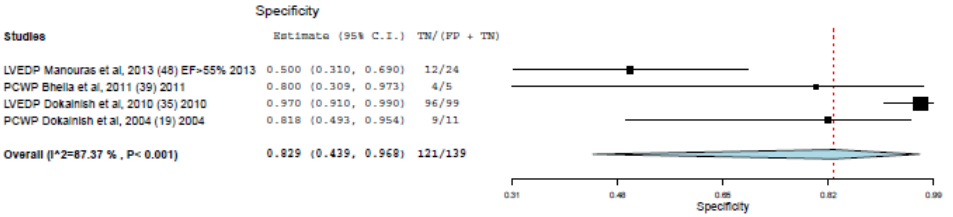
Primary Simultaneous studies





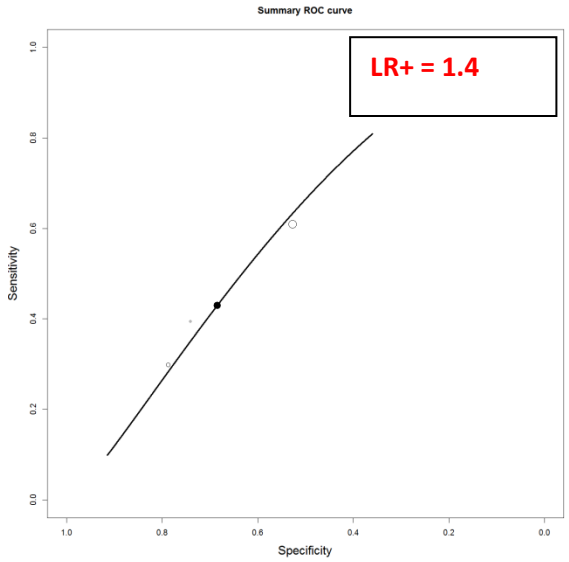
All Primary studies



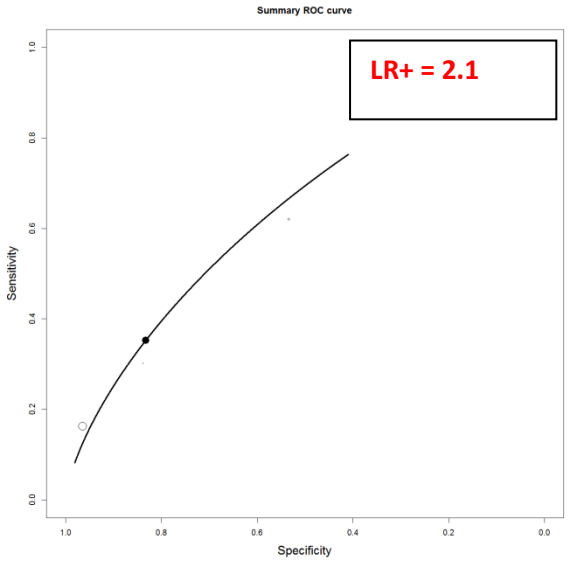


HSROC analysis

Primary Simultaneous studies (n=3)
Sensitivity (summary) 0.43 (0.01 – 0.81)
Specificity (summary) 0.69 (0.35 – 1.0)



All Primary studies (n=4)
Sensitivity (summary) 0.36 (0.03 - 0.74)
Specificity (summary) 0.83 (0.49- 1.0)



8.3. Subgroup analysis for E/e'_{septal} <8 to identify normal LVFP

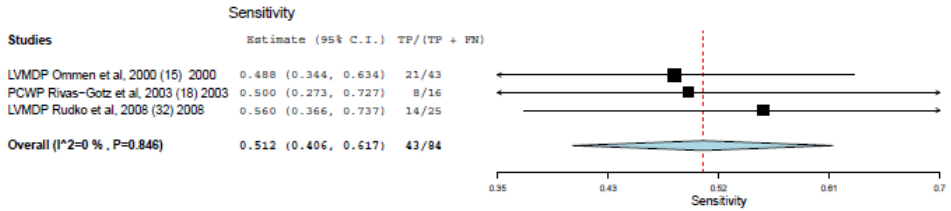
E/e'_{septal}: Dataset for subgroup analysis (see also Tables 1 and 2)

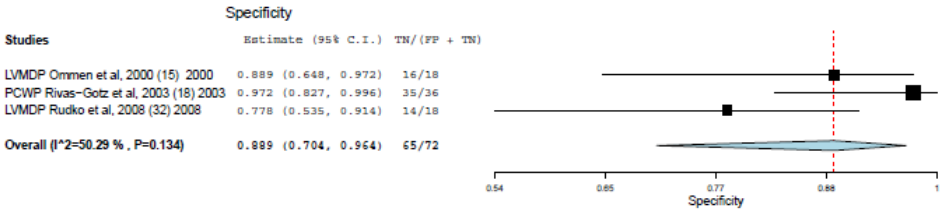
study	TP	FN	FP	TN	SENS.	lower	upper	SPEC.	lower	upper	Data	Timing	% HFpEF	% CAD	% HTN	% DM	Indication for cath	LR+
LVMDP Ommen et al, 2000 (15)	21	22	2	16	**0.488**	0.344	0.634	**0.889**	0.648	0.972	Primary	Simultaneously	Unclear	Unclear	Unclear	Unclear	Unclear	4.4
PCWP Rivas-Gotz et al, 2003 (18)	8	8	1	35	**0.500**	0.273	0.727	**0.972**	0.827	0.996	Primary	Simultaneously	Unclear	Unclear	Unclear	Unclear	ICU/Cath lab	17.9
LVMDP Rudko et al, 2008 (32)	14	11	4	14	**0.560**	0.366	0.737	**0.778**	0.535	0.914	Primary	Simultaneously	~20% HF	~80% CAD	~50% HTN	Unclear	Unclear	2.5
LVEDP Penicka et al, 2010 (38) Uncertainty with 10% patients	6	4	8	12	**0.600**	0.297	0.842	**0.600**	0.380	0.786	Supplemer	Simultaneously	~70% HF	no CAD	~70% HTN	~30% DM	dyspnea	1.5

LVFP=left ventricular filling pressure; LVEDP=left ventricular end diastolic pressure; LVMDP=left ventricular mean diastolic pressure; Pre-A DP=left ventricular pre–A wave diastolic pressure; PCWP=pulmonary capillary wedge pressure; CI=confidence interval; HFpEF=heart failure with preserved Ejection Fraction; CAD=coronary artery disease; HTN=hypertension; DM=diabetes mellitus; ICU=intensive care unit; TP=true positive; FP= false positive; FN= false negative; TN=true negative; Sens.= sensitivity; Spec.=specificity; LR+=positive likelihood ratio. Studies are identified by the first author, year of publication, and reference number (in brackets) as cited in the main text.

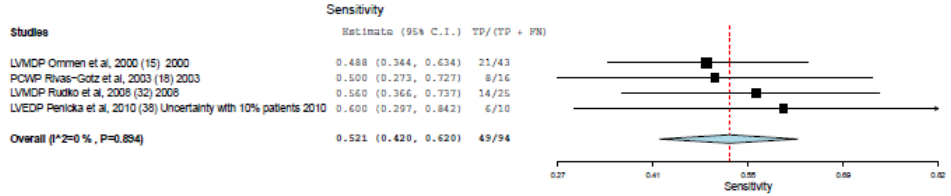
A. Combined LVFP (primary and supplemental data)

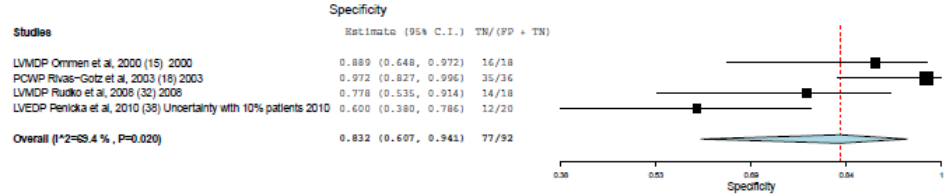
Primary studies





All studies



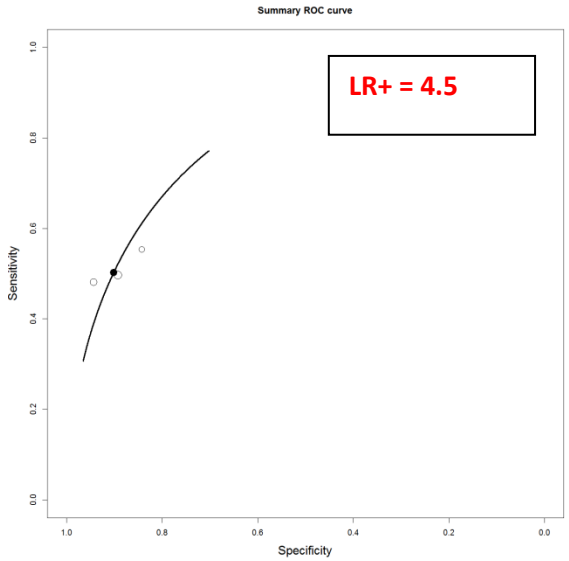


HSROC analysis

Primary studies (n=3)

Sensitivity (summary) 0.50 (0.14 – 0.81)

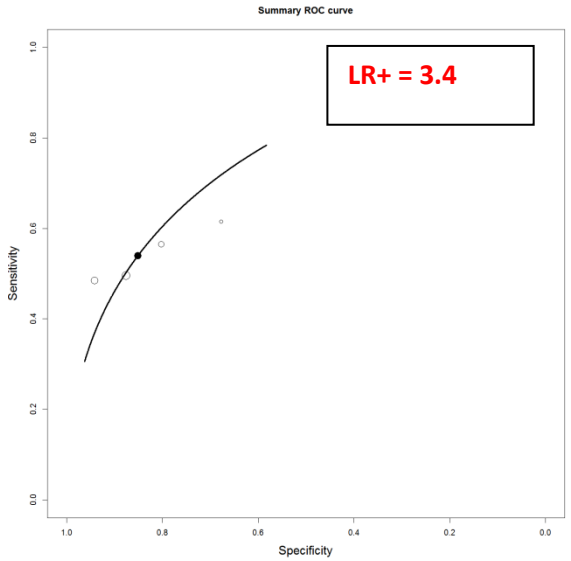
Specificity (summary) 0.89 (0.66 – 1.0)



All studies (n=4)

Sensitivity (summary) 0.54 (0.25 - 0.82)

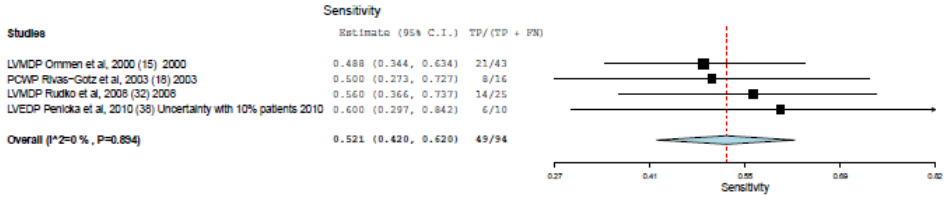
Specificity (summary) 0.84 (0.61 – 1.0)

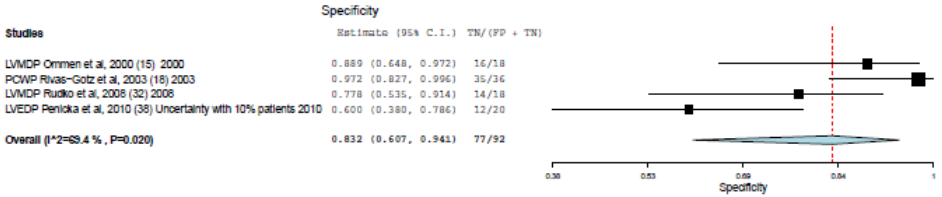


TP=true positive; FP= false positive; FN= false negative; TN=true negative; Sens.= sensitivity; Spec.=specificity; LR+=positive likelihood ratio; HSROC=hierarchical summary receiver operating characteristic. Heterogeneity amongst the studies was estimated by I2 statistic. Studies are identified by the first author, year of publication, and reference number (in brackets) as cited in the main text. OpenMetaAnalyst software (12) for Windows (64-bit version) was used for statistical analysis including graphical presentations of forest plots.

B. Combined LVFP (Simultaneous and not simultaneous measurements)

All studies are simultaneous



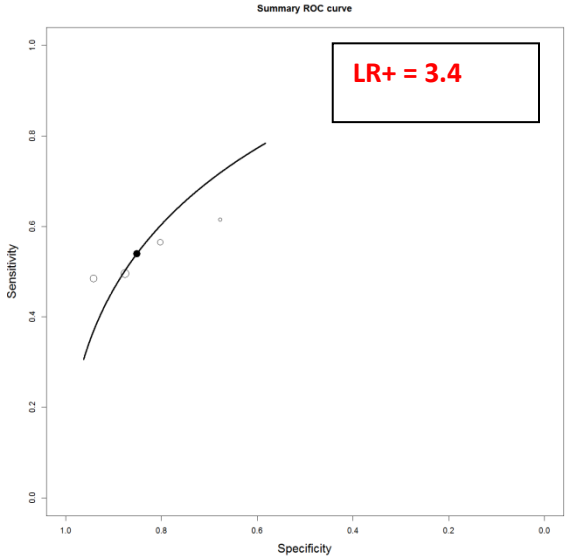


HSROC analysis

All studies are simultaneous (n=4)

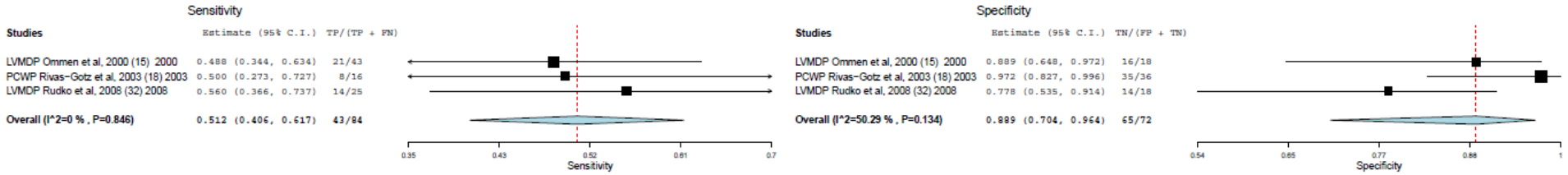
Sensitivity (summary) 0.54 (0.25 - 0.82)

Specificity (summary) 0.84 (0.61 – 1.0)



C. PRIMARY DATA SUMMARY - Primary studies only (Simultaneous and Not Simultaneous)

All Primary studies are simultaneous



HSROC analysis

Primary studies (n=3)

Sensitivity (summary) 0.50 (0.14 – 0.81)

Specificity (summary) 0.89 (0.66 – 1.0)