Assessment of Prognostic Models for Patients with Acute Pulmonary Embolism



Antoine ELIAS

Kellogg College

University of Oxford

A thesis submitted for the degree of

Doctor of Philosophy

Michaelmas Term 2016

Volume II

(Appendices)

Table of Contents

Appendices A4 - Prognostic Models in Acute Pulmonary Embolism: a Systematic Review and Meta-Analysis. 1

TABLES A4.1 (SEARCH METHODS AND RESULTS) **1**

Table A4.1.1: Search methods 2

Table A4.1.2: Search strategy - Search terms 3

Table A4.1.3: Data extraction form content 4

TABLE A4.1.4: SEARCH RESULTS - OVID MEDLINE(R) 1946 to 2016 August 22 5

TABLE A4.1.5: SEARCH RESULTS - EMBASE 1974 to 2016 August 29 6

TABLE A4.1.6A: SEARCH RESULTS - THE COCHRANE LIBRARY 2016 August 18 7

Table A4.1.6B: SEARCH RESULTS IN THE DIFFERENT DATABASES in The COCHRANE LIBRARY 7

TABLE A4.1.7: SUMMARY OF SEARCH RESULTS FROM MEDLINE, EMBASE and COCHRANE DATABASES. 8

Table A4.1.8: Reasons for non-inclusion of studies that did not meet selection criteria and potential eligible prognostic models. 8

Table A4.1.9: Publications excluded after review of the articles and reasons for exclusion 9

Table A4.1.10: Publications included after review of the articles 12

Table A4.1.11: Sources of included studies 13

Table A4.1.12: Ongoing studies 14

REFERENCES 15

TABLES A4.2 (ORIGINAL MODELS) 28

TABLES A4.3 (MODELS VARIABLES) 42

TABLES A4.4 (STUDY CHARACTERISTICS) 46

Table A4.4.1: Prognostic models - Construction studies 46

Table A4.4.2: Prognostic models - External validation studies (including those that also updated the model) 52

Table A4.4.3: Prognostic models – Update studies 67

Table A4.4.4: Prognostic models – Impact studies 72

Table A4.4.5: Other types of models 76

REFERENCES 80

TABLES A4.5 (PATIENT CHARACTERISTICS) 88

A4.5.1.a: Prognostic Models - Construction studies (1): Patient characteristics. 89

A4.5.1.b: Prognostic Models - Construction studies (2): Patient characteristics. 92

A4.5.2.a: Prognostic Models - External validation studies (1) including those that also updated the model: Patient characteristics. 95

A4.5.2.b: Prognostic Models - External validation studies (2) including those that also updated the model: Patient characteristics. 101

A4.5.3.A: PROGNOSTIC MODELS – UPDATE STUDIES (1): PATIENT CHARACTERISTICS. 107

A4.5.3.b: Prognostic models – Update studies (2): Patient characteristics. 110

A4.5.4.a: Prognostic models – Impact studies (1): Patients characteristics. 112

A4.5.4.b: Prognostic models – Impact studies (2): Patients characteristics. 114

A4.5.5.A: OTHER MODELS (1): PATIENT CHARACTERISTICS. 116

A4.5.5.B: OTHER MODELS (2): PATIENT CHARACTERISTICS. 118

REFERENCES 120

TABLES A4.6 (POPULATION EVENT RATES) 127

FIGURES A4.1 (STUDY QUALITY) 130

Figure A4.1.1: Study Quality - Model Construction studies 131

Figure A4.1.2: Summary of Study Quality in Model Construction Studies 133

Figure A4.1.3a: Study Quality - External Validation Studies (1) 134

Figure A4.1.3b: Study Quality - External Validation Studies (2) 136

Figure A4.1.3c: Study Quality - External Validation Studies (3).....138

Figure A4.1.4: Summary of Study Quality in External Validation Studies 140

Figure A4.1.5: Study Quality - Update Studies 141

Figure A4.1.6: Summary of Study Quality in Update Studies.....143

Figure A4.1.7: Study Quality - Impact studies 144

Figure A4.1.8: Summary of Study Quality in Impact studies.....146

Figure A4.1.9: Study Quality - Type 2 model Studies.....147

Figure A4.1.10: Summary of Study Quality in Type 2 model Studies 149

Figure A4.1.11: Study Quality - Type 3 model studies 150

Figure A4.1.12: Summary of Study Quality in Type 3 model studies.....152

Appendices A5 - Net Benefit of Prognostic Models in Acute Pulmonary Embolism in Direct Comparison Studies. 154

TABLES AND FIGURES A5.1 TO A5.23 (COMPETING MODELS) 154

A5.1: PESI - 2008 ESC 155
A5.2: PESI - GPS 156
A5.3: PESI - PREP - eStiMaTe (PREP cohort) 157
A5.4: PESI - PREP 158
A5.5: sPESI – 2008 ESC 159
A5.6: sPESI – 2008 ESC (TUPEG cohort) 160
A5.7: sPESI - 2014 ESC 161
A5.8: sPESI - FAST - ESC (FAST cohort). 162
A5.9: sPESI - Hestia (Hestia cohort) 163
A5.10: sPESI - Shock Index 164
A5.11: sPESI - Spanish model 165
A5.12: sPESI - TELOS (TELOS cohort) 166
A5.13 (1): sPESI - GPS - ESC - SI 167
A5.13 (2): sPESI - GRACE-ACS - GRACE-PE (GRACE-PE cohort) 168
A5.14: PESI - PE Algorithm - sPESI (PESI derivation and internal validation cohort) 169
A5.15: PESI - sPESI (sPESI derivation cohort) 170
A5.16: PESI - sPESI 171
A5.17: PESI - sPESI - GPS 172
A5.18: PESI - sPESI 173
A5.19: PESI - sPESI - RIETE (RIETE cohort) 174
A5.20: PESI - sPESI 175
A5.21 (1): 2008 ESC - 2014 ESC 176
A5.21 (2): 2008 ESC - 2014 ESC 177
A5.21 (3): 2008 ESC - 2014 ESC 178
A5.21 (4): 2008 ESC - 2014 ESC 179
A5.22: 2014 ESC - Bova 180
A5.23: Bova - TELOS - 2014 ESC 181

REFERENCES 182

TABLES AND FIGURES A5.24 TO A5.39 (UPDATED MODELS VERSUS ORIGINAL MODELS) .185

A5.24: PESI - cTn 186

A5.25: PESI - BNP - cTn - TTE-RVD (PREP cohort) 187

A5.26: PESI - CT-RVD 188

A5.27: PESI - H-FABP 189

A5.28: PESI - WBC - SIRS 190

A5.29: sPESI - cTn 191

A5.30: sPESI - hs-cTnT 192

A5.31: sPESI - hs-cTnT 193

A5.32: sPESI - NT-proBNP 194

A5.33: sPESI - Lactate (TELOS cohort) 195

A5.34: sPESI - ESC 196

A5.35: sPESI – modified-sPESI 197

A5.36: Bova - Lactate 198

A5.37: Hestia - CT-RVD (Hestia cohort) 199

A5.38: PREP - BNP - TTE-RVD (PREP cohort) 200

A5.39: Shock Index - TTE-RVD 201

REFERENCES 202

Appendices A6 - Opinion and Practice Survey about the Use of Prognostic Models in Acute Pulmonary Embolism (OPSUM-PE)..... 204

Table A6.1: Practice Survey Questionnaire 204

Table A6.2: Sample size calculation 209

Appendices A7 - Development and Assessment of Ascertainment Strategy in Acute Pulmonary Embolism 210

A7.1: RESEARCH ETHICS 210

A7.2: INSTITUTIONAL REVIEW BOARD 211

A7.3: PROTOCOL AND PRACTICAL ISSUES 214

A7.4: RESULTS 222

Table A7.4.1. Patient characteristics - Source of patients and in-hospital healthcare pathways. 223

Table A7.4.2: Risk classification according to PESI/s-PESI models and to detection methods, and all-cause death at different time-points in the whole study cohort including “both stable and unstable PE” patients. 224

Table A7.4.3: Risk classification according to PESI and s-PESI models in “both stable and unstable PE” patients - Proportion of patients in risk groups and all-cause death within risk groups. 225

Table A7.4.4: Risk classification according to PESI/s-PESI models and to detection methods, and all-cause death at different time-points in “stable PE” patients. 226

Table A7.4.5: Risk classification according to PESI and s-PESI models in “stable PE” patients - Proportion of patients in risk groups and all-cause death within risk groups 227

APPENDICES A8 - Physician’s Clinical Judgment in Addition to Simplified PESI for Selecting Patients with Acute Pulmonary Embolism for Out-Of-Hospital Management. 228

Table A8.1: Strategies for selecting patients for early discharge or home treatment. 229

Table A8.2: Pulmonary Embolism Severity Index (PESI): original and simplified versions[1]. 230

Table A8.3: Davies criteria[2]- Hospital criteria 231

Table A8.4: Ottawa criteria [3 4]- Home criteria 231

Table A8.5: Hestia criteria[5-8] - Hospital criteria 232

Table A8.6: Anticoagulant treatment 233

Sample Size (Supplementary Material) 234

REFERENCES 237

Appendices A4 - Prognostic Models in Acute Pulmonary Embolism: a Systematic Review and Meta-Analysis.

TABLES A4.1 (SEARCH METHODS AND RESULTS)

Table A4.1.1: Search methods

Search Methods: Electronic searches

Studies were searched for through electronic databases:
OVID versions of MEDLINE and Embase, and Cochrane Library databases, since inception to July 2012
Cochrane Library databases (http://www.thecochranelibrary.com/view/0/index.html) included

- the Cochrane Peripheral Vascular Diseases and the Cochrane Heart Groups' Specialised Registers,
- the Cochrane Database of Systematic Reviews (CDSR; for Cochrane Reviews),
- the Database of Abstracts and Reviews of Effects (DARE; for other reviews),
- the Cochrane Central Register of Controlled Trials (CENTRAL; for clinical trials) and
- the Cochrane Methodology Register (+ Technology Assessments, Economic Evaluations, and Cochrane Groups)

Databases of systematic reviews were first screened in order to check if a review of this topic had been published, and to identify referenced articles and search terms used for any such reviews. Date of publication was not restricted in order to include as many as possible of the potentially relevant studies that might have been missed by previous reviews if these had not searched far enough into the past.
Searching was also done by Internet (in Google scholar) using citations, authors and keywords.

Search Methods: Other searches

Searches were not restricted to literature databases. In order to minimise bias, searching was expanded to different sources of "grey literature" to identify published, unpublished and ongoing studies. There were no date or language restrictions. As there is more interest in this area and as many conference abstracts/posters were not published as articles, correspondence with authors and further searching were done in Google and Databases to confirm articles were not about to be published. Further searches included also the reference lists of relevant articles and books, citation index of journal websites and databases and was completed by hand-search of issues in relevant journals.

The following "grey literature" sources were used:

- Reference list of search of overviews or guidelines,
- Thrombosis websites (Investigators Against ThromboEmbolism INATE, The Thrombosis Interest Group of Canada TIGC, Thrombosis Clinic),
- Conference abstracts and protocols: conference proceedings for meetings of the International Society of Thrombosis and Haemostasis (ISTH), and the European Society of Cardiology (ESC)
- Theses and dissertation abstracts online (http://www.proquest.com/en-US/products/dissertations/),
- Research registers: trial registries and websites including BioMed Central (http://www.biomedcentral.com/), ClincalTrials.gov (http://clinicaltrials.gov/), and Current Controlled Trials (http://www.controlled-trials.com/), International Clinical Trials Registry Platform (ICTRP) (http://www.who.int/ictrp/en/) for ongoing studies
- Registers for systematic reviews: International Prospective Register of Systematic Reviews (PROSPERO) (http://www.crd.york.ac.uk/PROSPERO/)
- Industry websites.
- Contact of authors, experts, and researchers for unpublished or ongoing studies.

Further searches included

- Reference lists of relevant articles and books,
- Index of relevant journal websites either general or specific to the topic (for example, Ann Intern Med, Arch Intern Med, BMJ, Chest, Circulation, J Vasc Surg, Lancet, N Engl J Med, J Thromb Haemost, Thromb Haemost),
- Section on "related articles" of relevant studies in the U.S. National Library of Medicine's PubMed Database (http://www.ncbi.nlm.nih.gov/PubMed) and journal websites, and Science Citation Index to identify articles that have cited relevant studies.
- Handsearch of issues of relevant journals.

Other terms and text-words either related to prognostic factors specific to the topic or to the methodology of systematic reviews and meta-analyses of prognostic studies and prognostic models were used.

Articles were collected in EndNote X4 version reference manager software.

Table A4.1.2: Search strategy - Search terms

(“MESH terms” and text-words)

1. pulmonary embolism.tw.
2. exp Pulmonary Embolism/
3. exp Venous Thromboembolism/
4. prognos*.tw.
5. exp Prognosis/
6. predict*.tw.
7. cohort stud*.tw.
8. exp Cohort Studies/
9. course.tw.
10. exp Incidence/
11. score.tw.
12. model*.tw.
13. index.tw.
14. rule.tw.
15. criteria.tw.
16. tool*.tw.
17. severity index*.tw.
18. geneva.tw.
19. davies.tw.
20. 1 or 2 or 3
21. 4 or 5 or 6 or 7 or 8 or 9 or 10
22. 11 or 12 or 13 or 14 or 15 or 16
23. 20 and 21 and 22
24. 17 or 18 or 19
25. 20 and 24
26. 23 or 25

Table A4.1.3: Data extraction form content

Six detailed sections were incorporated within the data extraction form:

- Review, reviewer and study information
- Verification of study eligibility
- Information about the study (research objective, characteristics of the study, characteristics of the population, prognostic variables, follow-up, outcome variables, sample size and events, missing data and confounding variables, analysis)
- Study quality (sample of patients, follow-up, outcome, prognostic variables, treatment subsequent to inclusion in cohort, sample size and analysis)
- Methods specific to the relevant type of prognostic model (model development, external validation, model updating and model impact studies).
- Study results including general findings (patients characteristics, events, predictors/ model description), model performance (risk-group distribution, risk-group specific incidence of outcome, area under ROC curve, classification/ reclassification, calibration) preferably as compared with the original study derivation sample

Most of these sections are common to all type of studies, but some are more specific. Special considerations were given to model construction studies that include a derivation sample with multivariable/ multivariate analysis and an internal validation sample. Other specific considerations were also used as necessary for the other types of studies.

TABLE A4.1.4: SEARCH RESULTS - OVID MEDLINE(R) 1946 to 2016 August 22

In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)

# ▲	Searches	Results
1	pulmonary embolism.tw.	26019
2	exp Pulmonary Embolism/	34565
3	exp Venous Thromboembolism/	6628
4	prognos*.tw.	443728
5	exp Prognosis/	1287376
6	predict*.tw.	1144983
7	cohort stud*.tw.	122194
8	exp Cohort Studies/	1581235
9	course.tw.	469148
10	exp Incidence/	211364
11	score.tw.	369468
12	model*.tw.	2098717
13	index.tw.	563234
14	rule.tw.	63379
15	criteria.tw.	433361
16	tool*.tw.	498790
17	severity index*.tw.	7198
18	geneva.tw.	3632
19	davies.tw.	992
20	1 or 2 or 3	49089
21	4 or 5 or 6 or 7 or 8 or 9 or 10	3838453
22	11 or 12 or 13 or 14 or 15 or 16	3584042
23	20 and 21 and 22	4017
24	17 or 18 or 19	11808
25	20 and 24	242
26	23 or 25	4074

TABLE A4.1.5: SEARCH RESULTS - EMBASE 1974 to 2016 August 29

# ▲	Searches	Results
1	pulmonary embolism.tw.	38076
2	exp Pulmonary Embolism/	73872
3	exp Venous Thromboembolism/	116984
4	prognos*.tw.	648139
5	exp Prognosis/	553838
6	predict*.tw.	1488965
7	cohort stud*.tw.	169656
8	exp Cohort Studies/	256196
9	course.tw.	620782
10	exp Incidence/	316872
11	score.tw.	586823
12	model*.tw.	2583558
13	index.tw.	767506
14	rule.tw.	80500
15	criteria.tw.	651772
16	tool*.tw.	654580
17	severity index*.tw.	11564
18	geneva.tw.	4914
19	davies.tw.	1263
20	1 or 2 or 3	121598
21	4 or 5 or 6 or 7 or 8 or 9 or 10	3132039
22	11 or 12 or 13 or 14 or 15 or 16	4651770
23	20 and 21 and 22	8358
24	17 or 18 or 19	17709
25	20 and 24	596
26	23 or 25	8570

TABLE A4.1.6A: SEARCH RESULTS - THE COCHRANE LIBRARY 2016 August 18

```
ID     Search (Hit)
#1     pulmonary embolism (2913)
#2     MeSH descriptor: [Pulmonary Embolism] explode all trees (984)
#3     MeSH descriptor: [Venous Thromboembolism] explode all trees (519)
#4     prognos* (28046)
#5     MeSH descriptor: [Prognosis] explode all trees (127979)
#6     predict* (59627)
#7     cohort stud* (30470)
#8     MeSH descriptor: [Cohort Studies] explode all trees (126587)
#9     course (35014)
#10    MeSH descriptor: [Incidence] explode all trees (8966)
#11    score (77251)
#12    model* (86059)
#13    index (149690)
#14    rule (3769)
#15    criteria (99125)
#16    tool* (21254)
#17    severity index* (26803)
#18    geneva (2022)
#19    davies (3401)
#20    (#1 or #2 or #3) (3254)
#21    (#4 or #5 or #6 or #7 or #8 or #9 or #10) (292102)
#22    (#11 or #12 or #13 or #14 or #15 or #16) (288145)
#23    (#20 and #21 and #22) (1061)
#24    (#17 or #18 or #19) (31849)
#25    (#20 and #24) (318)
#26    (#23 or #25) (1155)
```

Table A4.1.6b: Search results in the different databases in The COCHRANE LIBRARY

	N hits	N eligible	N selected
Cochrane Reviews	416	7	0
DARE - Other Reviews	224	32	0
Clinical Trials	352	31	6
Methods Studies	0	0	0
Technology Assessments	12	0	0
Economic Evaluations	148	1	0
Cochrane Groups	3	0	0
TOTAL	1155	71	6

Databases: Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Cochrane Central Register of Controlled Trials, Cochrane Methodology Register, Health Technology Assessment Database, NHS Economic Evaluation Database, About “The Cochrane Collaboration”.

TABLE A4.1.7: SUMMARY OF SEARCH RESULTS FROM MEDLINE, EMBASE and COCHRANE DATABASES.

	N hits	N eligible	Potential Prognostic Models
MEDLINE	4074	585	137
Embase	8570	885	129
Cochrane	1155	71	6
All databases	13799	1541	272

A publication may be found in different databases.

Table A4.1.8: Reasons for non-inclusion of studies that did not meet selection criteria and potential eligible prognostic models.

Database	review	conference abstract	prognostic indicator	population based	specific population	not acute PE	surrogate outcomes	long term prognosis	not prognostic model	other reasons	potential eligible prognostic models	Total
Ovid MEDLINE	70	0	201	5	15	1	6	25	29	96	137	585
Embase	71	265	249	4	33	6	13	30	41	44	129	885
Cochrane	35	3	1	0	1	0	2	1	0	22*	6	71
Total	176	268	451	9	49	7	21	56	70	162	272	1541

Asymptomatic PE not included. A publication may be found in different databases. (*including 5 protocols or provisional abstracts)

Table A4.1.9: Publications excluded after review of the articles and reasons for exclusion

N°	Author Year	MEDLINE	Embase	Cochrane	Other sources	Reasons for exclusion
1	Atasoy 2015 Journal of Computer Assisted Tomography	x	x			Very small sample size (67 patients)
2	Aujesky 2006 EHJ	x	x			Duplicate
3	Barra 2012 (LR-PED) Thromb Res	x	x			Selective population (include low-risk and asymptomatic patients)
4	Cameron 2012 Scottish Med J	x	x			**Not a model** -Triage for outpatient diagnostic management of PE using PESI
5	Choi 2014 Thrombosis Research	x	x			Duplicate
6	Chow 2013 Cardiovasc Ultras	x	x			Long term outcome
7	Coleman 2015 Current Medical Research and Opinion	x	x			Not hospital-based
8	Dunn 2012 Ann Intern Med	x	x			Journal Club
9	Duran 2014 Clinical Laboratory	x	x			Very small sample size (40 partients with PE)
10	Gallotta 2008 Int J Cardiol	x	x			Not a model
11	Golpe 2013 Respiration	x	x			Comment (letter)
12	Kaeberich 2015 European Respiratory Journal	x	x			Duplicate
13	Karatas 2016 Heart, Lung and Circulation	x	x			Not a prognostic model
14	Keller 2015 Netherlands Journal of Medicine	x	X			Not clinically relevant
15	Keller 2015 Experimental Gerontology	x	x			Not a prognostic model
16	Keller 2015 Advances in Medical Sciences	x	x			Not a prognostic model
17	Kilic 2014 Pakistan Journal of Medical Sciences	x	x			Very small sample size (50 patients)
18	Kohn 2016 International Journal of Clinical Practice	x	x			Not hospital-based
19	Masotti 2016 Journal of Thrombosis and Thrombolysis	x	x			Duplicate
20	Moores 2013 ERJ	x	x			Selective patients (class III PESI and a subset of sPESI) - Duplicate
21	Otero 2007 ERJ	x	x			Selective patients Only unstable patients
22	Paiva 2012 Em Med J	x	x			Not a model - Triage
23	Palla 2010 JTH	x	x			Not a model

24	Panigada 2016 Acta Clinica Belgica	x	x			Duplicate
25	Ruiz-Artacho 2016 Revista Clínica Española	x	x			Not a prognostic model
26	Sen 2014 WKW	x	x			Not a model
27	Stuck 2014 Thromb Res*	x	x	x		Selective population
28	Vinson 2015 Annals of the American Thoracic Society	x	x			Selective population
29	Vuilleumier 2015 Journal of Internal Medicine	x	x			Selective population
30	Weeda 2016 Thrombosis Journal	x	x			Not hospital-based
31	Werth 2015 Journal of Thrombosis and Thrombolysis	x	x			Long term
32	Wong 2016 Thrombosis and Haemostasis	x	x			Long term
33	Zondag 2013 (high low) ERJ	x	x	x		Duplicate
34	Zondag 2011 (outpatient) JTH	x	x			Duplicate
35	Al Otair 2014 An Thorac Med	x				Not a model
36	Almahameed 2007 Am J Med	x				Not a model
37	Bircan 2011 CATH	x				**Not a model** - surrogate
38	Bledsoe 2010 CPC	x				**Not a model** - Triage for treatment in chest pain unit
39	Budaj-Fidecka 2013 Int J Cardiol	x				Not a model
40	Fraga 2010 TH	x				Reliability study
41	Gould 2006 ACP Journal Club	x				Journal Club
42	Gul 2012 DIR	x				Not a model
43	Keller 2015 Heart and Vessels	x				Not a prognostic model
44	Lankeit 2013 duration Thromb Res	x				Not a model
45	McCabe 2013 Irish J Med Sc	x				**Not a model** – Suitability for outpatient management
46	O'Flaherty 2006 EBM	x				Journal Club
47	Rydman2013 Am J E Med	x				**Not a model** - Surrogate outcome
48	Sequeira 1992 Rev Port Cardiol	x				Old variables – Discriminant analysis – article not found

49	Spirk 2012 QJM	x				Not a model
50	Taylor 2013 J Em Med	x				Not a model
51	Tsai 2013 PLoS One	x				Not a model
52	Ahmad 2011 Thorax		x			**Not a model** - Algorithm
53	Coleman 2015 BMJ Open		x			Not hospital-based
54	George 2014 J Thoracic Imaging		x			Not a model
55	Goldhaber 1999 Lancet		x			Not a prognostic model
56	Hariharan 2012 (erratum) TH		x			**Duplicate** - Erratum
57	Kanbay 2007 Respir Med		x			**Not a model** - Surrogate
58	Kasper 1997 JACC		x			Not a prognostic model
59	Konstantinides 1997 Circulation		x			Not a prognostic model
60	Kucher 2003 EHJ		x			Not a model
61	Rodríguez-Cerrillo 2009 E J Int Med		x			Not a model
62	Wong 2016 International Journal of Cardiolology		x			Long term
63	Kline 2014 JTH			x		**Not a prognostic model** (RCT Thrombolysis versus placebo)

Studies excluded after review of the articles

Studies found in databases then excluded[1-63]: 63

Ovid MEDLINE and Embase: 62 studies[1-33 35-63] (34 common to databases[4-6 10-13 15 16 18 21 25 27 29 31-33 35 39 41 43-46 48 50 53 56-60 62 63], 17 extra found in MEDLINE[2 3 7-9 17 22 23 30 38 40 42 49 51 52 54 55] and 11 extra found in Embase[1 13 19 20 24 26 28 36 37 47 61])

Cochrane: 1 extra found in Cochrane[34] and 2 that were already found in the other databases[53 62] (total: 3 studies)

Studies found by other sources then excluded: none

Total of studies excluded: 63

Reasons for exclusion: Not a (prognostic) model[1-3 7-10 18-20 23 26-28 30-32 34 36-38 40 44 45 47-50 52 54 55] (n=31), duplicate [5 11 24 25 39 46 62 63] (n= 8), selective population/ patients[6 41 43 53 56 57] (n= 6), not hospital-based[13 14 35 58] (n= 4), long term outcome[12 59-61] (n= 4), reliability study[17] (n= 1), journal club[15 22 42] (n= 3), comment letter[21] (n= 1), not clinically relevant[29] (n= 1), very small sample size (< 80 patients)[4 16 33] (n= 3), very old variables in the model[51] (n= 1).

Table A4.1.10: Publications included after review of the articles

N°	Author Year	MEDLINE	Embase	Cochrane	Other sources
1	Agterof 2009 TH	x	x		
2	Agterof 2010 JTH	x	x		
3	Agterof 2011 Am J haematol	x	x		
4	Akgüllü 2015 The American Journal of Emergency Medicine	x	x		
5	Aujesky 2005 AJRCCM	x	x		
6	Aujesky 2006 Arch Intern Med	x	x		
7	Aujesky 2007 J Intern Med	x	x		
8	Aujesky 2011 Lancet	x	x	x	
9	Bach 2016 PLoS One	x	x		
10	Becattini 2013 Chest	x	x		
11	Bertoletti 2013 Thromb Res	x	x		
12	Bova 2009 JTH	x	x		
13	Bova 2014 Eur Respir J	x	x		
14	Chan 2010 JTH	x	x		
15	Chan 2012 J Hosp Med	x	x		
16	Choi 2014 Thromb Res	x	x		
17	Choi 2009 Korean JIM	x	x		
18	Cordeanu 2016 International Journal of Cardiology	x	x		
19	Davies 2007 ERJ	x	x		
20	Dellas 2014 TH	x	x		
21	Donze 2008 TH	x	x		
22	Erkens 2012 Thromb Res	x	x		
23	Ferman 2015 Acad Emerg Med	x	x	x	
24	Fernandez 2015 Chest	x	x		
25	Ferrer 2013 Arch de Bronconeumo	x	x		
26	Hakemi 2015 Chest	x	x		
27	Hariharan 2011 TH	x	x		
28	Hobohm 2016 European Respiratory Journal	x	x		
29	Jimenez 2016 Thrombosis and Haemostasis	x	x		
30	Jimenez 2007 Chest	x	x		
31	Jimenez 2010 Arch Intern Med	x	x		
32	Jimenez 2011 Thorax	x	x		
33	Jimenez 2014 AJRCCM	x	x		
34	Jo 2013 BMC Med	x	x		
35	Kara 2015 Acta Clinica Belgica	x	x		
36	Kostrubiec 2005 EHJ	x	x		
37	Kukla 2009 Kardiologia Polska	x	x		
38	Kundi 2015 Heart & Lung	x	x		
39	Lankeit 2014 ERJ	x	x		
40	Lankeit 2013 Clin Res Cardiol	x	x		
41	Lankeit 2012 Chest	x	x		
42	Lankeit 2011 Circulation	x	x		
43	Lauque 2014 Academic Emergency Medicine	x	x		
44	Maestre 2015 Annals of the American Thoracic Society	x	x		
45	Masotti 2016 International Journal of Cardiology	x	x		
46	Masotti 2016 Thrombosis Research	x	x		
47	Mizuno 2015 Circulation Journal	x	x		
48	Moores 2010 JTH	x	x		
49	Nendaz 2004 TH	x	x		
50	Ng 2013 Respiration	x	x		
51	Nordenholz 2011 JEM	x	x		
52	Ostovan 2016 Heart, Lung and Circulation	x	x		
53	Otero 2010 Thromb Res	x	x	x	
54	Ozsu 2015 Lung	x	x		
55	Ozsu 2014 Thromb Res	x	x		

56	Ozsu 2013 Multi Discipl Med	x	x		
57	Paiva 2013 Am J Cardiol	x	x		
58	Palmieri 2008 Int Em Med	x	x		
59	Papaioannou 2013 Am J Med Sc	x	x		
60	Righini 2011 JTH	x	x		
61	Roca 2012 RMCSMSNDI **Romanian**	x	x		
62	Rozjabek 2016 Thrombosis Research	x	x		
63	Sam 2011 ERJ	x	x		
64	Sanchez D 2011 JTH	x	x		
65	Sanchez O 2010 AJRCCM	x	x		
66	Sanchez O 2013 ERJ	x	x		
67	Singanayagam 2010 Respir Med	x	x		
68	Singanayagam 2011 QJM	x	x		
69	Soares 2013 BCF	x	x		
70	Spirk 2011 TH	x	x		
71	Stamm 2014 SMJ	x	x		
72	Subramaniam 2009 JMIRO	x	x		
73	Tong 2014 Zhonghua Jie He He Hu Xi Za Zhi **Chineese**	x	x		
74	Toosi 2008 Am J Cardiol	x	x		
75	Uresandi 2007 Arch de Bronconeu	x	x		
76	Vanni 2011 JTH	x	x		
77	Vennetz 2011 TH	x	x		
78	Volschan 2009 Arquiv Brasil Cardiol	x	x		
79	Wicki 2000 TH	x	x		
80	Yamaki 2009 EJEVS	x	x		
81	Zhu 2009 **Chineese**	x	x		
82	Zondag 2013 (Hestia - sPESI) TH	x	x		
83	Zondag 2013 (Hestia – CT-RVD) JTH	x	x		
84	Casazza 2014 Thromb Haemost	x			
85	Kabrhel 2014 Thorax	x			
86	Xu 2016 Zhonghua Jie He He Hu Xi Za Zhi **Chineese**	x			
87	Keller 2015 Phlebologie		x		
88	Barra 2014 Em Med J				x
89	Becattini 2016 European Respiratory Journal				x
90	Beer JTH 2003				x
91	den Exter 2016 AJRCCM				x
92	Huang 2011 Clin Bioch				x
93	Jakobsson 2010 JTH				x
94	Labyk 2012 Kardiologia Polska				x
95	Meyer 2014 NEJM				x
96	Vanni 2015 Thorax				x
97	Vanni 2016 Internal and Emergency Medicine				x
98	Vuilleumier 2010 JTH				x
99	Weeda 2016 Clinical and Applied Thrombosis/Hemostasis				x

TABLE A4.1.11: SOURCES OF INCLUDED STUDIES

Studies found in databases and included: 87 Ovid MEDLINE and Embase: 87 studies[64-150] (83 common to databases[64-76 78-98 100 102-145 147-150], 3 extra found in MEDLINE[77 99 146] and 1 extra found in Embase[101]) Cochrane: 3 studies[71 87 119] that were already found in the other databases
Studies found by other sources[151-162]: **12** (some of them published shortly after the search period, one missed in MEDLINE and Embase)
Total of studies included: 99

TABLE A4.1.12: ONGOING STUDIES

Assessing the Prognosis of Pulmonary Embolism Using Clinical and Imaging Biomarkers (Retrospective & Prospective). ClinicalTrials.gov Identifier: NCT00805246
Prognostic Value of Heart-type Fatty Acid-Binding Protein (h-FABP) in Acute Pulmonary Embolism. ClinicalTrials.gov Identifier: NCT01326507
Prognostication of Acute Pulmonary Embolism (IPEP). ClinicalTrials.gov Identifier: NCT02733198
Clinical Characteristics of Acute Pulmonary Embolism in Chinese Population. ClinicalTrials.gov Identifier: NCT02214043
A Study of Rivaroxaban for Early Discharge of Low Risk Pulmonary Embolism From the Emergency Department (MERCURY PE). ClinicalTrials.gov Identifier: NCT02584660
Validation of Different Risk Assessment Strategies in Normotensive Pulmonary Embolism. ClinicalTrials.gov Identifier: NCT02843243
Identifying Low-Risk Patients With Pulmonary Embolism. ClinicalTrials.gov Identifier: NCT00086151
Hospitalization or Out-treatment ManagEment of Patients With Pulmonary Embolism: a Randomized Controlled Trial (HOME-PE). ClinicalTrials.gov Identifier: NCT02811237
Study on the Clinical Course Of Pulmonary Embolism (SCOPE). ClinicalTrials.gov Identifier: NCT01781858

REFERENCES

1. Ahmad N, Srinivasan K, Moudgil H. Risk stratification in pulmonary embolism: An algorithmic tool approach. Thorax 2011;**66 (12)**:1098-99.

2. Al Otair HA, Al-Boukai AA, Ibrahim GF, et al. Outcome of pulmonary embolism and clinico-radiological predictors of mortality: Experience from a university hospital in Saudi Arabia. Annals of Thoracic Medicine 2014;**9**(1):18-22.

3. Almahameed A, Carman TL. Outpatient management of stable acute pulmonary embolism: proposed accelerated pathway for risk stratification. American Journal of Medicine 2007;**120**(10 Suppl 2):S18-25.

4. Atasoy MM, Sariman N, Levent E, et al. Non severe acute pulmonary embolism: prognostic CT pulmonary angiography findings. J Comput Assist Tomogr 2015;**39**(2):166-70.

5. Aujesky D, Roy PM, Le Manach CP, et al. Validation of a model to predict adverse outcomes in patients with pulmonary embolism. European heart journal 2006;**27 (4)**:476-81.

6. Barra S, Paiva L, Providencia R, et al. LR-PED rule: low risk pulmonary embolism decision rule - a new decision score for low risk pulmonary embolism. Thrombosis research 2012;**130**(3):327-33.

7. Bircan A, Karadeniz N, Ozden A, et al. A simple clinical model composed of ECG, shock index, and arterial blood gas analysis for predicting severe pulmonary embolism. Clinical & Applied Thrombosis/Hemostasis 2011;**17**(2):188-96.

8. Bledsoe J, Hamilton D, Bess E, et al. Treatment of low-risk pulmonary embolism patients in a chest pain unit. Crit 2010;**9**(4):212-5.

9. Budaj-Fidecka A, Kurzyna M, Fijałkowska A, et al. In-hospital major bleeding predicts mortality in patients with pulmonary embolism: An analysis of ZATPOL Registry data. International Journal of Cardiolology 2013;**168**(4):3543-49.

10. Cameron A, Ogilvie C, Teckchandani S, et al. Outpatient imaging for pulmonary embolism may only be suitable for a minority. Scottish Medical Journal 2012;**57**(1):14-7.

11. Choi K-J, Cha S-I, Shin K-M, et al. Central emboli rather than saddle emboli predict adverse outcomes in patients with acute pulmonary embolism. Thrombosis research 2014;**134**(5):991-96.

12. Chow V, Ng AC, Chung T, et al. Right atrial to left atrial area ratio on early echocardiography predicts long-term survival after acute pulmonary embolism. Cardiovasc Ultrasound 2013;**11**:17.

13. Coleman CI, Kohn CG, Bunz TJ. Derivation and validation of the In-hospital Mortality for PulmonAry embolism using Claims daTa (IMPACT) prediction rule. Current Medical Research and Opinion 2015;**31**(8):1461-68.

14. Coleman CI, Kohn CG, Crivera C, et al. Validation of the multivariable In-hospital Mortality for PulmonAry embolism using Claims daTa (IMPACT) prediction rule within an all-payer inpatient administrative claims database. BMJ Open 2015;**5**(10):e009251.

15. Dunn AS. ACP Journal Club. The simplified Pulmonary Embolism Severity Index and high-sensitivity troponin T predicted prognosis in PE. Annals of internal medicine 2012;**156**(8):JC4-12.

16. Duran L, Kayhan S, Guzel A, et al. The prognostic values of GDF-15 in comparison with NT-proBNP in patients with normotensive acute pulmonary embolism. Clinical Laboratory 2014;**60**(8):1365-71.

17. Fraga M, Taffe P, Mean M, et al. The inter-rater reliability of the Pulmonary Embolism Severity Index. Thrombosis and haemostasis 2010;**104 (6)**:1258-62.

18. Gallotta G, Palmieri V, Piedimonte V, et al. Increased troponin I predicts in-hospital occurrence of hemodynamic instability in patients with sub-massive or non-massive pulmonary embolism independent to clinical, echocardiographic and laboratory information. International journal of cardiology 2008;**124**(3):351-7.

19. George E, Kumamaru KK, Ghosh N, et al. Computed tomography and echocardiography in patients with acute pulmonary embolism: part 2: prognostic value. Journal of Thoracic Imaging 2014;**29**(1):W7-12.

20. Goldhaber SZ, Visani L, De Rosa M. Acute pulmonary embolism: clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPER). The Lancet 1999;**353**(9162):1386-89.

21. Golpe R, Perez-de-Llano LA, Castro-Anon O. Prognostic value of the Charlson comorbidity index in pulmonary embolism. Respiration 2013;**85**(5):438.

22. Gould MK. A clinical prediction model was sensitive but not specific for predicting mortality in pulmonary embolism. ACP journal club 2006;**145**(2):53.

23. Gul EE, Can I, Guler I, et al. Association of pulmonary artery obstruction index with elevated heart-type fatty acid binding protein and short-term mortality in patients with pulmonary embolism at intermediate risk. Diagnostic and Interventional Radiology 2012;**18**(6):531-6.

24. Hariharan P, Takayesu JK, Kabrhel C. Erratum to: Association between the Pulmonary Embolism Severity Index (PESI) and short-term clinical deterioration by Hariharan et al. (Thromb Haemost 2011; 105: 706–711). Thrombosis and haemostasis 2012;**107**(3):599-99.

25. Kaeberich A, Seeber V, Jiménez D, et al. Age-adjusted high-sensitivity troponin T cut-off value for risk stratification of pulmonary embolism. European Respiratory Journal 2015;**45**(5):1323-31.

26. Kanbay A, Kokturk N, Kaya MG, et al. Electrocardiography and Wells scoring in predicting the anatomic severity of pulmonary embolism. Respiratory Medicine 2007;**101**(6):1171-6.

27. Karatas MB, Gungor B, Ipek G, et al. Association of Serum Cholesterol Levels with Short-term Mortality in Patients with Acute Pulmonary Embolism. Heart, Lung and Circulation 2016;**25**(4):365-70.

28. Kasper W, Konstantinides S, Geibel A, et al. Management Strategies and Determinants of Outcome in Acute Major Pulmonary Embolism: Results of a Multicenter Registry. Journal of the American College of Cardiology 1997;**30**(5):1165-71.

29. Keller K, Beule J, Balzer JO, et al. Modified Bova score for risk stratification and short-term outcome in acute pulmonary embolism. Netherlands Journal of Medicine 2015;**73**(9):410-6.

30. Keller K, Beule J, Coldewey M, et al. Impact of advanced age on the severity of normotensive pulmonary embolism. Heart and Vessels 2015;**30**(5):647-56.

31. Keller K, Beule J, Coldewey M, et al. The risk factor age in normotensive patients with pulmonary embolism: Effectiveness of age in predicting submassive pulmonary embolism, cardiac injury, right ventricular dysfunction and elevated systolic pulmonary artery pressure in normotensive pulmonary embolism patients. Experimental Gerontology 2015;**69**:116-21.

32. Keller K, Beule J, Schulz A, et al. D-dimer for risk stratification in haemodynamically stable patients with acute pulmonary embolism. Advances in Medical Sciences 2015;**60**(2):204-10.

33. Kilic T, Gunen H, Gulbas G, et al. Prognostic role of simplified Pulmonary Embolism Severity Index and the European Society of Cardiology Prognostic Model in short- and long-term risk stratification in pulmonary embolism. Pakistan Journal of Medical Sciences 2014;**30**(6):1259-64.

34. Kline JA, Nordenholz KE, Courtney DM, et al. Treatment of submassive pulmonary embolism with tenecteplase or placebo: cardiopulmonary outcomes at 3 months: multicenter double-blind, placebo-controlled randomized trial. Journal of Thrombosis and Haemostasis 2014;**12**(4):459-68.

35. Kohn CG, Peacock WF, Fermann GJ, et al. External validation of the In-hospital Mortality for PulmonAry embolism using Claims daTa (IMPACT) multivariable prediction rule. International Journal of Clinical Practice 2016;**70**(1):82-8.

36. Konstantinides S, Geibel A, Olschewski M, et al. Association Between Thrombolytic Treatment and the Prognosis of Hemodynamically Stable Patients With Major Pulmonary Embolism: Results of a Multicenter Registry. Circulation 1997;**96**(3):882-88.

37. Kucher N, Wallmann D, Carone A, et al. Incremental prognostic value of troponin I and echocardiography in patients with acute pulmonary embolism. European heart journal 2003;**24**(18):1651-6.

38. Lankeit M, Dellas C, Benz V, et al. The predictive value of heart-type fatty acid-binding protein is independent from symptom duration in normotensive patients with pulmonary embolism. Thrombosis research 2013;**132**(5):543-47.

39. Masotti L, Panigada G, Landini G, et al. Simplified PESI score and sex difference in prognosis of acute pulmonary embolism: a brief report from a real life study. Journal of Thrombosis and Thrombolysis 2016;**41**(4):606-12.

40. McCabe A, Hassan T, Doyle M, et al. Identification of patients with low-risk pulmonary embolism suitable for outpatient treatment using the pulmonary embolism severity index (PESI). Irish Journal of Medical Science 2013;**182**(2):291-5.

41. Moores L, Zamarro C, Gómez V, et al. Changes in PESI scores predict mortality in intermediate-risk patients with acute pulmonary embolism. European Respiratory Journal 2013;**41**(2):354-59.

42. O'Flaherty M, Gandara E. A simple prediction rule identified patients with pulmonary embolism at low risk of short term death. Evid Based Med 2006;**11**(4):121.

43. Otero R, Trujillo-Santos J, Cayuela A, et al. Haemodynamically unstable pulmonary embolism in the RIETE Registry: systolic blood pressure or shock index? European Respiratory Journal 2007;**30**(6):1111-6.

44. Paiva L, Providencia R, Faustino A, et al. Manchester triage in acute pulmonary embolism: can it unmask the grand impersonator? Emergency Medicine Journal 2012;**29**(12):e6.

45. Palla A, Ribas C, Rossi G, et al. The clinical course of pulmonary embolism patients anticoagulated for 1 year: results of a prospective, observational, cohort study. Journal of Thrombosis & Haemostasis 2010;**8**(1):68-74.

46. Panigada G, Masotti L, Rosi C, et al. Thromboembolic burden, prognostic assessment and outcomes of females compared to males in acute pulmonary embolism. Acta Clinica Belgica 2016;**71**(3):142-8.

47. Rodríguez-Cerrillo M, Alvarez-Arcaya A, Fernández-Díaz E, et al. A prospective study of the management of non-massive pulmonary embolism in the home. Eur 2009;**20**(6):598-600.

48. Ruiz-Artacho P, Rodriguez-Lopez I, Perez Pena C, et al. Prognostic value of a previous medical or surgical admission in outpatients with symptomatic pulmonary embolism. Revista Clínica Española 2016;**216**(2):68-73.

49. Rydman R, Söderberg M, Larsen F, et al. d-Dimer and simplified pulmonary embolism severity index in relation to right ventricular function. The American journal of emergency medicine 2013;**31**(3):482-86.

50. Sen HS, Abakay O, Tanrikulu AC, et al. Is a complete blood cell count useful in determining the prognosis of pulmonary embolism? Wiener Klinische Wochenschrift 2014;**126**(11-12):347-54.

51. Sequeira JF, Duarte PC, Madruga IM, et al. [Pulmonary embolism--mortality risk]. Revista Portuguesa de Cardiologia 1992;**11**(9):749-57.

52. Spirk D, Willenberg T, Aujesky D, et al. Use of biomarkers or echocardiography in pulmonary embolism: the Swiss Venous Thromboembolism Registry. Quarterly Journal of Medicine 2012;**105**(12):1163-69.

53. Stuck AK, Stone RA, Pugh N, et al. Comparison of the Pulmonary Embolism Severity Index to a Simplified Version: Classification and Clinical Outcomes. Thrombosis research 2014;**133**(3):515-16.

54. Taylor RA, Davis J, Liu R, et al. Point-of-Care Focused Cardiac Ultrasound for Prediction of Pulmonary Embolism Adverse Outcomes. The Journal of emergency medicine 2013;**45**(3):392-99.

55. Tsai J, Abe K, Boulet SL, et al. Predictive accuracy of 29-comorbidity index for in-hospital deaths in US adult hospitalizations with a diagnosis of venous thromboembolism. PLoS One 2013;**8**(7):e70061.

56. Vinson DR, Drenten CE, Huang J, et al. Impact of Relative Contraindications to Home Management in Emergency Department Patients with Low-Risk Pulmonary Embolism. Annals of the American Thoracic Society 2015;**12**(5):666-73.

57. Vuilleumier N, Limacher A, Mean M, et al. Cardiac biomarkers and clinical scores for risk stratification in elderly patients with non-high-risk pulmonary embolism. Journal of internal medicine 2015;**277**(6):707-16.

58. Weeda ER, Kohn CG, Fermann GJ, et al. External validation of prognostic rules for early post-pulmonary embolism mortality: assessment of a claims-based and three clinical-based approaches. Thrombosis Journal 2016;**14**:7.

59. Werth S, Kamvissi V, Stange T, et al. Outpatient or inpatient treatment for acute pulmonary embolism: a retrospective cohort study of 439 consecutive patients. Journal of Thrombosis and Thrombolysis 2015;**40**(1):26-36.

60. Wong CC, Ng AC, Lau JK, et al. High mortality in patients presenting with acute pulmonary embolism and elevated INR not on anticoagulant therapy. Thrombosis and haemostasis 2016;**115**(6):1191-9.

61. Wong CC, Ng AC, Lau JK, et al. The prognostic impact of chest pain in 1306 patients presenting with confirmed acute pulmonary embolism. International Journal of Cardiolology 2016;**221**:794-99.

62. Zondag W, Hiddinga BI, Crobach MJT, et al. Hestia criteria can discriminate high- from low-risk patients with pulmonary embolism. European Respiratory Journal 2013;**41**(3):588-92.

63. Zondag W, Mos ICM, Creemers-Schild D, et al. Outpatient treatment in patients with acute pulmonary embolism: the Hestia Study. Journal of Thrombosis and Haemostasis 2011;**9**(8):1500-7.

64. Agterof MJ, Schutgens RE, Moumli N, et al. A prognostic model for short term adverse events in normotensive patients with pulmonary embolism. American Journal of Hematology 2011;**86 (8)**:646-49.

65. Agterof MJ, Schutgens REG, Snijder RJ, et al. Out of hospital treatment of acute pulmonary embolism in patients with a low NT-proBNP level. Journal of Thrombosis and Haemostasis 2010;**8**(6):1235-41.

66. Agterof MJ, Van Bladel ER, Schutgens REG, et al. Risk stratification of patients with pulmonary embolism based on pulse rate and D-dimer concentration. Thrombosis and haemostasis 2009;**102 (4)**:683-87.

67. Akgüllü Ç, Ömürlü İK, Eryılmaz U, et al. Predictors of early death in patients with acute pulmonary embolism. The American journal of emergency medicine 2015;**33**(2):214-21.

68. Aujesky D, Obrosky DS, Stone RA, et al. Derivation and validation of a prognostic model for pulmonary embolism. American journal of respiratory and critical care medicine 2005;**172 (8)**:1041-46.

69. Aujesky D, Obrosky DS, Stone RA, et al. A prediction rule to identify low-risk patients with pulmonary embolism. Archives of internal medicine 2006;**166 (2)**:169-75.

70. Aujesky D, Perrier A, Roy PM, et al. Validation of a clinical prognostic model to identify low-risk patients with pulmonary embolism. Journal of internal medicine 2007;**261 (6)**:597-604.

71. Aujesky D, Roy PM, Verschuren F, et al. Outpatient versus inpatient treatment for patients with acute pulmonary embolism: An international, open-label, randomised, non-inferiority trial. Lancet 2011;**378 (9785)**:41-48.

72. Bach AG, Taute BM, Baasai N, et al. 30-Day Mortality in Acute Pulmonary Embolism: Prognostic Value of Clinical Scores and Anamnestic Features. PLoS One 2016;**11**(2):e0148728.

73. Becattini C, Casazza F, Forgione C, et al. Acute pulmonary embolism: external validation of an integrated risk stratification model. Chest 2013;**144**(5):1539-45.

74. Bertoletti L, Le Gal G, Aujesky D, et al. Prognostic value of the Geneva prediction rule in patients with pulmonary embolism. Thrombosis research 2013;**132**(1):32-36.

75. Bova C, Pesavento R, Marchiori A, et al. Risk stratification and outcomes in hemodynamically stable patients with acute pulmonary embolism: a prospective, multicentre, cohort study with three months of follow-up. Journal of Thrombosis and Haemostasis 2009;**7**(6):938-44.

76. Bova C, Sanchez O, Prandoni P, et al. Identification of intermediate-risk patients with acute symptomatic pulmonary embolism. European Respiratory Journal 2014;**44**(3):694-703.

77. Casazza F, Becattini C, Guglielmelli E, et al. Prognostic significance of free-floating right heart thromboemboli in acute pulmonary embolism Results from the Italian Pulmonary Embolism Registry. Thrombosis and haemostasis 2014;**111**(1):53-57.

78. Chan CM, Woods C, Shorr AF. The validation and reproducibility of the pulmonary embolism severity index. Journal of Thrombosis and Haemostasis 2010;**8 (7)**:1509-14.

79. Chan CM, Woods CJ, Shorr AF. Comparing the pulmonary embolism severity index and the prognosis in pulmonary embolism scores as risk stratification tools. J Hosp Med 2012;**7**(1):22-27.

80. Choi K-J, Cha S-I, Shin K-M, et al. Prognostic implications of computed tomographic right ventricular dilation in patients with acute pulmonary embolism. Thrombosis research 2014;**133**(2):182-86.

81. Choi WH, Sung UK, Yoon JJ, et al. The pulmonary embolism severity index in predicting the prognosis of patients with pulmonary embolism. Korean Journal of Internal Medicine 2009;**24 (2)**:123-27.

82. Cordeanu M, Gaertner S, Faller A, et al. Prognostic value of the simplified PESI score in comparison with the 2014 ESC risk model in pulmonary embolism. International journal of cardiology 2016;**220**:623-4.

83. Davies CWH, Wimperis J, Green ES, et al. Early discharge of patients with pulmonary embolism: a two-phase observational study. European Respiratory Journal 2007;**30**(4):708-14.

84. Dellas C, Tschepe M, Seeber V, et al. A novel H-FABP assay and a fast prognostic score for risk assessment of normotensive pulmonary embolism. Thrombosis and haemostasis 2014;**111**(5):996-1003.

85. Donze J, Le Gal G, Fine MJ, et al. Prospective validation of the Pulmonary Embolism Severity Index: A clinical prognostic model for pulmonary embolism. Thrombosis and haemostasis 2008;**100 (5)**:943-48.

86. Erkens PMG, Gandara E, Wells PS, et al. Does the Pulmonary Embolism Severity Index accurately identify low risk patients eligible for outpatient treatment? Thrombosis research 2012;**129 (6)**:710-14.

87. Fermann GJ, Erkens PM, Prins MH, et al. Treatment of pulmonary embolism with rivaroxaban: outcomes by simplified Pulmonary Embolism Severity Index score from a post hoc analysis of the EINSTEIN PE study. Academic Emergency Medicine 2015;**22**(3):299-307.

88. Fernandez C, Bova C, Sanchez O, et al. Validation of a Model for Identification of Patients at Intermediate to High Risk for Complications Associated With Acute Symptomatic Pulmonary Embolism. Chest 2015;**148**(1):211-18.

89. Ferrer M, Morillo R, Elias T, et al. Validation of two clinical prognostic models in patients with acute symptomatic pulmonary embolism. Archivos de bronconeumologia 2013;**49**(10):427-31.

90. Hakemi EU, Alyousef T, Dang G, et al. The prognostic value of undetectable highly sensitive cardiac troponin I in patients with acute pulmonary embolism. Chest 2015;**147**(3):685-94.

91. Hariharan P, Takayesu JK, Kabrhel C. Association between the pulmonary embolism severity index (PESI) and short-term clinical deterioration. Thrombosis and haemostasis 2011;**105 (4)**:706-11.

92. Hobohm L, Hellenkamp K, Hasenfuss G, et al. Comparison of risk assessment strategies for not-high-risk pulmonary embolism. European Respiratory Journal 2016;**47**(4):1170-8.

93. Jimenez D, Aujesky D, Moores L, et al. Simplification of the pulmonary embolism severity index for prognostication in patients with acute symptomatic pulmonary embolism. Archives of internal medicine 2010;**170 (15)**:1383-89.

94. Jimenez D, Aujesky D, Moores L, et al. Combinations of prognostic tools for identification of high-risk normotensive patients with acute symptomatic pulmonary embolism. Thorax 2011;**66 (1)**:75-81.

95. Jiménez D, Kopecna D, Tapson V, et al. Derivation and Validation of Multimarker Prognostication for Normotensive Patients with Acute Symptomatic Pulmonary Embolism. American journal of respiratory and critical care medicine 2014;**189**(6):718-26.

96. Jimenez D, Lobo JL, Fernandez-Golfin C, et al. Effectiveness of prognosticating pulmonary embolism using the ESC algorithm and the Bova score. Thrombosis and haemostasis 2016;**115**(4):827-34.

97. Jimenez D, Yusen RD, Otero R, et al. Prognostic models for selecting patients with acute pulmonary embolism for initial outpatient therapy. Chest 2007;**132**(1):24-30.

98. Jo J, Lee M, Lee J, et al. Leukocytes and systemic inflammatory response syndrome as prognostic factors in pulmonary embolism patients. BMC Pulmonary Medicine 2013;**13**(1):74.

99. Kabrhel C, Okechukwu I, Hariharan P, et al. Factors associated with clinical deterioration shortly after PE. Thorax 2014;**69**(9):835-42.

100. Kara H, Degirmenci S, Bayir A, et al. Pulmonary embolism severity index, age-based markers and evaluation in the emergency department. Acta Clinica Belgica 2015;**70**(4):259-64.

101. Keller K, Coldewey M, Dippold W, et al. Simplified CRB-65 for risk stratification and predicting prognosis in acute pulmonary embolism. Phlebologie 2015;**44**(4):192-99.

102. Kostrubiec M, Pruszczyk P, Bochowicz A, et al. Biomarker-based risk assessment model in acute pulmonary embolism. European heart journal 2005;**26 (20)**:2166-72.

103. Kukla P, Bryniarski L, Dlugopolski R, et al. Acute pulmonary embolism registry in the Malopolska region - clinical course. Kardiologia polska 2009;**67**(7):735-41.

104. Kundi H, Balun A, Cicekcioglu H, et al. The relation between platelet-to-lymphocyte ratio and Pulmonary Embolism Severity Index in acute pulmonary embolism. Heart & Lung: The Journal of Acute and Critical Care 2015;**44**(4):340-43.

105. Lankeit M, Friesen D, Schafer K, et al. A simple score for rapid risk assessment of non-high-risk pulmonary embolism. Clin 2013;**102**(1):73-80.

106. Lankeit M, Gomez V, Wagner C, et al. A strategy combining imaging and laboratory biomarkers in comparison with a simplified clinical score for risk stratification of patients with acute pulmonary embolism. Chest 2012;**141 (4)**:916-22.

107. Lankeit M, Jimenez D, Kostrubiec M, et al. Predictive value of the high-sensitivity troponin T assay and the simplified pulmonary embolism severity index in hemodynamically stable patients with acute pulmonary embolism: A prospective validation study. Circulation 2011;**124 (24)**:2716-24.

108. Lankeit M, Jiménez D, Kostrubiec M, et al. Validation of N-terminal pro-brain natriuretic peptide cut-off values for risk stratification of pulmonary embolism. European Respiratory Journal 2014;**43**(6):1669-77.

109. Lauque D, Maupas-Schwalm F, Bounes V, et al. Predictive value of the heart-type fatty acid-binding protein and the Pulmonary Embolism Severity Index in patients with acute pulmonary embolism in the emergency department. Academic Emergency Medicine 2014;**21**(10):1143-50.

110. Maestre A, Trujillo-Santos J, Riera-Mestre A, et al. Identification of Low-Risk Patients with Acute Symptomatic Pulmonary Embolism for Outpatient Therapy. Annals of the American Thoracic Society 2015;**12**(8):1122-9.

111. Masotti L, Panigada G, Landini G, et al. Predictive ability of the new 2014 ESC prognostic model in acute pulmonary embolism. International journal of cardiology 2016;**202**:801-03.

112. Masotti L, Verdiani V, Cei M, et al. The predictive role of the Bova risk score in acute normotensive pulmonary embolism: A retrospective analysis on a real life cohort. Thrombosis research 2016;**137**:221-23.

113. Mizuno A, Yamamoto T, Tanabe Y, et al. Pulmonary Embolism Severity Index and Simplified Pulmonary Embolism Severity Index Risk Scores Are Useful to Predict Mortality in Japanese Patients With Pulmonary Embolism. Circulation Journal 2015;**79**(4):889-91.

114. Moores L, Aujesky D, Jimenez D, et al. Pulmonary Embolism Severity Index and troponin testing for the selection of low-risk patients with acute symptomatic pulmonary embolism. Journal of Thrombosis and Haemostasis 2010;**8 (3)**:517-22.

115. Nendaz MR, Bandelier P, Aujesky D, et al. Validation of a risk score identifying patients with acute pulmonary embolism, who are at low risk of clinical adverse outcome. Thrombosis and haemostasis 2004;**91 (6)**:1232-36.

116. Ng AC, Chow V, Yong AS, et al. Prognostic impact of the Charlson comorbidity index on mortality following acute pulmonary embolism. Respiration 2013;**85**(5):408-16.

117. Nordenholz K, Ryan J, Atwood B, et al. Pulmonary embolism risk stratification: Pulse oximetry and pulmonary embolism severity index. Journal of Emergency Medicine 2011;**40 (1)**:95-102.

118. Ostovan MA, Ghaffari S, Pourafkari L, et al. Modification of Simplified Pulmonary Embolism Severity Index and its Prognostic Value in Patients with Acute Pulmonary Embolism. Heart, Lung and Circulation 2016;**25**(2):184-90.

119. Otero R, Uresandi F, Jimenez D, et al. Home treatment in pulmonary embolism. Thrombosis research 2010;**126**(1):e1-5.

120. Ozsu S, Abul Y, Orem A, et al. Predictive value of troponins and simplified pulmonary embolism severity index in patients with normotensive pulmonary embolism. Multidiscip 2013;**8**(1):34.

121. Ozsu S, Bektas H, Abul Y, et al. Value of Cardiac Troponin and sPESI in Treatment of Pulmonary Thromboembolism at Outpatient Setting. Lung 2015;**193**(4):559-65.

122. Ozsu S, Ozlu T, Şentürk A, et al. Combination and comparison of two models in prognosis of pulmonary embolism: Results from TUrkey Pulmonary Embolism Group (TUPEG) study. Thrombosis research 2014;**133**(6):1006-10.

123. Paiva LV, Providencia RC, Barra SN, et al. Cardiovascular risk assessment of pulmonary embolism with the GRACE risk score. The American journal of cardiology 2013;**111**(3):425-31.

124. Palmieri V, Gallotta G, Rendina D, et al. Troponin I and right ventricular dysfunction for risk assessment in patients with nonmassive pulmonary embolism in the Emergency Department in combination with clinically based risk score. Internal and emergency medicine 2008;**3 (2)**:131-38.

125. Papaioannou AI, Kastanis A, Malli F, et al. Predicting short-term mortality in patients with pulmonary embolism: a simple model. American Journal of the Medical Sciences 2013;**345**(6):462-9.

126. Righini M, Roy PM, Meyer G, et al. The Simplified Pulmonary Embolism Severity Index (PESI): Validation of a clinical prognostic model for pulmonary embolism. Journal of Thrombosis and Haemostasis 2011;**9 (10)**:2115-17.

127. Roca IC, Aursulesei V, Roca M, et al. [Comparative evaluation of prognostic scores in pulmonary embolism]. Revista Medico-Chirurgicala a Societatii de Medici Si Naturalisti Din Iasi 2012;**116**(1):69-74.

128. Rozjabek HM, Coleman CI, Weeda ER, et al. Effect of vital sign measurement timing on Pulmonary Embolism Severity Index (PESI) and simplified PESI 30-day mortality risk determination. Thrombosis research 2016;**141**:8-10.

129. Sam A, Sanchez D, Gomez V, et al. The shock index and the simplified PESI for identification of low-risk patients with acute pulmonary embolism. European Respiratory Journal 2011;**37 (4)**:762-66.

130. Sanchez D, De Miguel J, Sam A, et al. The effects of cause of death classification on prognostic assessment of patients with pulmonary embolism. Journal of Thrombosis and Haemostasis 2011;**9 (11)**:2201-07.

131. Sanchez O, Trinquart L, Caille V, et al. Prognostic factors for pulmonary embolism: The PREP study, a prospective multicenter cohort study. American journal of respiratory and critical care medicine 2010;**181 (2)**:168-73.

132. Sanchez O, Trinquart L, Planquette B, et al. Echocardiography and pulmonary embolism severity index have independent prognostic roles in pulmonary embolism. European Respiratory Journal 2013;**42**(3):681-88.

133. Singanayagam A, Chalmers JD, Scally C, et al. Right ventricular dilation on CT pulmonary angiogram independently predicts mortality in pulmonary embolism. Respiratory Medicine 2010;**104**(7):1057-62.

134. Singanayagam A, Scally C, Al-Khairalla MZ, et al. Are biomarkers additive to pulmonary embolism severity index for severity assessment in normotensive patients with acute pulmonary embolism? Quarterly Journal of Medicine 2011;**104**(2):125-31.

135. Soares TH, de Bastos M, de Carvalho BV, et al. Prognostic value of computed tomographic pulmonary angiography and the pulmonary embolism severity index in patients with acute pulmonary embolism. Blood Coagulation & Fibrinolysis 2013;**24**(1):64-70.

136. Spirk D, Aujesky D, Husmann M, et al. Cardiac troponin testing and the simplified pulmonary embolism severity index the swiss venous thromboembolism registry (SWIVTER). Thrombosis and haemostasis 2011;**106 (5)**:978-84.

137. Stamm JA, Long JL, Kirchner HL, et al. Risk Stratification in Acute Pulmonary Embolism: Frequency and Impact on Treatment Decisions and Outcomes. Southern Medical Journal 2014;**107**(2):72-78.

138. Subramaniam RM, Mandrekar J, Blair D, et al. The Geneva prognostic score and mortality in patients diagnosed with pulmonary embolism by CT pulmonary angiogram. Journal of medical imaging and radiation oncology 2009;**53 (4)**:361-65.

139. Tong C, Zhang Z, Ma C, et al. [The value of simplified pulmonary embolism severity index and biomarkers in evaluating pulmonary embolism prognosis]. Zhonghua jie he he hu xi za zhi = Zhonghua jiehe he huxi zazhi = Chinese journal of tuberculosis and respiratory diseases 2014;**37**(2):104-8.

140. Toosi MS, Merlino JD, Leeper KV. Prognostic Value of the Shock Index Along With Transthoracic Echocardiography in Risk Stratification of Patients With Acute Pulmonary Embolism. American Journal of Cardiology 2008;**101 (5)**:700-05.

141. Uresandi F, Otero R, Cayuela A, et al. A clinical prediction rule for identifying short-term risk of adverse events in patients with pulmonary thromboembolism. [Spanish]. Archivos de bronconeumologia 2007;**43 (11)**:617-22.

142. Vanni S, Nazerian P, Pepe G, et al. Comparison of two prognostic models for acute pulmonary embolism: Clinical vs. right ventricular dysfunction-guided approach. Journal of Thrombosis and Haemostasis 2011;**9 (10)**:1916-23.

143. Venetz C, Jimenez D, Mean M, et al. A comparison of the original and simplified pulmonary embolism severity index. Thrombosis and haemostasis 2011;**106 (3)**:423-28.

144. Volschan A, Albuquerque D, Tura BR, et al. Predictors of hospital mortality in hemodynamically stable patients with pulmonary embolism. [Portuguese, Spanish, English]. Arquivos brasileiros de cardiologia 2009;**93 (2)**:135-40.

145. Wicki J, Perrier A, Perneger TV, et al. Predicting adverse outcome in patients with acute pulmonary embolism: A risk score. Thrombosis and haemostasis 2000;**84 (4)**:548-52.

146. Xu NL, Xue H, Chen YS, et al. [Establishment and evaluation of a prognostic model for acute pulmonary embolism]. Zhonghua jie he he hu xi za zhi = Zhonghua jiehe he huxi zazhi = Chinese journal of tuberculosis and respiratory diseases 2016;**39**(4):304-10.

147. Yamaki T, Nozaki M, Sakurai H, et al. Presence of Lower Limb Deep Vein Thrombosis and Prognosis in Patients with Symptomatic Pulmonary Embolism: Preliminary Report. European Journal of Vascular and Endovascular Surgery 2009;**37 (2)**:225-31.

148. Zhu L, Wang C, Yang Y-h, et al. [Prognostic value of right ventricular dysfunction and derivation of a prognostic model for patients with acute pulmonary thromboembolism]. Chung-Hua Liu Hsing Ping Hsueh Tsa Chih Chinese Journal of Epidemiology 2009;**30**(2):184-8.

149. Zondag W, den Exter PL, Crobach MJT, et al. Comparison of two methods for selection of out of hospital treatment in patients with acute pulmonary embolism. Thrombosis and haemostasis 2013;**109**(1):47-52.

150. Zondag W, Vingerhoets LMA, Durian MF, et al. Hestia criteria can safely select patients with pulmonary embolism for outpatient treatment irrespective of right ventricular function. Journal of Thrombosis and Haemostasis 2013;**11**(4):686-92.

151. Barra SNC, Paiva LV, Providência R, et al. Atrial fibrillation in acute pulmonary embolism: prognostic considerations. Emergency Medicine Journal 2014;**31**(4):308-12.

152. Becattini C, Agnelli G, Lankeit M, et al. Acute pulmonary embolism: mortality prediction by the 2014 European Society of Cardiology risk stratification model. European Respiratory Journal 2016;**48**(3):780-6.

153. Beer JH, Burger M, Gretener S, et al. Outpatient treatment of pulmonary embolism is feasible and safe in a substantial proportion of patients. Journal of Thrombosis and Haemostasis 2003;**1**(1):186-7.

154. den Exter PL, Zondag W, Klok FA, et al. Efficacy and Safety of Outpatient Treatment Based on the Hestia Clinical Decision Rule With or Without NT-proBNP Testing in Patients With Acute Pulmonary Embolism: A Randomized Clinical Trial. American journal of respiratory and critical care medicine 2016.

155. Huang CM, Lin YC, Lin YJ, et al. Risk stratification and clinical outcomes in patients with acute pulmonary embolism. Clinical Biochemistry 2011;**44**(13):1110-5.

156. Jakobsson C, Jimenez D, Gomez V, et al. Validation of a clinical algorithm to identify low-risk patients with pulmonary embolism. Journal of Thrombosis and Haemostasis 2010;**8**(6):1242-7.

157. Labyk A, Ciurzynski M, Jankowski K, et al. Acute pulmonary embolism: analysis of consecutive 353 patients hospitalised in a single centre. A 3-year experience. Kardiologia polska 2012;**70**(1):15-22.

158. Meyer G, Vicaut E, Danays T, et al. Fibrinolysis for patients with intermediate-risk pulmonary embolism. New England Journal of Medicine 2014;**370**(15):1402-11.

159. Vanni S, Jimenez D, Nazerian P, et al. Short-term clinical outcome of normotensive patients with acute PE and high plasma lactate. Thorax 2015;**70**(4):333-8.

160. Vanni S, Nazerian P, Bova C, et al. Comparison of clinical scores for identification of patients with pulmonary embolism at intermediate–high risk of adverse clinical outcome: the prognostic role of plasma lactate. Internal and emergency medicine 2016:1-9.

161. Vuilleumier N, Le Gal G, Cornily JC, et al. Is N-terminal pro-brain natriuretic peptide superior to clinical scores for risk stratification in non-massive pulmonary embolism? Journal of Thrombosis and Haemostasis 2010;**8**(6):1433-5.

162. Weeda ER, Kohn CG, Peacock WF, et al. External Validation of the Hestia Criteria for Identifying Acute Pulmonary Embolism Patients at Low Risk of Early Mortality. Clinical and Applied Thrombosis/Hemostasis 2016.

TABLES A4.2 (ORIGINAL MODELS)

Type 1: model variables specific to the domain and to the prognosis of PE (Prognostic models) - Type 2: model originally not specific to PE or to its prognosis (models from other domains applied to PE, or diagnostic prediction rules in PE applied to the prognosis of PE) – Type 3: models using hospital criteria checklists which comprise not only prognostic but also practical variables used as exclusion criteria from early discharge or home treatment (studies included when the objective was clearly to derive and validate the checklist or to compare it to existing prognostic models).

Author, Year	Model	Variables	Points assigned	Risk Stratification/ Management
Prognostic Model				
(Wicki, Perrier et al. 2000)	Geneva Prognostic Score (GPS)	Cancer	2	Low-risk: score ≤ 2
		Heart failure	1	High-risk: score ≥3
		Previous deep vein thrombosis	1	
		Systolic blood pressure < 100 mmHg	2	
		PaO2 < 8 kPa	1	
		Deep vein thrombosis shown by ultrasound	1	
		Total score	0-8	
(Kostrubiec, Pruszczyk et al. 2005)	No acronym (Polish model)	SBP ≤90 mm Hg		In patients with SBP > 90 mmHg
		NT-proBNP ≥ 600 ng/L		Low risk: none of these variables (NT-proBNP, cTnT)
		cTnT ≥ 0,07 µg/L		Medium risk (NT-proBNP ≥ 600 ng/L, cTnT < 0.07 µg/L)
				High risk (NT-proBNP ≥ 600 ng/L, cTnT ≥ 0,07 µg/L)
(Aujesky, Obrosky et al. 2005)	Pulmonary Embolism Severity index (PESI)	**Demographic characteristics**		Class I (very low risk): ≤65
		Age, per yr	Age, in yr	Class II (lowrisk): 66 - 85
		Male sex	10	Class III (intermediaterisk): 86 - 105
		Comorbidillness		Class IV (high risk): 106 - 125
		Cancer	30	Class V (very high risk): > 125

		Heart failure	10	
		Chronic lung disease	10	**Low risk ≤ class II**
		Clinical findings		**High risk ≥ class III**
		Pulse ≥ 110/min	20	
		Systolic blood pressure < 100 mmHg	30	
		Respiratory rate ≥ 30/min	20	
		Temperature < 36°C	20	
		Altered mental status*	60	
		Arterialoxygen saturation < 90%**	20	
		* Defined as disorientation, lethargy, stupor, or coma ** With and without the administration of supplemental oxygen		
(Aujesky, Obrosky et al 2006)	**PE Prognostic Algorithm**	**Demographiccharacteristics**		**Low-risk: none of these variables**
		Age ≥70		**High-risk≥ 1**
		Comorbid conditions		
		Cancer		
		Heartfailure		
		Chronic lung disease		
		Chronic renal disease		
		Cerebrovascular disease*		
		Clinical findings		
		Pulse ≥ 110/min		
		Systolicblood pressure < 100 mmHg		
		Altered mental status**		
		Arterial oxygen saturation < 90%***		
		* Includes transient ischemic attack or stroke ** Includes as disorientation, lethargy, stupor, or coma		

		*** With or without supplemental oxygen		
(Uresandi, Otero et al. 2007)	**No acronym (Spanish model)**	Recent bleeding	4	**Low-risk: score ≤2**
		Metastatic cancer	4	**Higherrisk: score ≥3**
		Creatinine> 2 mg/dL	3	
		Non-metastatic cancer	2	
		History of immobilisation due to medical condition	2	
		No recentsurgery	1	
		Age > 60	1	
(European Society of Cardiology Guidelines 2008)	**2008 ESC**	**Shock or hypotension (1)**		**High risk: (1)**
		SBP < 90 mmHG or SBP drop by ≥ 40 mmHG for > 15 minutes if not caused by new-onset arrhythmia, hypovolaemia or sepsis		**Intermediate-high: (2) + (3)**
				Intermediate-low: either (2) or (3)
				Low: None
		Sign of RVD dysfunction on imaging test (2)		
		CT angio or TTE		
		Elevated cardiac biomarkers (3)		
		cTnT or cTnI, or BNP or NT-proBNP		
(Toosi M. S. et al, 2008)	**Shock index**	**Heart rate/ Systolic blood pressure**		**High-risk: shock index (HR/SBP) ≥ 1**
(Agterof, van Bladel et al 2009)	**No Acronym (Dutch model)**	Pulse rate ≥100 bpm		**Low-risk: none of the two variables**
		D-dimer concentration ≥3,000 µg/ ml		**High-risk: pulse rate ≥100 bpm and/or a D-dimer concentration ≥3,000 µg/ml**
(Volschan, Albuquerque et al 2009)	**EstudoMulticentrico di EmboliaPulmonar (EMEP)**	Age > 65	3	**Lowrisk: 0 - 3**
		Bed rest> 72 h	2	**Moderaterisk: 4 - 6**
		Chronic cor pulmonale	4	**High risk: ≥7**
		Sinus tachycardia	2	
		Tachypnea	2	

(Yamaki, Nozaki et al 2009)	**No acronym (Japanese model)**	Active cancer	2	**Low-risk: score ≤4**
		Inadequate anticoagulation	1	**High-risk: score ≥5**
		Legsymptoms	1	
		Male gender	2	
		Presence of DVT	1	
		Presence of proximal DVT	1	
		Previoushistory of DVT	2	
		Total score	0 - 10	
(Zhu, Wang et al 2009)	**No acronym (Chinese model)**	Constant	-7.3680	**Formulae**
		Right ventricular dysfunction (echocardio)	2.4826	
		Right/ left end diastolic diameter ratio > 0.6	1.3515	
		White blood cells < 4 x 10^9/L or > 10x10^9/L	1.2011	
		Syncope	1.4428	
		Accentuation of P2	0.8165	
		Systolic pulmonary artery pressure > 60 mmHg	0.9145	
		Pulse rate > 110/ min	1.1256	
		Abnormal creatin phosphokinase	0.0039	
(Jimenez, Aujesky et al 2010)	**Simplified PESI (sPESI)**	Age > 80	1	**Low risk: 0**
		History of cancer	1	**High risk: ≥ 1**
		History of heart failure **or** History of chronic lung disease	1	
		Pulse ≥ 110 bpm	1	
		Systolic blood pressure < 100 mmHg	1	
		Arterial oxyhemoglobin saturation level < 90%	1	
(Sanchez, Trinquart et al. 2010)	**Facteurs PRonostiques dans l'Embolie Pulmonaire**	Altered mental state *	10	**Class I (low risk): ≤ 6**
		Cardiogenic shock	6	**Class II (intermediate risk): 7 - 17**

	(PREP)	Cancer	6	**Class III (high risk): ≥ 18**
		BNP (ng/L)		
		<100:	0	
		100-249:	1	
		250-499:	2	
		500-999:	4	
		≥1000:	8	
		RV/LV ratio		
		0.2-0.49	0	
		0.5-0.74	3	
		0.75-1.00	5	
		1.00-1.25	8	
		≥1.25	11	
		Total score	0 - 41	
		*Defined as disorientation, stupor, or coma		
(Agterof, Schutgens et al. 2011)	**Utrecht Prediction Score (UPS)**	Active malignancy	2	**Low risk score (no active malignancy, pulse rate <90 bpm, NT-proBNP<500 pg/ml, and D-dimer <3,000 µg/l FEU)**
		D-dimer (µg/l FEU)		
		< 500	0	
		500 – 3,000	1	
		>3,000	7	
		NT-proBNP (pg/ml)		
		< 500	0	
		500 – 1,000	9	
		> 1,000	15	
		Pulse rate (bpm)		
		< 90	**0**	
		90 - 110	6	
		>110	13	

(Huang, Lin et al. 2011)	**No acronym**	Heart rate ≥ 110/ mn		**Low risk : ≤ 1 risk factor**
		Chronic pulmonary disease		**Intermediaterisk : 2 riskfactors**
		White blood cells ≥ 11,000/ mm^3		**High risk : ≥ 3 riskfactors**
		D-dimer level > 4.0 µg/ mL		
(Lankeit, Friesen et al. 2013)	**FAST score**	H-FABP bedside test > 7 ng/ml	1.5	**Low risk: <3**
(Dellas, Tschepe et al 2013)*		Syncope	1.5	**High risk: ≥3**
		Tachycardia (HR > 100/mn)	2	
		*H-FABP ≥ 6ng/ml		
		(Immunoturbidimetry > ELISA)		
(Jo, Lee et al. 2013)	**No acronym**	Shock		**No risk stratification**
		Altered mental status		
		Active cancer		
		CT right-to-left ventricle diameter ratio		
		Renal dysfunction		
		Systemic inflammatory response syndrome*		
		* SIRS "satisfying WBC criteria" [Body temperature >38.5°C or <36.0°C, Heart rate > 90 beats/min, Respiratory rate > 20 breaths/min, WBC <4,000 or >12,000 mL]		**Score 0 to 4**
(Bova, Sanchez et al 2014)	**No acronym**	Systolic blood pressure 90–100 mmHg	2	**Low risk : (0–2 points)**
		Heart rate ≥ 110 beats per min	1	**Intermediate risk : (3–4 points)**
		Elevated cardiac troponin	2	**High risk : (> 4 points)**
		Right ventricular dysfunction (TTE or CT)	2	

(Jiménez, Kopecna et al 2014)	**PROTECT**	sPESI ≥ 1		**Low-risk: sPESI 0 point and BNP levels less than 100 pg/ml**
		BNP > 100 pg/ml		**High risk : cTnI, BNP, sPESI, and CCUS**
		cTnI > 0.05 ng/ml		
		US-DVT		**Risk calculator eStiMaTe (Score, Marker, Thrombus)**
(European Society of Cardiology Guidelines 2014)	**2014 ESC**	**Shock or hypotension (1)**		**High risk: (1)**
		SBP < 90 mmHG or SBP drop by ≥ 40 mmHG		**Intermediate-high: (4) + (2) + (3)**
		for > 15 minutes if not caused by new-onset		**Intermediate-low: (4) and (either (2) or (3) or none)**
		arrhythmia, hypovolaemia or sepsis		**Low: None**
		Sign of RVD dysfunction on imaging test (2)		
		CT angio or TTE		
		Elevated cardiac biomarkers (3)		
		cTnT or cTnI, or BNP or NT-proBNP		
		PESI ≥ III or sPESI ≥ 1 (4)		
(Akgüllü, Ömürlü et al 2014)	**No Acronym**	cTNI		**Formula for probability (early death)**
		Creatnine (Cr)		
		Mean platelet volume (MPV)		
		Neutrophil-to-Lymphocyte ratio (NLR)		
		QT interval dispersion (QTcd)		
		P wave dispersion (Pd)		
(Kundi, Balun et al 2015)	**Platelet-to-lymphocyte ratio**	PLR		**High-risk: PLR ≥ 149**
(Maestre, Trujillo-Santos et al 2015)	**RIETE score**	**Clinical characteristics**		**Low-risk: RIETE score < 1 point**
		Chronic heart failure	1	
		Recent immobility ≥ 4 d	1	
		Cancer without metastases	1	
		Cancer with metastases	2	

		Recent major bleeding	2	
		Underlying conditions		
		CrCl 30–60 ml/min	1	
		CrCl < 30 ml/min	3	
		Platelet count < 100,000/µl or > 450,000/µl	1	
		Initial PE presentation		
		SBP levels < 100 mm Hg	1	
		Heart rate > 110 bpm	1	
		SpO2 levels < 90%	1	
(Vanni, Jimenez et al 2015)	**TELOS (Thrombo-embolism lactate outcome study)**	Elevated lactate (≥ 2 mmol/L)		**Intermediate-high: all variables**
		RV dysfunction		
		Heart rate ≥ 110 beats per minute		
(Ostovan, Ghaffari et al 2016)	**modified sPESI**	Age > 80	1	**Low risk: 0**
		History of cancer	1	
		Chronic cardiopulmonary disease	1	
		Pulse ≥ 110 bpm	1	
		Systolic blood pressure < 100 mmHg	1	
		PaO2 / PaCO2 ≤ 1.8	1	
		ST elevation in aVR lead and/or	1	
		ST depression in V1-V3 leads		
(Xu, Xue et al 2016)	**No acronym**	Tricuspid systolic murmur	2.529	**Formulae**
		Triglycerides	1.965	
		Circulatory failure (during hospitalization)	1.957	
		Low molecular weight heparin and warfarin sodium	−1.467	
		Mechanical Ventilation	3.406	
		Recent (<1 month) surgery or fracture	1.416	

Prognostic Model Update

Added value of prognostic variables to existing models	**Biomarkers of right ventricular dysfunction or myocardial injury (ischemia)**	Troponin: cTnT, cTnI, hs-cTnT		**(in Model Validation and Model Update sections)**
		Brain natriuretic peptides: BNP, NT-proBNP		
		Heart-Fatty Acid Binding Protein: H-FABP		
	Markers of hypercoagulable state	D-dimer		
	Vascular and cardiac imaging	Lower limb venous ultrasound		
		Echocardiography right ventricular dysfunction		
		CT right ventricular dysfunction		
	Other variables	Plasma lactate		

Other Models

Type 2	**Model variables originally not specific to PE or to its prognosis**			
(Bertoletti, Le Gal et al 2013)	**Revised Geneva Score**	Age > 65 years old	1	**Low probability : 0-3**
		Previous history of DVT or PE	3	**Intermediate probability : 4-10**
		Surgery or fracture within 1 month	2	**High probability :≥11**
		Active malignancy	2	
		Unilateral leg pain	3	
		Hemoptysis	2	
		Heart rate (bpm):		
		75-94	3	
		≥95	5	

		Pain on lower- limb deep venous palpation and unilateral oedema	4	
	Simplified Geneva Score	Age > 65 years old	1	**Low probability : 0-1**
		Previous history of DVT or PE	1	**Intermediate probability : 2-4**
		Surgery or fracture within 1 month	1	**High probability :≥5**
		Active malignancy	1	
		Unilateral leg pain	1	
		Hemoptysis	1	
		Heart rate (bpm):		
		75-94	1	
		≥95	1	
		Pain on lower- limb deep venous palpation and unilateral oedema	1	
(Ng, Chow et al 2012)	**No acronym**	In-hospital all-cause mortality: CCI *score and serum sodium level Post-discharge mortality: age, CCI score, hyperlipidemia, serum sodium level and hemoglobin level *The Charlson Comorbidity Index (CCI) score is a measure of the burden of disease related to comorbidities including cardiovascular disorders, malignancies, chronic pulmonary and neurological diseases, connective tissue diseases and others		**Low risk: CCI score = 0 and no comorbidity** **High risk: CCI score ≥, presence of comorbidities**
(Paiva, Providencia et al 2013)	**GRACE - PE risk score**	Age >80 Heart failure and/or chronic lung disease Active or past malignancy,		**Global Registry of Acute Coronary Events (GRACE): PE risk score** **Low risk : <114** **Intermediate risk : 114-153**

		Heart rate ≥110 beats/min, Respiratory rate >30 breaths/min Arterial oxyhemoglobin saturation <90%, Shock Troponin I >0.034 ng/ml Right ventricular dysfunction		**High risk : >153**
(Papaioannou, Kastanis et al 2013)	**No acronym**	Age ≥67 Charlson index** ≥2 Alveolar to arterial (A-a) gradient* ≥52.8 mmHg Congestive heart failure Diabetes melitus *A-a gradient =(713xFiO2-1.25 PCO2)-PaO2 ** An electronic application for rapidly calculating Charlson comorbidity score	1 1 1 1 1	**Low risk : index ≤ 2** **High risk : index ≥ 3**
(Keller, Coldewey et al 2015)	**Simplified CRB-65**	Dyspnea (no assessment of respiratory rate), Systolic blood pressure < 90 mmHg or Diastolic blood pressure ≤ 60 mmHg Age ≥ 65	1 1 1	**Risk class 1 (0 point)** **Risk class 2 (1 point)** **Risk class 3 (2 points)** **Risk class 4 (3 points)** **No specific cut-off reported**
(Bach, Taute et al 2016)	**APACHE II** **Glasgow Coma Scale** **EuroSCORE II**			
Type 3	**Models using hospital criteria checklists**			

(Davies, Wimperis et al 2007)	**Exclusion criteria from early discharge**	1/Admission to hospital for another medical reason (significant respiratory and/or cardiovascular disease and/or treatment for active malignancy) 2/Additional monitoring required, such as ECG monitoring, or administration of any form of oxygen therapy for hypoxaemia or of any intravenous drugs, including analgesia 3/ History of previous PE or further PEs developing while currently on anticoagulation 3/ History of previous PE or further PEs developing while currently on anticoagulation treatment 4/ Showing co-existing major DVT (high-segment femoral and above) confirmed by radiological imaging. 5) Bleeding disorders or active bleeding. 6) Pregnancy. 7) Likelihood of poor compliance or difficulty ensuring appropriate follow-up, including complex elderly patients, the infirm and those with significant immobility, geographical inaccessibility or a history of non-compliance, and intravenous drug abusers. 8) Patient preference	**Patients who fulfill criteria for safe discharge are early discharged and treated at home** **Needs post-discharge organisation.** - **who follows-up the patient (LMWH daily injection in the hospital or by local ambulatory DVT service),** - **information leaflet,** - **24-h emergency telephone number,** - **contact with GP if patient does no attend the service or is not contactable**
(Zondag , den Exter et al 2013)	**Hestia criteria**	Haemodynamically instable? Thrombolysis or embolectomy necessary? High risk for bleeding?	**If one of the questions is answered with YES, the patient cannot be treated at home.**

	Oxygen supply to maintain oxygen saturation >90%>24 h? Pulmonary embolism diagnosed during anticoagulant treatment? Intravenous pain medication >24 h? Medical or social reason for treatment in the hospital >24 h? Creatinine clearance of less than 30 ml/min? Severe liver impairment Pregnant? Documented history of heparin-induced thrombocytopenia?

TABLES A4.3 (MODELS VARIABLES)

Table A4.3: Variables used in the original prognostic models (only type 1 prognostic models presented). N is the number of times a variable has been included across studies.

Models		**Geneva prognostic score (GPS)**	**No acronym (Polish model)**	**PE severity index (PESI)**	**PE Prognostic algorithm**	**No acronym (Spanish model)**	**(2008 ESC)**	**(Shock index)**	**No Acronym (Dutch model)**	**EMEP (Estudo Multicentrico di Embolia Pulmonar)**	**No acronym (Japanese model)**	**No acronym (Chinese model)**	**sPESI**	**PREP (Facteurs PRonostiques dans l'Embolie Pulmonaire)**	**UPS (Utrecht Prediction Score)**	**No acronym**	**Simple score FAST**	**SIRS-WBC**	**No acronym**	**eStiMaTe (PROTECT)**	**(ESC)**	**No acronym**	**PLR - sPESI**	**RIETE score**	**TELOS**	**modified sPESI**	**No acronym**
Studies		**(Wicki, Perrier et al. 2000)**	**(Kostrubiec, Pruszczyk et al. 2005)**	**(Aujesky, Obrosky et al. 2005)**	**(Aujesky, Obrosky et al 2006)**	**(Uresandi, Otero et al. 2007)**	**(ESC)**	**(Toosi M. S. et al, 2008)**	**(Agterof, van Bladel et al 2009)**	**(Volschan, Albuquerque et al 2009)**	**(Yamaki, Nozaki et al 2009)**	**(Zhu, Wang et al 2009)**	**(Jimenez, Aujesky et al 2010)**	**(Sanchez, Trinquart et al. 2010)**	**(Agterof, Schutgens et al. 2011)**	**(Huang, Lin et al. 2011)**	**(Lankeit, Friesen et al 2013) & (Dellas, Tschepe et al 2014)**	**(Jo, J., M. Lee, et al. 2013)**	**(Bova, Sanchez et al 2014)**	**(Jiménez, Kopecna et al 2014)**	**2014 ESC)**	**(Akgüllü, Ömürlü et al 2014)**	**(Kundi, Balun et al 2015)**	**(Maestre, Trujillo-Santos et al 2015)**	**(Vanni, Jimenez et al 2015)**	**(Ostovan, Ghaffari et al 2016)**	**(Xu, Xue et al 2016)**
N candidate variables		14	20	29	29	30	0	0	7	20	16	NR	11	30	7	38	20	27	22	13	0	NR	22	33	14	NR	NR
N variables in final model		6	2	11	10	7	3	2	2	5	7	8	6	5	4	4	3	4	4	4	4	6	2	11	3	7	6
Proposed risk assessment method		Score	Scoring rule	Score	Scoring rule	Score	Scoring rule	Value	Scoring rule	Score	Score	Equation	Score	Score	Scoring rule	score	Score	None	Score	Calculator	Scoring rule	Equation	Value	Scoring rule	Scoring rule	Score	Equation
Variables in final model	N																										
Demographic characteristics																											
age	7			x	x	x				x			x							x						x	

gender (male sex)	2			x							x																	
Clinical conditions																												
syncope	2											x					x											
leg symptoms	1										1																	
immobilisation/ bed rest	3					x				x																x		
no recent surgery	1					x																						
recent surgery	2																					x						x
active cancer	8	x		x	x						x		x	x	x					x						x		
metastatic cancer	2					x																				x		
non metastatic cancer	2					x																				x		
previous DVT/ PE	2	x									x																	
heart failure	4	x		x	x																					x		
chronic lung disease	3			x	x											x												
chronic cor pulmonale	1									x																		
heart failure or chronic lung disease	3												x							x						x		
chronic renal disease	1				x																							
cerebrovascular disease	1				x																							
recent (major) bleeding	2					x																				x		
anticoagulation	3										x											x						x
mechanical ventilation	2																					x						x
Clinical findings																												
cardiogenic shock	3													x				x				x						x
HR	16			x	x			x	x	x		x	x		x	x	x	x	x	x					x	x	x	
SBP	11	x		x	x		x	x					x						x	x	x				x		x	
RR	3			x						x								x										
t°	2			x														x										
altered mental status	4			x	x									x				x										
PaO2/ SpO2	6	x		x	x								x							x					x			
PaO2 / PaCO2	1																										x	
accentuation of P2	1											x																
tricuspid systolic murmur	2																					x						x
ECG	1																										x	
Laboratory findings																												
Platelets	2																						x	x				

Lymphocytes	1																						x				
WBC	3											x				x		x									
Creatinine (Clearance)	2					x																		x			
CPK	1											x															
cTnI	1																			x							
cTnT	1		x																								
hs-cTn	0																										
cTn	1																		x								
BNP	2													x						x							
NT-proBNP	2		x												x												
D-dimer	3								x						x	x											
H-FABP	1																x										
Triglycerides	2																					x					x
Lactate	1																							x			
Biomarker	2						x														x						
Imaging findings																											
US-DVT	3	x									x									x							
US-Proximal DVT	1										x																
TTE-RVD	1											x												x			
TTE-RV/LV ratio	2											x		x													
TTE-SPAP	1											x															
CT-RVD	1																	x									
RVD (TTE or CT)	3						x												x		x						
Other markers																											
PESI - sPESI																					x						

TABLES A4.4 (STUDY CHARACTERISTICS)

Table A4.4.1: Prognostic models - Construction studies

Author, Year **Model Acronym** **Development phase** **Date study was conducted**	**Research objective**	**Type of study** **Study design**	**Setting** **Hospital**	**Country** **N centres**	**Age** [median, IQR, Range] or (mean ± SD) **Male sex (%)**	**Patients** **Sample size in analysis**	**Outcome**	**Time-point**	**Events (%)**
(Wicki, Perrier et al. 2000)[1] Geneva prognostic score (GPS) Derivation October 1992 - October 1997	Risk stratification	Inception (on admission) Cohort - Retrospective (Diagnosis)	ED Primary /tertiary care hospitals	Switzerland Single centre	(67. 5 ± 16.7) (48.3)	Unclear 296 patients (derivation 268 patients - bootstrap and cross validation)	All-cause death, VTE or major bleeding All-cause death PE-related death VTE Clinically relevant or major bleeding Fatal bleeding	3-month 3-month 3-month 3-month 3-month 3-month	30 (10.1) 25 (8.4) 14 (4.7) 2 (0.68) 3 (1.01) 1 (0.34)
(Kostrubiec, Pruszczyk et al. 2005)[2] No acronym (Polish model) Derivation 1999 - 2004	Risk stratification	Inception (on admission, imaging <24h) Cohort - Prospective (Prognosis)	Non-ED University hospital	Poland Single centre	(62 ± 18) 35 (35)	Stable 100 patients	All-cause death, PE-related death or SAE including death (in-hospital) All-cause death PE-related death	40-day 40-day 40-day	21 (21) 15 (15) 8 (8)
(Aujesky, Obrosky et al. 2005)[3] PE severity index (PESI) Derivation, internal validation & external validation January 2000 - November 2002	Risk stratification	Inception (at presentation) Cohort - Retrospective (Databases - Prognosis)	Not reported Acute care hospitals	USA 186 hospitals	52.8 - 53.1% for age > 65 (39.6%- 41.1%)	Not reported 15,531 patients (derivation 10,354 patients - internal validation 5,177 patients)	All-cause death (30-d)or non-fatal SAE (7-d)	7-day 30-day	925 (5.96) 1437 (9.2)

(Aujesky, Obrosky et al 2006)[4] PE Prognostic algorithm Derivation, internal validation & external validation January 2000 - November 2002	To identify low-risk	Inception (at presentation) Cohort - Retrospective (Databases - Prognosis)	Not reported Acute care hospitals	USA 186 hospitals	52.8 - 53.1% for age > 65 (39.6% - 41.1%)	Not reported 15,531 patients (derivation 10,354 patients - internal validation 5,177 patients)	All-cause death (30-d) or non-fatal SAE (7-d)	7-day 30-day	925 (5.96) 1437 (9.2)
(Uresandi, Otero et al. 2007)[5] No acronym (Spanish model) Derivation March 2001 - August 2004	To identify low-risk	Inception (Not reported) Cohort Prospective (Register - Prognosis)	ED Not reported	Spain 8 centres	(68) - 76.5% for age > 60 336 (49.34)	Not reported 681 patients (derivation 681 patients - no internal validation)	All-cause death, VTE or major/ clinically relevant bleeding All-cause death PE-related death VTE Clinically relevant or major bleeding Fatal bleeding	10-day 10-day 10-day 10-day 10-day 10-day	43 (6.3) 33 (4.8) 16 (2.3) 0 (0) 18 (2.6) 4 (0.6)
(Agterof, van Bladel et al 2009)[6] No Acronym (Dutch model) Derivation January 2000 - January 2007	Risk stratification	Inception (on admission) Cohort - Retrospective (Prognosis)	ED Academic	Netherlands Single centre	(59.6 ± 15.3) 218 (49.5)	Both stable and unstable 440 patients (derivation 440 patients - no internal validation)	All-cause death, VTE or major bleeding All-cause death PE-related death VTE Major bleeding	10-day 10-day 10-day 10-day 10-day	20 (4.5) 17 (3.9) 15 (3.4) 0 (0) 3 (0.7)
(Volschan, Albuquerque et al 2009)[7] EMEP (Estudo Multicentrico di Embolia Pulmonar) Derivation January 1988 - May 2003	Risk stratification	Inception (Not reported) Cohort Prospective (Prognosis)	ED, ICU Tertiary care hospitals	Brazil 24 centres	[73, 18 - 102] 245 (42.1)	Stable 582 patients (derivation 582 patients - no internal validation)	All-cause death	In-hospital	(14.1)

(Yamaki, Nozaki et al 2009)[8] No acronym (Japanese model) Derivation February 2002 - May 2007	Risk stratification	Inception (Not reported) Cohort Prospective (Prognosis)	Non-ED University hospital	Japan Single centre	(62.8 ± 15.9) 78 (38.4)	Stable 203 patients (derivation 203 patients - no internal validation)	All-cause death or VTE All-cause death PE-related death VTE	1-year 1-year 1-year 1-year	32 (15.8) 23 (11.3) 5 (2.5) 14 (6.9)
(Zhu, Wang et al 2009) [9] No acronym (Chinese model) Derivation June 2002 - February 2005	Risk stratification	Inception (< 24h from admission) Cohort Prospective (RCT)	Not reported Not reported	China 41 hospitals	(57.4 ± 14.1) 323 (62.1)	Both stable and unstable 520 patients (derivation 520 patients - unclear)	All-cause death Adverse events	14-day 14-day	5/468 (1.1) 79/468 (16.9)
(Jimenez, Aujesky et al 2010) [10] PESI - sPESI (simplified PESI) Derivation (Update of PESI) and external validation January 1, 2003 - October 31, 2008	To identify low risk	Inception (on admission) Cohort Retrospective (Register - Prognosis)	ED University hospital	Spain Single centre	67.4% for age > 65 24.6% for age > 80 (45.1)	Both stable and unstable 995 patients (derivation)	All-cause death	30-day	78 (7.8)
(Sanchez, Trinquart et al. 2010) [11] PREP (Facteurs PRonostiques dans l'Embolie Pulmonaire) Derivation & Update January 2006 - May 2007	Risk stratification	Inception (on admission, TTE < 24h) Cohort Prospective (Prognosis)	ED and others University hospitals	France, Belgium and Switzerland 11 centres	[68, 52 - 77] 268 (47)	Both stable and unstable 570 patients (derivation 570 patients - bootstrap)	All-cause death/ equivalent AE or VTE All-cause death PE-related death VTE	30-day 30-day 30-day 30-day	42 (7.4) 26 (4.6) 12 (2.1) 11 (1.9)
(Agterof, Schutgens et al. 2011) [12] UPS (Utrecht Prediction Score) Derivation September 2006 - November 2008	To identify low-risk	Inception (on admission) Cohort Unclear (Prognosis)	ED Teaching hospitals	Netherlands 2 hospitals	(56 ± 16.8) 96 (45.71)	Stable 210 patients (derivation 210 patients - no internal	All-cause death, VTE, major bleeding or adverse clinical outcome All-cause death PE-related death	10-day 10-day 10-day	12 (5.7) 3 (1.4) 1 (0.5)

						validation)			
(Huang, Lin et al. 2011) [13] No acronym Derivation December 2004 - September 2009	Risk stratification	Inception (on admission) Cohort Retrospective (Prognosis)	ED University hospital	Taiwan Single centre	(71.3 ±14.8) 96 (64)	Unclear 150 patients	All-cause death PE-related death	30-day 30-day	18 (12) 12 (8)
(Lankeit, Friesen et al 2013)[14] & (Dellas, Tschepe et al 2014)[15] Simple score FAST Derivation October 2005 - April 2009	Risk stratification	Inception (on admission) Cohort Prospective (Prognosis)	Non-ED University hospital	Germany Single centre	[68, 56–76] 56 (41)	Stable 136 patients	All-cause death or haemodynamic deterioration All-cause death PE-related death	30-day 30-day 30-day	11 (8.1) 7 (5.1) 4 (2.9)
(Jo, J., M. Lee, et al. 2013) [16] Leucocytes – SIRS-based criteria – PESI - PREP Derivation & Update January 2005 - December 2011	Risk stratification	Inception (Not reported) Cohort Retrospective (Prognosis)	ED and others University hospital	Korea Single centre	(66.4 ± 13.3) 295 (44.2)	Both stable and unstable 667 patients	All-cause death PE-related death	30-day 30-day	57 (8.5) 33 (4.9)
(Bova, Sanchez et al 2014) [17] No acronym Derivation & Internal validation Not applicable (IPD analysis)	Risk stratification intermediate high-risk	Inception (on admission) Cohort (x6) Prospective (Prognosis) IPD analysis (Retrospective)	ED and others Not all university hospitals	European countries Multicentre	[72, 60–80] 23% for age > 80 1122 (39)	Stable 2874 patients	PE-related death, haemodynamic collapse or adjudicated recurrent PE All-cause death PE-related death VTE	30-day 30-day 30-day 30-day	198 (6.9) 176 (6.1) 90 (3.1) 18 (0.6)
(Jiménez, Kopecna et al 2014) [18] eStiMaTe – PROTECT: sPESI - BNP - cTnI – US Derivation & External validation January 1, 2009 - May 31, 2011	Risk stratification	Inception (on admission) PROTECT Prospective cohort (Prognosis)	ED 5 academic 7 general urban	Spain 12 hospitals	72 [59–80], 22% for age > 80 416 (49)	Stable 848 patients (derivation)	All-cause death, haemodynamic collapse or adjudicated recurrent PE All-cause death PE-related death VTE Clinically relevant or major bleeding	30-day 30-day 30-day 30-day 30-day	63 (7.4%) 38 (4.5) 11 (1.3) 1 (0.1) 19 (2.2)

							Fatal bleeding	30-day	3 (0.3)
(Akgüllü, Ömürlü et al 2014)[19] No acronym Derivation January 2011 - April 2013	Risk estimation	Inception (not reported) Cohort Retrospective	University hospital data	Turkey Single centre	(61.8 ± 11.8) 97 (47)	Not reported 206 patients	All-cause death	In-hospital	30 (14.6)
(Kundi, Balun et al 2015)[20] Platelet-to-Lymphocyte ratio (PLR) - sPESI Derivation External validation Date not reported	Construction Validation	Inception (not reported) Retrospective	Hospital database	Turkey Single centre	(60 ± 16) 294 (45.5)	Not reported 646 patients	All-cause death	In-hospital	42 (6.5)
(Maestre, Trujillo-Santos et al 2015)[21] RIETE score PESI and sPESI Derivation & Internal validation External vaidation From 2001 to July 2014	Risk stratification and comparison	Inception (not reported) RIETE register (Prospective) Retrospective analysis	Centres involved in management of VTE	Multinational Multicentre	(67,2± 16) 8,796 (47)	Not reported 18,707	All-cause death, VTE, major bleeding All-cause death VTE Major bleeding	10-day 10-day 10-day 10-day	677 (3.62) 471 (2.5) 46 (0.25) 203 (1.09)
(Vanni, Jimenez et al 2015)[22] TELOS - sPESI Derivation - External validation - Update 1 December 2012 to 31 January 2014	Derivation	Inception (not reported) Prospective cohort	ED	Italy and Spain 7 academic and 2 general urban hospitals	(69±16.5) 242 (48.8)	Stable 496	PE-related complications (PE-related death, non-fatal haemodynamic collapse) PE-related death All-cause death	7-day 30-day 30-day	20 (4.0) 12 (2.4) 27 (5.4)
(Ostovan, Ghaffari et al 2016)[23] modified sPESI	Risk stratification	Inception (Not reported)	Heart centre	Iran	(62.38 ± 17.27)	Both stable and unstable	All-cause death	In-hospital	38 (12.7)

sPESI Derivation External validation March 2011 to July 2013		Prospective		Single centre	153 (51)	300 patients			
(Xu, Xue et al 2016)[24] No acronym Derivation January 1, 2007 to September 30, 2013	Model derivation	Inception (not reported) Retrospective	Respiratory Medicine	China Single centre	(62 ± 11) 141 (42.6)	Both stable and unstable 331 patients	All-cause death, clinical deterioration All-cause death	In-hospital In-hospital	13 (3.9) 11 (3.3)

Table A4.4.2: Prognostic models - External validation studies (including those that also updated the model)

Author, Year **Model Acronym** **Development phase** **Date study was conducted**	**Research objective**	**Type of study** **Study design**	**Setting** **Hospital**	**Country** **N centres**	**Age** [median, IQR, Range] or (mean ± SD) **Male sex (%)**	**Patients** **Sample size in analysis**	**Outcome**	**Time-point**	**Events (%)**
(Nendaz, Bandelier et al. 2004)[25] Geneva prognostic score (GPS) External validation October 1, 2000 - June 30, 2002	To identify low-risk	Inception (Not reported) Cohort Retrospective (Diagnosis)	ED University hospitals	Switzerland and France 3 centres	(65.6 ± 18.3) 100 (45)	Stable 199 patients	All-cause death, VTE or major bleeding VTE Clinically relevant or major bleeding Fatal bleeding	3-month 3-month 3-month 3-month	19 (9.5) 4 (2) 5 (2.5) 2 (1)
(Aujesky, Perrier et al. 2007)[26] PESI External validation 03/1998 - 11/2003 and 01/2003 -02/2003	To identify low-risk	Inception (Not reported) Cohort Retrospective (Diagnosis)	ED Teaching and non-teaching hospitals	Switzerland, Belgium and France 119 centres	64% for age > 65 382 (42)	Not reported for all studies included 899 patients	All-cause death PE-related death	3-month 3-month	58 (6.5) 21 (2.3)
(Jimenez, Yusen et al. 2007)[27] GPS - PESI External validation January 1, 2003 - September 30, 2006	Risk stratification for ambulatory treatment	Inception (Not reported) Cohort Retrospective (Register - Prognosis)	ED University hospital	Spain Single centre	67% for age > 65 (45.1)	Unclear 599 patients	All-cause death VTE or major bleeding	30-day 30-day	43 (7.2) 32 (5.3)
(Donze, Le Gal et al. 2008)[28] PESI External validation January 1, 2005 - August 31, 2006	To identify low-risk	Inception (Not reported) Cohort Retrospective (Diagnosis)	ED University hospitals	Switzerland, France and Belgium 6 centres	(64 ± 18) 158 (44)	Not reported 357 patients	All-cause death PE-related mortality	3-month 3-month	21 (5.9) 9 (2.5)

(Palmieri, Gallota et al 2008)[29] PESI - cTnI – RVD External validation & Update June 1, 2002 - June 30, 2003	Risk stratification Added value of cTnI and RVD -	Inception (on admission – ED – cTnI < 8h) Cohort Prospective (Prognosis)	ED University hospital	Italy Single centre	69.7% for age > 65 27 (30.3)	Stable 89 patients	All-cause death Adverse outcome (Haemodynamic instability) All-cause death	In-hospital In-hospital	33 (37.1) 12 (13.5)
(Toosi, Merlino et al. 2008)[30] Shock Index (SI = HR/ SBP) External validation & Update January 2000 - December 2004	Risk stratification	Inception (on admission) Cohort Retrospective (Prognosis)	Medicine University hospitals	USA 2 centres	(58.9 ±17.7), Range 20 – 93 70 (45,2)	Not reported 155 patients for SI, 100 patients for TTE	All-cause death	In-hospital	11 (7.1)
(Bova, Pesavento et al. 2009)[31] GPS + 5 prognostic markers (TELESIO) External validation March 2005 - February 2008	Identifying hemodynamically stable patients at higher risk	Inception (at study entry, biomarkers and TTE < 12h) Cohort Prospective (Prognosis)	ED (68.1%) + In-patients University and non-university hospitals	Italy 6 (3 tertiary, 3 secondary)	(68.2 ± 17.5) 83 (41.3)	Stable 201 patients	Clinical deterioration or death due to PE All-cause death All-cause death All-cause death VTE	In-hospital In-hospital 30-day 3-month 3-month	1 (0.5) 4 (2) 12 (6) 18 (9) 1 (0.5)
(Choi, Kwon et al. 2009)[32] PESI External validation December 1999 - March 2007	Risk stratification	Inception (Not reported) Cohort Retrospective (Prognosis)	Not reported (In and outpatients) University hopsital	Korea Single centre	(60.4±16) 37 (41.1)	Not reported 99 patients	Unclear (All-cause death)	Unclear (in-hospital, 30-day)	
(Kukla, Bryniarski et al 2009)[33] 2008-ESC	Descriptive analysis of an acute PE register in	Inception (Not reported) Cohort Retrospective	Cardiology University and non-university	Poland 5 centres	(65.1 ± 15.3) 81 (39.5)	Both stable and unstable	All-cause death Adverse outcome	In-hospital In-hospital	23 (11.2 57 (27.8)

External validation 1 January 2005 - 30 September 2007	Poland	(Register)	hospitals			205 patients			
(Nordenholz, Ryan et al. 2009)[34] PESI - Pulse oximetry External validation June 2004 - June 2008	Risk stratification and ability to identify low risk	Inception (on admission) Cohort Retrospective (Prognosis)	ED University hospital	USA Single centre	No AE [53, 40–66] AE [58, 41–72] 72 (43)	Both stable and unstable 168 patients	All-cause death All-cause death/ equivalent adverse events	In-hospital In-hospital	5 (3) 12 (7.1)
(Subramaniam, Mandrekar et al 2009)[35] GPS External validation March 2003 - October 2004	Risk stratification	Inception (Not reported) Cohort Unclear	ED (51%), Medicine (23%) and surgery (26%) Tertiary	New Zealand Single centre	[58, IQR not reported, 16 - 96] 239 (45.7)	Unclear 105 patients	All-cause death All-cause death	3-month 12-month	7 (6.7) 13 (12.4)
(Chan CM, Woods C, Shorr AF. 2010 & 2012)[36 37] – PESI – PREP External validation October 2007 - February 2009	Risk stratification and inter-rater variability.	Inception (Unclear) Cohort Retrospective (Prognosis)	ED + in-patients University hospital	USA Single centre	(59.7 ± 17.2) 133 (44)	Unclear 302 patients	All-cause death All-cause death	30-day 3-month	9 (3) 12 (4)
(Jakobsson, Jimenez et al 2010)[38] Prognostic algorithm External validation January 1, 2003 - November 30, 2008	To identify low-risk	Inception (Not reported) (baseline data) Cohort Retrospective (Register - Prognosis)	ED University hospital	Spain Single centre	60.7% for age ≥ 70 448 (45.6)	Both stable and unstable 983 patients	All-cause death All-cause death PE-related death or bleeding-related death	30-day 7-day 30-day	110 (11.2) 59 (6) 55 (5.6)

(Jimenez, Aujesky et al 2010)[10] PESI - sPESI (simplified PESI) External validation (PESI) January 1, 2003 - October 31, 2008	To identify low-risk and compare sPESI with PESI	Inception (on admission - ED) Cohort Retrospective (Register - Prognosis)	ED (for derivation) University hospital	Spain Single centre for derivation	67.4% for age > 65 24.6% for age > 80 (45.1)	Both stable and unstable 995 patients	All-cause death	30-day	78 (7.8)
(Jimenez, Aujesky et al 2010)[10] PESI - sPESI (simplified PESI) External validation (sPESI) Date Not reported	To identify low-risk and validate sPESI	Inception (Not reported) Cohort Retrospective (RIETE register - Prognosis)	Not reported Multicentre register for validation	Spain RIETE multinational register	68.2% for age > 65 23.5% for age > 80 (45.9)	Both stable and unstable 7106 patients	All-cause death	30-day	434 (6.1)
(Vuilleumier, Le Gal et al 2010)[39] NTproBNP vs GPS vs PESI External validation January 2005 - 30 August 2006	To identify low-risk	Inception (on admission) Cohort Retrospective (RCT - Diagnosis)	ED University hospitals	Switzerland, France & Belgium 3 centres	[72, 21–94] 61 (42)	Stable 145 patients for GPS, 146 patients for PESI	ICU on admission, all-cause death, hospitalization for PE complications (recurrence, bleeding), dyspnea All-cause death VTE Clinically relevant or major bleeding Fatal bleeding	3-month 3-month 3-month 3-month 3-month	18 (12.4) 5 (3.4) 9 (6.2) 1 (0.7) 0 (0)
(Erkens, Gandara etal, 2011)[40] PESI – sPESI External validation January 1, 2007 - December 31, 2008	External validation of PESI and sPESI	Inception (Not reported but data from ED) Cohort Retrospective (Prognosis)	ED University hospital	Canada Single centre	PESI low-risk (45.9 ± 17.0), high-risk (68.1 ± 11.7) 116 (47,7)	Not reported 243 patients	All-cause death PE-related death VTE Any (including major or clinically relevant bleeding)	30-day/ 3-month 3-month 3-month 3-month 14-day/30-day/3-	10 (4.1)/32 (13.2) None 10 (4.1) 48 (19.7) 8 (3.3)/ 10 (4.11)/

							Clinically relevant or major bleeding	month	12 (4.9)
(Hariharan, Takayesu & Kabrhel, 2011)[41] PESI External validation May 1, 2006 - April 30, 2008	To identify low-risk	Inception (< 24 h from admission) Cohort Retrospective (Prognosis)	ED Urban, tertiary care centre	USA Single centre	(57 ± 17) 115 (47)	Both stable and unstable 245 patients	Composite outcome All-cause death	5-day 30-day	63 (25.7) 11 (4.5)
(Righini, Roy et al 2011)[42] sPESI External validation Jan 10, 2005 - August 30, 2006	External validation of sPESI	Inception (at baseline) Cohort Retrospective (RCT - Diagnosis)	ED General and teaching hospitals	Switzerland, France and Belgium 6 centres	64 y (44.0)	Not reported 357 patients	All-cause death All-cause death PE-related death PE-related death	30-day 3-month 30-day 3-month	11 (3.1) 21 (5.9) 7 (2) 9 (2.5)
(Sam, Sanchez et al 2011)[43] Shock Index (SI = HR/ SBP) sPESI External validation January 1, 2003 - December 31, 2009	To identify low-risk	Inception (Not reported but from ED) Cohort Retrospective (Register - Prognosis)	ED University hospital	Spain Single centre	(69.3 ± 16.1) 25% for age > 80 536 (44)	Both stable and unstable 1206 patients	All-cause death PE-related death VTE VTE or major bleeding Clinically relevant or major bleeding	30-day 30-day 30-day 30-day 30-day	119 (9.9) 58 (4.8) 14 (1.1) 42 (3.5) 32 (2.6)
(Singanayagam, Scally et al, 2011)[44] PESI – Biomarkers External validation & Update January 2005 - July 2007	Risk stratification - Added value of cTnI and Ddimers	Inception (on admission) Cohort Retrospective (Prognosis)	Not reported Teaching hospitals	East Scotland 3 teaching hospitals	55.4% for age > 65 177 (43.1)	Stable 411 patients	All-cause death	30-day	21 (5.1)

(Spirk, Aujesky et al 2011)[45] sPESI – cTn External validation & Update January 2009 - May 2010	Risk stratification - Added value of cTn	Inception (sPESI at baseline, cTn < 24h) Cohort Retrospective (SWIVTER Register - Prognosis)	Not reported 4 academic and 14 non-academic acute care hospitals	Switzerland 18 centres	21% for age >80 195 (52.8)	Both stable and unstable 332 patients	All-cause death or VTE Clinically relevant or major bleeding	30-day 30-day	20 (6) Unclear
(Vanni, Nazerian et al, 2011)[46] PESI – 2008 ESC External validation January 2000 - April 2009	External validation and comparison PESI - 2008-ESC	Inception (Not reported, TTE <1h from diagnosis) Cohort Retrospective (Register - Prognosis)	ED A level II teaching hospital	Italy Single centre	73,3% for age > 65 223 (43,7)	Both stable and unstable 510 patients	All-cause death PE-related death Composite	In-hospital	41/510 (8) 27/ 510 (5.3) 32/463 (6.9) or 31/485 (6.4)
(Venetz, Jimenez et al, 2011)[47] sPESI – PESI External validation January 2000 - November 2002	External validation and comparison PESI - sPESI	Inception Cohort (at presentation) Retrospective (Prognosis)	Not reported Not reported	USA 186 hospitals	[67, 52–77] 6227 (40.1)	Not reported 15,531 patients	All-cause death All-cause death Non-fatal cardiogenic shock, cardiorespiratory arrest	30-day 14-day 14-day	1439 (9.3) 976 (6.3) 342 (2.2)
(Labyk, Ciurzyński, et al 2012)[48] 2008 ESC External validation 2007 - 2009	Risk stratification	Inception (on admission) Cohort Retrospective (Prognosis)	Internal diseases and cardiology University hospital	Poland Single centre	(64.7 ± 18.12), Range 18–97 141 (39.9)	Both stable and unstable 353 patients	All-cause death PE-related death Clinically relevant or major bleeding Fatal bleeding	In-hospital In-hospital In-hospital In-hospital	28 (7) 19 (5.4) 16 (4.5) 5 (1.4)
(Lankeit, Gomez et al 2012)[49] sPESI - 2008-ESC External vadidation of ESC	Risk stratification	Inception (at baseline for sPESI, cTn < 12h, TTE < 24h) Cohort	ED University hospital	Spain Single centre	[74, 61 to 80], 22% for age > 80	Both stable and unstable 526 patients	All-cause death PE-related death	30-day 30-day	40 (7.6) 22 (4.2) 2 (0.4)

& Update of sPESI (added value of ESC) Date Not reported		Retrospective (Register - Prognosis)			227 (43)		VTE All-cause death, VTE or major bleeding Clinically relevant or major bleeding Fatal bleeding	30-day 30-day 30-day 30-day	61 (11,6) 19 (3.6) 1 (0.2)
(Roca, Aursulesei et al 2012)[50] PESI - sPESI – SI External validation 2004 - 2010	External validation and comparison PESI - sPESI - Shock Index	Inception (Not reported) Cohort Prospective (Prognosis)	ED - Cardiology University hospital	Romania 2 centres	Not reported Not reported	Not reported 362 patients	All-cause death	In-hospital	78 (21.5)
(Soares, de Bastos et al 2012)[51] PESI - CT-RVD - CT-VOI External validation January 2008 - January 2010	External validation and comparison PESI - CT-RVD - CT-VOI	Inception (on admission or at first symptom. day for in-patients) Cohort Retrospective (Prognosis)	Outpatients from ED (87.5%) and in-patients University hospital	Brazil Single centre	71.9% for age > 40 45 (46.9)	Both stable and unstable 96 patients	All-cause death PE-related death	3-month 3-month	6 (6.3) 3 (3.1)
(Becattini, Casazza et al 2013)[52] 2008-ESC (Integrated RSM) External validation September 1, 2006 - August 31, 2010	External validation of 2008-ESC (integrated RSM)	Inception (on admission) Cohort Prospective (IPER Register - Prognosis) Retrospective analysis	ED - Internal Medicine - Cardiology University and community hospitals	Italy 49 departments 47 Italian hospitals	(70 ± 15), Range 18-96 390 (45)	Stable 869 patients	All-cause death or clinical deterioration PE-related death or clinical deterioration PE-related death	In-hospital In-hospital In-hospital	48 (5.5) 30 (3.4) 12 (1.4)
(Ferrer, Morillo et al 2013)[53] Spanish – sPESI External validation	External validation and comparison Spanish - sPESI	Inception (on admission) Cohort Retrospective then	ED University hospital	Spain Single centre	[73, 60-80], 24% for age > 80	Both stable and unstable 1447 patients	All-cause death PE-related death VTE	30-day 30-day 30-day	138 (9.5) 62 (4.3) 11 (0.8)

January 2003 - December 2011		Prospective (Prognosis)			669 (46)		VTE or major bleeding Clinically relevant or major bleeding Fatal bleeding	30-day 30-day 30-day	47 (3.2) 38 (2.6) 7 (0.5)
(Jo, J., M. Lee, et al. 2013)[16] Leucocytes – SIRS-based criteria – PESI - PREP (Derivation) - External validation - Update January 2005 - December 2011	Risk stratification	Inception (Not reported) Cohort Retrospective (Prognosis)	ED and others University hospital	Korea Single centre	(66.4 ± 13.3) 295 (44.2)	Both stable and unstable 667 patients	All-cause death PE-related death	30-day 30-day	57 (8.5) 33 (4.9)
(Ozsu, Abul et al 2013)[54] sPESI - cTnT - hs-cTnT External validation & Update Date Not reported	External validation of sPESI and update (cTnT - hs-cTnT)	Inception (on admission, TTE < 24h) Cohort Prospective (Prognosis)	Not reported University hospital	Turkey Single centre	[70, 55-76], 11% for age > 80 52 (43)	Stable 121 patients	All-cause death PE-related death	30-day 30-day	16 (13) 6 (5)
(Sanchez, Trinquart et al 2013)[55] PESI - TTE-RVD - BNP - cTnI External validation & Update January 2006 - May 2007	External validation of PESI and update (TTE-RVD - BNP - cTnI)	Inception (on admission) Cohort Prospective (Prognosis)	ED and others University hospitals	France, Belgium and Switzerland 11 centres	[67, 52–77] 247 (47)	Stable 529 patients	Adverse event (all-cause death, secondary cardiogenic shock or VTE recurrence) All-cause death PE-related death VTE	30-day 30-day 30-day 30-day	25 (4.7) 15 (2.8) 6 (1.1) 8 (1.5)
(Choi, Cha et al 2014)[56] PESI - CT-RVD - NT-proBNP - cTnI External validation & Update March 2003 – December 2012	External validation of PESI and update (CT-RVD - NT-proBNP - cTnI)	Inception (on admission start time unclear) Cohort Retrospective (Prognosis)	Internal medicine, Radiology Tertiary referral university hospital	South Korea Single centre	68 (not provided) 362 (55.1)	Both stable and unstable 657 patients	Adverse outcome (PE-related death or serious clinical conditions) All-cause death VTE	In-hospital In-hospital In-hospital	69 (10.5) 52 (7.9) 11 (1.7)

(Dellas, Tschepe et al 2014) [15] FAST - sPESI - 2008-ESC External validation October 2005 - August 2011	External validation of FAST and comparison with sPESI and ESC	Inception (on admission, TTE < 48h) Cohort Prospective (Prognosis)	Cardiology and Pulmonology University hospital	Germany Single centre	[70, 52–76] 119 (43.9)	Stable 271 patients	All-cause death or equivalent adverse event (haemodynamic deterioration) All-cause death PE-related death	30-day 30-day 30-day	20 (7.4) 12 (4.4) 5 (1.8)
(Jiménez, Kopecna et al 2014)[18] eStiMaTe (PROTECT) – External validation in PREP cohort January 2006 - May 2007	External validation (PROTECT)	Inception (on admission, TTE < 24h) Cohort Retrospective (Prognosis)	ED and others University hospitals	France, Belgium 11 centres and Switzerland	[68, 52–78], 19% for age > 80 246 (47)	Stable 528 patients	All-cause death, haemodynamic collapse or adjudicated recurrent PE) All-cause death PE-related death VTE	30-day 30-day 30-day 30-day	24 (4.5) 14 (2.6) 6 (1.1) 4 (0.7)
(Ozsu, Ozlu et a 2014)[57] sPESI - 2008-ESC (TUPEG study) External validation January 1, 2013 - June 30, 2013	External validation and comparison sPESI - 2008-ESC	Inception (on admission, TTE < 24h) Cohort Prospective (Register - Prognosis)	Pulmonary Medicine 30 university or community hospitals	Turkey 36 centres from 30 hospitals	[67, 52–76] 484 (45)	Both stable and unstable 1078 patients	All-cause death PE-related death VTE Clinically relevant or major bleeding VTE or major bleeding	30-day 30-day 30-day 30-day 30-day	95 (8.8) 63 (5.8) 12 (1.1) 21 (1.9) 32 (3)
(Casazza, Becattini et al 2014)[58] 2008 ESC - Right heart thrombus External validation Update September 1st , 2006 - August 31st , 2010	External validation and update	Inception (< 48h from admission) Cohort prospective (IPER Register - Prognosis) Retrospective analysis	Hospital register (cardiology 52%, internal or emergency medicine 48%)	Italy 47 hospitals	[74, 18–97] 550 (43.1)	Both stable and unstable (11.7%) 1275 patients	All-cause death	In-hospital	90 (7.1)

(Kabrhel, Okechukwu et al 2014)[59] Prognostic factors PESI, sPESI, GPS External validation October 2008 to December 2011	External validation	Inception (<24h) Prospective	ED University hospital	USA Single centre	(59 ± 17) 152 (51)	Stable 298 patients	Clinical deterioration Severe clinical deterioration Severe bleeding All-cause death	5-day 5-day 5-day 5-day 30-day	101 (34) 27 (9) 7 (2) 1 (0.3) 12 (4)
(Lauque, Maupas-Schwalm et al 2014)[60] H-FABP, BNP and hs- cTnI PESI External validation, and Update October 1, 2009, to May 30, 2011,	Risk estimation	Inception (on admission) Cohort Prospective (Prognosis)	University hospitals	France, UK Two centres	69.3 ± 21.4 68 (51.5)	Both stable and unstable 132 patients	Death and adverse outcomes Death PE-related death	30-day 30-day 30-day	14 (10.6) 8 (6.1) 6 (4.5)
(Tong, Zhang et al 2014)[61] sPESI External validation January 2010 to January 2012	External validation	Inception (not reported) Retrospective	Respiratory Medicine, Cardiology, ED and ICU University hospital	China Single centre	(Not reported) 68 (42)	Both stable and unstable 162 patients	All-cause death Adverse outcome	In-hospital	20 (12.3)
(Fermann, Erkens et al 2015)[62] sPESI External validation Post-hoc analysis	Identifying low-risk patients	Inception (not reported) Post-hoc analysis of EINSTEIN study RCT	RCT Rivaroxaban LMWH-VKA	International (38 countries) Multicenter	(57.9 ± 17.3) 1,309 (54.1)	Stable 4,831 patients	All-cause death VTE	7-day 14-day 30-day 7-day 14-day	10 (0.2) 15 (0.3) 33 (0.7) 21 (0.4) 35 (0.7)

							Fatal PE Major bleeding	30-day 7-day 14-day 30-day 7-day 14-day 30-day	49 (1.0) 5 (0.1) 7 (0.1) 9 (0.2) 17 (0.35) 27 (0.6) 36 (0.7)
(Fernandez, Bova et al 2015)[63] Bova's score External validation Reproducibility January 1, 2003 to December 31, 2013	External validation	Inception (< 24h from diagnosis) Retrospective (Register – Prognosis)	ED University hospital	Spain Single centre	[74, 63-81] 486 (44.9)	Stable 1,083 patients	PE-related complications All-cause death PE-related death Hemodynamic collapse Nonfatal recurrent PE	30-day	91 (8.4) 87 (8.0) 44 (4.1) 49 (4.5) 7 (0.6)
(Kara, Degirmenci et al 2015)[64] PESI, SI External validation January 2011 to October 2014	External validation	Inception (not reported) Retrospective	ED University hospital	Turkey Single centre	(63 + 17) 75(43)	Not reported 173 patients	All-cause death	30-day	15 (8.7)
(Kundi, Balun et al 2015)[20] Derivation Platelet-to-Lymphocyte ratio (PLR) - sPESI	Construction Validation	Inception (not reported)	Hospital database	Turkey Single centre	(60 ± 16) 294 (45.5)	Not reported 646 patients	All-cause death	In-hospital	42 (6.5)

External validation (sPESI) Date not reported		Retrospective							
(Maestre, Trujillo-Santos et al 2015)[21] RIETE score PESI, sPESI Derivation & Internal validation External vaidation for PESI and sPESI From 2001 to July 2014	Risk stratification and comparison	Inception (not reported) RIETE register (Prospective) Retrospective analysis	ED Centres involved in the management of VTE	Multinational Multicentre	(67,2± 16) 8,796 (47)	Not reported 18,707	All-cause death, VTE, major bleeding All-cause death VTE Major bleeding	10-day 10-day 10-day 10-day	677 (3.62) 471 (2.5) 46 (0.25) 203 (1.09)
(Mizuno, Yamamoto et al 2015)[65] PESI sPESI External validation January 2011 to December 2012	External validation	Inception (not reported) Tokyo Cardiovascular Care Units Network Retrospective	Cardiovascular Care Units	Japan 67 hospitals	(63.9±17.2) 127 (42.1)	Not reported 302 patients	All-cause death	30-day	7 (2.3)
(Vanni, Jimenez et al 2015)[22] TELOS - sPESI Derivation - External validation - Update 1 December 2012 to 31 January 2014	Derivation	Inception Prospective cohort	ED	Italy and Spain 7 academic and 2 general urban hospitals	(69±16.5) 242 (48.8)	Stable 496	PE-related complications (PE-related death, non-fatal haemodynamic collapse) PE-related death All-cause death	7-day 30-day 30-day	20 (4.0) 12 (2.4) 27 (5.4)
(Bach, Taute et al 2016)[66] Acute Physiology and Chronic Health Evaluation II (APACHE II), PESI, sPESI,	Risk prediction	Inception (not reported) Cohort	University hospital data	USA Single centre	[65, 18–91] 178 (48.8)	Not reported 365 patients	All-cause death	30-day	39 (10.7)

Glasgow Coma Scale, and euroSCORE II. External validation June 2005 – January 2010		Retrospective							
(Becattini, Agnelli et al 2016)[67] 2008 ESC - 2014 ESC External validation 2010 to 2014	External validation	Inception (not reported) 3 prospective cohorts Retrospective analysis	Internal and cardiovascular Medicine and Stroke units	European countries Collaborative database	(68±16) 417 (46)	Both stable and unstable 906 patients	All-cause death PE-related death	30-day 30-day	65 (7.2) 37 (4.1)
(Cordeanu, Gartner et al 2016)[68] sPESI - 2014 ESC External validation November 2013 - February 2016	Model comparison	Inception (not reported) Retrospective (REMOTEV Register - Prognosis)	University hospital Vascular Medicine	France Single centre	(65.9 ± 17.6) … (49)	Not reported (*stable*) 587 patients	All-cause death VTE Clinically relevant or major bleeding Composite (death, VTE and bleeding)	30-day 30-day 30-day 30-day	9 (1.5) 7 (1.1) 16 (2.7) 29 (4.9)
(Hobohm, Hellenkamp et al 2016)[69] 2008 ESC - 2014 ESC - Bova score - Modified FAST External validation September 2007 to August 2014	External validation and comparison	Inception (< 48h from admission) Retrospective (PERGO Register– prognosis)	University hospital	Germany Single centre	[70.5, 54.0 – 77.0] 179 (46.1)	Stable 388 patients	Adverse outcome All-cause death PE-related death	30-day 30-day 30-day	25 (6.4) 15 (3.6) 8 (2.1)

(Jimenez, Lobo et al 2016)[70] 2014 ESC, Bova External validation January 1, 2009 to May 31, 2011	External validation and comparison	Inception (on admission) Retrospective (PROTECT prospective cohort)	ED 5 academic 7 general urban	Spain 12 hospitals	72 [59–80], 22% for age > 80 416 (49)	Stable 848 patients	Complicated course All-cause death PE-related death Haemodynamic collapse Non-fatal recurrent PE	30-day 30-day 30-day 30-day 30-day	63 (7.4 %) 38 (4.5 %) 11 (1.3 %) 28 (3.0 %) 1 (0.1 %)
(Masotti, Panigada et al 2016)[71] sPESI - Shock index - 2008 ESC - 2014 ESC External validation Date (not reported)	External validation of 2014 ESC	Inception (not reported) Retrospective TUSCAN-PE cohort	Internal medicine	Italy (Tuscany) 28 wards	(75.3 ± 12.8) 124 (40)	Both stable and unstable 312 patients	All-cause death PE-related death	In-hospital In-hospital	26 (8.4) 15 (4.8)
(Masotti, Verdiani et al 2016)[72] Bova score External validation Date not reported	External validation of Bova score	Inception (not reported) Retrospective TUSCAN-PE cohort	Internal medicine	Italy (Tuscany) 28 wards	(75.8± 12.5) 105 (40.4)	Both stable and unstable 260 patients	All-cause death PE-related death	In-hospital In-hospital	26 (7.7) 11 (4.2)
(Ostovan, Ghaffari et al 2016)[23] modified sPESI sPESI Derivation External validation March 2011 to July 2013	Risk stratification External validation	Inception (Not reported) Prospective	Heart centre	Iran Single centre	(62.38 ± 17.27) 153 (51)	Both stable and unstable 300 patients	All-cause death	In-hospital	38 (12.7)

(Rozjabek, Coleman et al 2016)[73] PESI – sPESI External validation 10/21/2010–1/31/2014	Effect of vital signs measurement timing	Inception (on admission) Retrospective	University hospital	USA Single centre	(64.4 ± 16.54) 260 (45.4)	Stable 573 patients	All-cause death	30-day	33 (5.8)
(Vanni, Nazerian et al 2016)[74] Bova - TELOS - 2014 ESC - Bova and lactates External validation Update September 2002 to January 2014	Identifying Intermediate-high risk	Inception (less than 24h) Retrospective 2 single-centre and 1 multicenter prospective cohorts	University and non-university hospitals	European centres (Italy and Spain)	[74, 64–81] 495 (49.8)	Stable 994 patients	PE-related complications (PE-related death, non-fatal haemodynamic collapse) All-cause death PE-related death	7-day 7-day 7-day	63 (6.3) 32 (3.2) 31 (3.1)

Table A4.4.3: Prognostic models – Update studies

Author, Year **Model Acronym** **Development phase** **Date study was conducted**	**Research objective**	**Type of study** **Study design**	**Setting** **Hospital**	**Country** **N centres**	**Age** [median, IQR, Range] or (mean ± SD) **Male sex (%)**	**Patients** **Sample size in analysis**	**Outcome**	**Time-point**	**Events (%)**
(Palmieri, Gallota et al 2008)[29] PESI - cTnI - RVD External validation & Update June 1, 2002 - June 30, 2003	Added value of cTnI and RVD - Risk stratification	Inception (on admission – ED – cTnI < 8h) Cohort Prospective (Prognosis)	ED University hospital	Italy Single centre	69.7% for age > 65 27 (30.3)	Stable 89 patients	Haemodynamic instability PE-related mortality	Unclear (1-year) Unclear (1-year)	33 (37.1) 12 (13.5)
(Toosi, Merlino et al. 2008)[30] Shock Index (SI = HR/ SBP) - TTE External validation & Update January 2000 - December 2004	Risk stratification	Inception (on admission, TTE < 72h) Cohort Retrospective (Prognosis)	Departments of medicine University hospitals	USA 2 centres	(58.9 ±17.7), Range 20 – 93 70 (45,2)	Not reported 155 patients for SI, 100 patients for TTE	All-cause death	In-hospital	11 (7.1)
(Moores, Aujesky et al. 2010)[75] PESI - cTn External validation & Update January 2003 - December 2008	To identify low risk acute PE patients for early discharge	Inception (Not reported, Biomarkers < 12h) Cohort Retrospective (Register - Prognosis)	ED University hospital	Spain Single centre	74% for age > 65 245 (43)	Stable 567 patients	All-cause death PE-related death	30-day 30-day	57 (10) 34 (6)
(Singanayagam, Chalmers et al 2010)[76] PESI - CT-RVD	Prognostic value of CT-RVD Additive prognostic information	Inception (on admission, CT-RVD at the time of diagnosis)	Not reported Teaching hospitals	East Scotland 3 teaching hospitals	55.4% for age > 65	Both stable and unstable	All-cause death	30-day	44 (7.5)

Update January 2005 July 2007		Cohort Retrospective (Prognosis)			N (43)	585 patients			
(Jimenez, Aujesky et al 2011)[77] PESI - RVD - cTnI - US-DVT Update Date Not reported	Added value of a two-test or a three-test strategy (high-risk PESI)	Inception (PESI at baseline, cTnI < 12h, TTE < 24h and venous US < 48h) Unclear Cohort Prospective (Prognosis)	ED University hospital	Spain Not reported but seems multicentre multinational	74 (65 to 82), 74% for age > 65 254 (43)	Stable 591 patients	Complicated course All-cause death PE-related death VTE Clinically relevant or major bleeding	30-day 30-day 30-day 30-day 30-day	59 (10) 59(10) 37 (6.3) 13 (2.2) 26/ 591 (4.4)
(Lankeit, Jimenez et al 2011)[78] sPESI - hscTnT Update August 2007 - October 2010	Additive prognostic information, identification of low-risk patients	Inception (Not reported) Cohort Prospective (Prognosis)	Not reported University and non-university hospitals	Germany, Poland and Spain 12 centres	[71, 55–79] 266 (51)	Stable 526 patients	All-cause death and adverse events All-cause death PE-related death VTE Clinically relevant or major bleeding Fatal bleeding	30-day 30-day 30-day 30-day 30-day 30-day	31 (5.9) 27 (5.1) 8 (1.5) 9 (1.7) 15 (2.9) 3 (0.6)
(Sanchez, de Miguel et al 2011)[79] sPESI - cTnI Update January 1, 2003 - June 30, 2010	To assess the effect of cause of death classification on sPESI and cTnI	Inception (sPESI at baseline, cTn < 24h) Cohort Retrospective (Register - Prognosis)	ED University hospital	Spain Single centre	(69 ± 16) 579 (44,8)	Unclear 1291 patients	All-cause death PE-related death	30-day 30-day	127 (9.8) 60 (4,6)
(Singanayagam, Scally et al, 2011)[44] PESI - Biomarkers External validation & Update	Added value of bioamarkers (cTnI and Ddimer)	Inception (on admission) Cohort Retrospective (Prognosis)	Not reported Teaching hospitals	East Scotland 3 teaching hospitals	55.4% for age > 65 177 (43.1)	Stable 411 patients	All-cause death	30-day	21 (5.1)

January 2005 - July 2007									
(Spirk, Aujesky et al 2011)[45] sPESI - cTn External validation & Update January 2009 - May 2010	Added value of cTn in high risk sPESI	Inception (sPESI at baseline, cTn < 24h) Cohort Retrospective (SWIVTER Register - Prognosis)	Not reported 4 academic and 14 non-academic acute care hospitals	Switzerland 18 centres	21% for age > 80 195 (52.8)	Both stable and unstable 369 patients	All-cause death or VTE Clinically relevant or major bleeding	30-day 30-day	20/332 (6) Unclear
(Jo, J., M. Lee, et al. 2013)[16] PESI - SIRS-based criteria + others Derivation & Update January 2005 - December 2011	SIRS - Added value to PESI	Inception (Not reported) Cohort Retrospective (Prognosis)	Not reported University hospital	Korea Single centre	(66.4 ± 13.3) 295 (44.2)	Both stable and unstable 667 patients	All-cause death PE-related death	30-day 30-day	57 (8.5) 33 (4.9)
(Ozsu, Abul et al 2013)[54] sPESI - cTnT - hs-cTnT External validation & Update Date Not reported	External validation of sPESI and additive value of cTnT - hs-cTnT	Inception (on admission, TTE < 24h) Cohort Prospective (Prognosis)	Not reported University hospital	Turkey Single centre	[70, 55-76] 13 (11) for age > 80 52 (43)	Stable 121 patients	All-cause death PE-related death All-cause death, VTE or major bleeding	30-day 30-day 6-month	16 (13) 6 (5) 28 (21.1
(Sanchez, Trinquart et al 2013)[55] PESI - TTE-RVD - BNP - cTnI External validation & Update January 2006 - May 2007	External validation of PESI and additive value of TTE-RVD - BNP - cTnI	Inception (on admission, TTE < 24h) Cohort Prospective (Prognosis)	ED and other departments University hospitals	France, Belgium and Switzerland 11 centres	[67, 52–77] 247 (47)	Stable 529 patients	Adverse event (all-cause death, secondary cardiogenic shock or VTE recurrence) All-cause death PE-related death VTE	30-day 30-day 30-day 30-day	25 (4.7) 15 (2.8) 6 (1.1) 8 (1.5)

(Barra, Paiva et al 2014)[80] sPESI – AF Update January 1, 2007 - April 30, 2011	Additive value of atrial fibrillation (AF) to sPESI	Inception (Unclear) Cohort Retrospective (Prognosis)	ED - Cardiology University hospital	Portugal Single centre	(70.1±15.8) 57 (40.1)	Not reported 270 patients	All-cause death All-cause death	In-hospital 30-day	41 (15.2) 56 (20.7)
(Choi, Cha et al 2014)[56] PESI - CT-RVD - NT-proBNP - cTnI External validation & Update March 2003 – December 2012	External validation of PESI and additive value of CT-RVD - NT-proBNP - cTnI	Inception (on admission but start time unclear) Cohort Retrospective (Prognosis)	Internal medicine, Radiology Tertiary referral university hospital	South Korea Single centre	68 (not reported) 362 (55.1)	Both stable and unstable 657 patients	Adverse outcome (PE-related death or serious clinical conditions) All-cause death VTE	In-hospital In-hospital In-hospital	69 (10.5) 52 (7.9) 11 (1.7)
(Lankeit, Jiménez et al 2014)[81] sPESI - NTproBNP - TTE-RVD Update Date Not reported	Additive value of NT-proBNP to sPESI	Inception (on admission, TTE < 48h) Cohort Prospective (Prognosis)	Not reported University and non-university hospitals	Germany, Poland and Spain 12 centres	[70, 54–78] 326 (47.4)	Stable 688 patients	PE-related death or complications All-cause death PE-related death	30-day 30-day 30-day	28 (4.1) 29 (4.2) 18 (2.6)
(Akgüllü, Ömürlü et al 2014)[19] No acronym - sPESI Derivation & Update January 2011 - April 2013	Risk estimation	Inception (not reported) Cohort Retrospective	University hospital data	Turkey Single centre	(61.8 ± 11.8) 97 (47%)	Not reported 206 patients	All-cause death	In-hospital	30 (14.6)
(Lauque, Maupas-Schwalm et al 2014)[60] H-FABP - BNP - hs- cTnI PESI External validation & Update October 1, 2009, to May 30, 2011,	Risk estimation	Inception (on admission) Cohort Prospective (Prognosis)	University hospitals	France, UK Two centres	69.3 ± 21.4 68 (51.5)	Both stable and unstable 132 patients	Death and adverse outcomes Death PE-related death	30-day 30-day 30-day	14 (10.6) 8 (6.1) 6 (4.5)

(Hakemi, Alyousef et al 2015)[82] PESI - hs-cTnI Update January 1, 2008, to December 31, 2012	Validation of hs-cTnI Update PESI	Inception (< 24h from diagnosis) Retrospective	Hospital records University hospital	USA Single centre	(56 ± 13) 151 (51)	Not reported 298 patients	All-cause death All-cause death, CPR, Thrombolysis	5-day 5-day	9 (3) 15 (5)
(Vanni, Jimenez et al 2015)[22] TELOS – sPESI and lactates Derivation - External validation - Update 1 December 2012 to 31 January 2014	Derivation	Inception Prospective cohort	ED	Italy and Spain 7 academic and 2 general urban hospitals	(69±16.5) 242 (48.8)	Stable 496	PE-related complications (PE-related death, non-fatal haemodynamic collapse) PE-related death All-cause death	7-day 30-day 30-day	20 (4.0) 12 (2.4) 27 (5.4)
(Vanni, Nazerian et al 2016)[74] Bova – TELOS - 2014 ESC - Bova and lactates External validation Update September 2002 to January 2014	Identifying Intermediate-high risk	Inception (less than 24h) Retrospective 2 single-centre and 1 multicenter prospective cohorts	University and non-university hospitals	European centres (Italy and Spain)	[74, 64–81] 495 (49.8)	Stable 994 patients	PE-related complications (PE-related death, non-fatal haemodynamic collapse) All-cause death PE-related death	7-day 7-day 7-day	63 (6.3) 32 (3.2) 31 (3.1)

Table A4.4.4: Prognostic models – Impact studies

Author, Year **Model Acronym** **Development phase** **Date study was conducted**	**Research objective**	**Type of study** **Study design**	**Setting** **Hospital**	**Country** **N centres**	**Age** [median, IQR, Range] or (mean ± SD) **Male sex (%)**	**Patients** **Sample size in analysis**	**Outcome**	**Time-point**	**Events (%)**
(Beer, Burger et al 2003)[83] GPS - Management study (Out-of-hospital treatment) Impact May 1999 - December 2001	Safety of home/ outpatient treatment for low-risk GPS patients	Inception (Not reported) Cohort Prospective (Management - Prognosis)	Not reported University and non-university hospital	Switzerland 2 centres	69, range 18-96 Not reported	Stable 45 patients	All-cause death, VTE or bleeding All-cause death PE-related death VTE Clinically relevant or major bleeding Fatal bleeding	3-month 3-month 3-month 3-month 3-month 3-month	1 (2.3) None None 1 (2.3) None None
(Agterof, Schutgens et al, 2010)[84] NTproBNP - Management study (Out-of-hospital treatment) Impact September 2006 - March 2009	Safety of home/ outpatient treatment for stable PE with low NT-proBNP	Inception (at presentation) Cohort Prospective (Management - Prognosis)	Emergency department Academic and non-academic	Netherlands 5 centres	(53.4 ± 14.3) 74 (48.7)	Stable 152 patients (43.3%)	Death due to PE or its treatment Readmission All-cause death, VTE or major bleeding All-cause death, VTE or major bleeding Clinically relevant or major bleeding Fatal bleeding	10-day 10-day 10-day 3-month 3-month 3-month	None 7 (4.6) None None None None
(Otero, Uresandi et al, 2010)[85] Spanish model - RCT (Early discharge group) Impact February 2005 - April 2007	Early discharge program versus standard hospitalization in low-risk PE	Inception (on diagnosis) Cohort Prospective (RCT - Prognosis)	Pneumology University and non-university hospitals	Spain 8 centres	(60 ±17.5) 36 (50)	Stable 72 patients	All-cause death All-cause death VTE Clinically relevant or major bleeding Fatal bleeding	Short-term 3-month 3-month 3-month 3-month	2 (2.8) 3 (4.2) 2 (2.8) 1 (1.4) 1 (1.4)

(Otero, Uresandi et al, 2010)[85] Spanish model - RCT (Hospitalisation group) Impact February 2005 - April 2007	Early discharge program versus standard hospitalization in low-risk PE	Inception (on diagnosis, not reported for cTn and TTE) Cohort Prospective (RCT - Prognosis)	Pneumology University and non-university hospitals	Spain 8 centres	(61.5 ± 16) 29 (48)	Stable 60 patients	All-cause death All-cause death VTE Clinically relevant or major bleeding Fatal bleeding	Short-term 3-month 3-month 3-month 3-month	None 5/60 (8.3) VTE 2/60 (3.3) 1/60 (1.6) None
(Aujesky, Roy et al, 2011)[86] PESI - OTPE - RCT (Outpatient group) Impact February 2007 - June 2010	Outpatient care Versus inpatient care in low risk patients PESI (I-II)	Inception (at presentation, < 23 h from diagnosis) Cohort Prospective (RCT - Prognosis)	ED, General Internal Medicine Most university hospitals	Switzerland, France, Belgium, USA 19 centres	(47 ± 16) 84 (49)	Stable 171 patients	VTE All-cause death Major bleeding Fatal bleeding	3-month 3-month 14-day/ 3-month 3-month	1 (0.6) 1 (0.6) 2 (1.2)/ 3 (1.7) None
(Aujesky, Roy et al, 2011)[86] PESI - OTPE - RCT (Inpatient group) Impact February 2007 - June 2010	Outpatient care Versus inpatient care in low risk patients PESI (I-II)	Inception Cohort (at presentation, < 23 h from diagnosis) Prospective (RCT - Prognosis)	ED, General Internal Medicine Most university hospitals	Switzerland, France, Belgium, USA 19 centres	(49 ± 15) 85 (51)	Stable 168 patients	VTE All-cause death Major bleeding Fatal bleeding	3-month 3-month 14-day/ 3-month 3-month	0 (0) 1 (0.6) 0 (0)/ 0(0) None
(Meyer, Vicaut et al 2014)[87] 2008-ESC - PEITHO - RCT (Tenecteplase + heparin) Impact November 2007 - July 2012	To compare thrombolytics with heparin in intermediate high-risk	Inception (at presentation, < 2h after risk group identification) Cohort Prospective (RCT - Prognosis)	Different specialties Most university hospitals	Many countries from Europe 76 sites in 13 countries	[70, 59–77] (66.5±14.7) 242 (47.8)	Stable 506 patients	All-cause death ± haemodynamic deterioration, All-cause death PE-related death VTE Major bleeding	7-day 7-day/ 30-day 7-day/ 30-day 7-day 7-day 7-day/ 30-day	13 (2.6) 6 (1.2)/ 12 (2.4) 0 (0)/ 1 (0.2) 1 (0.2) 58 (11.5)

							Fatal bleeding		1 (0.2)/ 2 (0.4)
(Meyer, Vicaut et al 2014)[87] 2008-ESC - PEITHO - RCT (Placebo + heparin) Impact November 2007 - July 2012	To compare thrombolytics with heparin in intermediate high-risk	Inception (at presentation, < 2h after risk group identification) Cohort Prospective (RCT - Prognosis)	Different specialties Most university hospitals	Many countries from Europe 76 sites in 13 countries	[70, 57–78] (65.8±15.9) 231 (46.3)	Stable 499 patients	All-cause death ± haemodynamic deterioration, All-cause death PE-related death VTE Major bleeding Fatal bleeding	7-day 7-day/ 30-day 7-day/ 30-day 7-day 7-day 7-day/ 30-day	28 (5.6) 9 (1.8)/ 16 (3.2) 0 (0)/ 1 (0.2) 5 (1.0) 12 (2.4) None/ None
(Stamm, Long et al 2014)[88] PESI - 2008-ESC - Risk stratified group Impact January 1, 2006 - December 31, 2011	To assess frequency use, impact on treatment decisions and outcomes	Inception (< 24h from admission) Cohort Retrospective (Observational - Prognosis)	Medicine - ED Two community-based teaching hospitals	USA (Pennsylvania) 2 centres	(62 ± 17) 275 (52)	Not reported 528 patients	All-cause death and adverse events All-cause mortality	In-hospital 30-day	(5.5) (8.5)
(Stamm, Long et al 2014)[88] PESI - 2008-ESC - Non risk stratified group Impact January 1, 2006 - December 31, 2011	To assess frequency use, impact on treatment decisions and outcomes	Inception (< 24h from admission) Cohort Retrospective (Observational - Prognosis)	Medicine - ED Two community-based teaching hospitals	USA (Pennsylvania) 2 centres	(58 ± 18) 191 (53)	Not reported 361 patients	All-cause death and adverse events All-cause mortality	In-hospital 30-day	(2.5) (7.5)
(Ozsu, Bektas et al 2015)[89] sPESI (without cancer) – cTnI or hs-cTnT Impact study	To investigate outpatient treatment in patients at low-risk sPESI and cTn(-)	Inception (not reported) Prospective	Pulmonary medicine University hospital	Turkey Single centre	71 (58–80) 82 (39.8)	Both stable and unstable 206 patients	All-cause death PE-related death All-cause death	In-hospital In-hospital 3-month	27 (13.1) 9 (4.4) 58 (28.2)

April 2012 to May 2014									

Table A4.4.5: Other types of models

RGS: REVISED GENEVA SCORE, SGS: SIMPLIFIED GENEVA SCORE, CCI: CHARLSON'S COMORBIDITY INDEX, GRACE: GLOBAL REGISTRY OF ACUTE CORONARY EVENTS

Author, Year **Model Acronym** **Development phase** **Date study was conducted**	**Research objective**	**Type of study** **Study design**	**Setting** **Hospital**	**Country** **N centres**	**Age** [median, IQR, Range] or (mean ± SD) **Male sex (%)**	**Patients** **Sample size in analysis**	**Outcome**	**Time-point**	**Events (%)**
Type 2 models Model variables originally not specific to PE or to its prognosis									
(Bertoletti, Le Gal et al 2013)[90] RGS - SGS versus PESI Validation for prognosis and comparison with PESI January 1, 2005 - August 31, 2006.	Validation of RGS and SGS for prognosis and comparison with PESI	Inception (on admission) Cohort Prospective for RGS (Diagnosis), retrospective for SGS and PESI	ED University hopsital	Switzerland, France and Belgium 6 centres	(64±17.9) 196 (54.9) for age > 65 157 (44)	Not reported 357 patients	All-cause death PE-related death	3-month 3-month	21 (5.9) 9 (2.5)
(Ng, Chow et al 2013)[91] CCI-based model Derivation January 2000 - December 2007	To identify low risk	Inception (on admission) Cohort Retrospective (Prognosis)	Mainly medicine departments University hospital	Australia 1 centre	[71.6, 57.6 - 80.4] 457 (45, 42–48)	Not reported 1023 patients	All-cause death All-cause death All-cause death PE-related death	In-hospital 30-day 3-month In-hospital	31 (3) 41 (4) 85 (8.3) 24 (2.3)
(Paiva, Providencia et al 2013)[92] GRACE versus GPS, sPESI, SI, 2008ESC Validation and comparison January 2007 - December	Risk stratification	Inception (on admission) - Cohort Retrospective (Prognosis)	ED University hospital	Portugal 1 centre	(70.3 ± 15.6) 85 (41.3)	Both stable and unstable 206 patients	All-cause death All-cause death	30-day In-hospital	39 (18.9) 33 (16)

2010									
(Papaioannou, Kastanis et al. 2013)[93] No acronym (includes CCI) Derivation & External validation February 2003 - January 2008	Risk stratification	Inception (on admission) Cohort Prospective (Prognosis)	Respiratory medicine department University hospital	Greece 1 centre	(68.6 ± …) 40 (40)	Stable 130 patients (derivation 100 patients, validation 30 patients)	All-cause death	30-day	10 (10)
(Keller, Coldewey et al 2015)[94] Simplified CRB-65 External validation May 2006 to June 2011	Risk stratification	Inception (not reported) Cohort Retrospective	Internal medicine University hospital	Germany Single centre	(68.5 ± 15.3) 70 (38.5)	Both stable and unstable 182 patients	All-cause death	In-hospital	5 (2.7)
(Bach, Taute et al 2016)[66] Acute Physiology and Chronic Health Evaluation II (APACHE II), PESI, sPESI, Glasgow Coma Scale, and euroSCORE II. External validation June 2005 – January 2010	Risk prediction	Inception (not reported) Cohort Retrospective	University hospital data	USA Single centre	[65, 18–91] 178 (48.8)	Not reported 365 patients	All-cause death	30-day	39 (10.7)
Type 3 models Models using hospital criteria checklists									

(Davies, Wimperis et al 2007)[95] Davies criteria Derivation August 2001 - August 2002	Derivation and validation of exclusion criteria for early discharge	Inception (on admission) Cohort Prospective (Management - Prognosis)	Not reported University hospitals	United Kingdom 5 centres	59, range 19–91 109 (48.4)	Not reported 225 patients 202 patients (complete FU)	All-cause death PE-related death VTE Clinically relevant or major bleeding Fatal bleeding	Early phase/ 3-month Early phase/ 3-month Early phase/ 3-month Early phase/ 3-month Early phase/ 3-month	None/ 9 (4.5) None/ 1 (0.5) None/ 6 (3.0) None/ 6 (3.0) Not reported
(Davies, Wimperis et al 2007)[95] Davies criteria Impact October 2003 - February 2006	Derivation and validation of exclusion criteria for early discharge	Inception (on admission) Cohort Prospective (Management - Prognosis)	Not reported Centres with nurse-led outpatient DVT services	United Kingdom 10 centres	58, range 18–85 86 (54.8)	Stable 157 patients	All-cause death PE-related death VTE Clinically relevant or major bleeding Fatal bleeding	Early phase/ 3-month Early phase/ 3-month Early phase/ 3-month Early phase/ 3-month Early phase/ 3-month	None/ 3 (1.9) None/ None None/ None None/ None None/ None
(Zondag, den Exter et al 2013)[96] Hestia criteria - sPESI Impact (Hestia) - External validation (sPESI) - Comparison 2008 - 2010	To identify low-risk	Inception (on admission) Cohort Prospective (Management - Prognosis) - Post-hoc analysis	Departments of internal Medicine, pulmonolgy and Haematology	Netherlands 12 centres 3 academic and 9 non academic	(58) 43 (9) for age > 80, 257 (55)	Both stable and unstable 465 patients	All-cause death VTE Clinically relevant or major bleeding	7-day/ 30-day/ 3-month 7-day/ 30-day 7-day/ 30-day	4 (0.8)/ 11 (2.4)/ 24 (5.2) 5 (1.1)/ 10 (2.1) 8 (1.7)/ 10 (2.1)
(Zondag, Vingerhoets et al 2013)[97] Hestia - sPESI - CT-RVD Impact - External validation - Update 2008 - 2010	To compare Hestia with Hestia + CT-RVD to identify low-risk patients	Inception (on admission) Cohort Prospective (Management - Prognosis) - Post-hoc analysis	Departments of internal Medicine, pulmonolgy and Haematology	Netherlands 12 centres 3 academic and 9 non academic	(58 ± 17) 268 (54)	Both stable and unstable 496 patients	All-cause death VTE Clinically relevant or major bleeding	7-day/ 30-day/ 3-month 7-day/ 30-day 7-day/ 30-day	4 (0.8)/ 11 (2.2)/ 23 (4.7) (1.1)/ (2.1) (1.7)/ (2.1)

(den Exter, Zondag et al 2016)[98] Hestia and NT-proBNP (less than 500 pg/mL) Impact study December 2010 to February 2014	Comparison of two strategies for management of low-risk PE patients	Inception (less than 24h) Cohort Prospective (RCT - Prognosis)	Various settings Academic (2) and non-academic (15) hospitals	Dutch 17 hospitals	(55 ± 15) 145 (52.7)	Stable 275 patients	Adverse outcome (PE- or bleeding-related mortality, cardiopulmonary resuscitation or intensive care admission, or requirement of thrombolytic therapy or surgical embolectomy) VTE Major bleeding All-cause death	30-day 3-month 3-month 3-month	0 (0) 2 (0.73) 1 (0.36) 4 (1.5)
(den Exter, Zondag et al 2016)[98] Hestia Impact study December 2010 to February 2014	Comparison of two strategies for management of low-risk PE patients	Inception (less than 24h) Cohort Prospective (RCT - Prognosis)	Various settings Academic (2) and non-academic (15) hospitals	Dutch 17 hospitals (2/17 academic)	(53 ± 15) 152 (55.3)	Stable 275 patients	Adverse outcome (PE- or bleeding-related mortality, cardiopulmonary resuscitation or intensive care admission, or requirement of thrombolytic therapy or surgical embolectomy) VTE Major bleeding All-cause death	30-day 3-month 3-month 3-month	3 (1.1) 3 (1.1) 3 (1.1) 3 (1.1)
(Weeda, Kohn et al 2016)[99] Hestia External validation from October 21, 2010, to January 31, 2014	External validation	Inception (less than 24h) Retrospective cohort	ED University hospital	USA Single centre	(64.1±16.88) Not reported	Both stable and unstable 577 patients	All-cause death All-cause death	In-hospital 30-day	19 (3.3) 35 (6.1)

REFERENCES

1. Wicki J, Perrier A, Perneger TV, et al. Predicting adverse outcome in patients with acute pulmonary embolism: A risk score. Thrombosis and haemostasis 2000;**84 (4)**:548-52.

2. Kostrubiec M, Pruszczyk P, Bochowicz A, et al. Biomarker-based risk assessment model in acute pulmonary embolism. European heart journal 2005;**26 (20)**:2166-72.

3. Aujesky D, Obrosky DS, Stone RA, et al. Derivation and validation of a prognostic model for pulmonary embolism. American journal of respiratory and critical care medicine 2005;**172 (8)**:1041-46.

4. Aujesky D, Obrosky DS, Stone RA, et al. A prediction rule to identify low-risk patients with pulmonary embolism. Archives of internal medicine 2006;**166 (2)**:169-75.

5. Uresandi F, Otero R, Cayuela A, et al. A clinical prediction rule for identifying short-term risk of adverse events in patients with pulmonary thromboembolism. [Spanish]. Archivos de bronconeumologia 2007;**43 (11)**:617-22.

6. Agterof MJ, Van Bladel ER, Schutgens REG, et al. Risk stratification of patients with pulmonary embolism based on pulse rate and D-dimer concentration. Thrombosis and haemostasis 2009;**102 (4)**:683-87.

7. Volschan A, Albuquerque D, Tura BR, et al. Predictors of hospital mortality in hemodynamically stable patients with pulmonary embolism. [Portuguese, Spanish, English]. Arquivos brasileiros de cardiologia 2009;**93 (2)**:135-40.

8. Yamaki T, Nozaki M, Sakurai H, et al. Presence of Lower Limb Deep Vein Thrombosis and Prognosis in Patients with Symptomatic Pulmonary Embolism: Preliminary Report. European Journal of Vascular and Endovascular Surgery 2009;**37 (2)**:225-31.

9. Zhu L, Wang C, Yang Y-h, et al. [Prognostic value of right ventricular dysfunction and derivation of a prognostic model for patients with acute pulmonary thromboembolism]. Chung-Hua Liu Hsing Ping Hsueh Tsa Chih Chinese Journal of Epidemiology 2009;**30**(2):184-8.

10. Jimenez D, Aujesky D, Moores L, et al. Simplification of the pulmonary embolism severity index for prognostication in patients with acute symptomatic pulmonary embolism. Archives of internal medicine 2010;**170 (15)**:1383-89.

11. Sanchez O, Trinquart L, Caille V, et al. Prognostic factors for pulmonary embolism: The PREP study, a prospective multicenter cohort study. American journal of respiratory and critical care medicine 2010;**181 (2)**:168-73.

12. Agterof MJ, Schutgens RE, Moumli N, et al. A prognostic model for short term adverse events in normotensive patients with pulmonary embolism. American Journal of Hematology 2011;**86 (8)**:646-49.

13. Huang CM, Lin YC, Lin YJ, et al. Risk stratification and clinical outcomes in patients with acute pulmonary embolism. Clinical Biochemistry 2011;**44**(13):1110-5.

14. Lankeit M, Friesen D, Schafer K, et al. A simple score for rapid risk assessment of non-high-risk pulmonary embolism. Clin 2013;**102**(1):73-80.

15. Dellas C, Tschepe M, Seeber V, et al. A novel H-FABP assay and a fast prognostic score for risk assessment of normotensive pulmonary embolism. Thrombosis and haemostasis 2014;**111**(5):996-1003.

16. Jo J, Lee M, Lee J, et al. Leukocytes and systemic inflammatory response syndrome as prognostic factors in pulmonary embolism patients. BMC Pulmonary Medicine 2013;**13**(1):74.

17. Bova C, Sanchez O, Prandoni P, et al. Identification of intermediate-risk patients with acute symptomatic pulmonary embolism. European Respiratory Journal 2014;**44**(3):694-703.

18. Jiménez D, Kopecna D, Tapson V, et al. Derivation and Validation of Multimarker Prognostication for Normotensive Patients with Acute Symptomatic Pulmonary Embolism. American journal of respiratory and critical care medicine 2014;**189**(6):718-26.

19. Akgüllü Ç, Ömürlü İK, Eryılmaz U, et al. Predictors of early death in patients with acute pulmonary embolism. The American journal of emergency medicine 2015;**33**(2):214-21.

20. Kundi H, Balun A, Cicekcioglu H, et al. The relation between platelet-to-lymphocyte ratio and Pulmonary Embolism Severity Index in acute pulmonary embolism. Heart & Lung: The Journal of Acute and Critical Care 2015;**44**(4):340-43.

21. Maestre A, Trujillo-Santos J, Riera-Mestre A, et al. Identification of Low-Risk Patients with Acute Symptomatic Pulmonary Embolism for Outpatient Therapy. Annals of the American Thoracic Society 2015;**12**(8):1122-9.

22. Vanni S, Jimenez D, Nazerian P, et al. Short-term clinical outcome of normotensive patients with acute PE and high plasma lactate. Thorax 2015;**70**(4):333-8.

23. Ostovan MA, Ghaffari S, Pourafkari L, et al. Modification of Simplified Pulmonary Embolism Severity Index and its Prognostic Value in Patients with Acute Pulmonary Embolism. Heart, Lung and Circulation 2016;**25**(2):184-90.

24. Xu NL, Xue H, Chen YS, et al. [Establishment and evaluation of a prognostic model for acute pulmonary embolism]. Zhonghua jie he he hu xi za zhi = Zhonghua jiehe he huxi zazhi = Chinese journal of tuberculosis and respiratory diseases 2016;**39**(4):304-10.

25. Nendaz MR, Bandelier P, Aujesky D, et al. Validation of a risk score identifying patients with acute pulmonary embolism, who are at low risk of clinical adverse outcome. Thrombosis and haemostasis 2004;**91 (6)**:1232-36.

26. Aujesky D, Perrier A, Roy PM, et al. Validation of a clinical prognostic model to identify low-risk patients with pulmonary embolism. Journal of internal medicine 2007;**261 (6)**:597-604.

27. Jimenez D, Yusen RD, Otero R, et al. Prognostic models for selecting patients with acute pulmonary embolism for initial outpatient therapy. Chest 2007;**132**(1):24-30.

28. Donze J, Le Gal G, Fine MJ, et al. Prospective validation of the Pulmonary Embolism Severity Index: A clinical prognostic model for pulmonary embolism. Thrombosis and haemostasis 2008;**100 (5)**:943-48.

29. Palmieri V, Gallotta G, Rendina D, et al. Troponin I and right ventricular dysfunction for risk assessment in patients with nonmassive pulmonary embolism in the Emergency Department in combination with clinically based risk score. Internal and emergency medicine 2008;**3 (2)**:131-38.

30. Toosi MS, Merlino JD, Leeper KV. Prognostic Value of the Shock Index Along With Transthoracic Echocardiography in Risk Stratification of Patients With Acute Pulmonary Embolism. American Journal of Cardiology 2008;**101 (5)**:700-05.

31. Bova C, Pesavento R, Marchiori A, et al. Risk stratification and outcomes in hemodynamically stable patients with acute pulmonary embolism: a prospective, multicentre, cohort study with three months of follow-up. Journal of Thrombosis and Haemostasis 2009;**7**(6):938-44.

32. Choi WH, Sung UK, Yoon JJ, et al. The pulmonary embolism severity index in predicting the prognosis of patients with pulmonary embolism. Korean Journal of Internal Medicine 2009;**24 (2)**:123-27.

33. Kukla P, Bryniarski L, Dlugopolski R, et al. Acute pulmonary embolism registry in the Malopolska region - clinical course. Kardiologia polska 2009;**67**(7):735-41.

34. Nordenholz K, Ryan J, Atwood B, et al. Pulmonary embolism risk stratification: Pulse oximetry and pulmonary embolism severity index. Journal of Emergency Medicine 2011;**40 (1)**:95-102.

35. Subramaniam RM, Mandrekar J, Blair D, et al. The Geneva prognostic score and mortality in patients diagnosed with pulmonary embolism by CT pulmonary angiogram. Journal of medical imaging and radiation oncology 2009;**53 (4)**:361-65.

36. Chan CM, Woods C, Shorr AF. The validation and reproducibility of the pulmonary embolism severity index. Journal of Thrombosis and Haemostasis 2010;**8 (7)**:1509-14.

37. Chan CM, Woods CJ, Shorr AF. Comparing the pulmonary embolism severity index and the prognosis in pulmonary embolism scores as risk stratification tools. J Hosp Med 2012;**7**(1):22-27.

38. Jakobsson C, Jimenez D, Gomez V, et al. Validation of a clinical algorithm to identify low-risk patients with pulmonary embolism. Journal of Thrombosis and Haemostasis 2010;**8**(6):1242-7.

39. Vuilleumier N, Le Gal G, Cornily JC, et al. Is N-terminal pro-brain natriuretic peptide superior to clinical scores for risk stratification in non-massive pulmonary embolism? Journal of Thrombosis and Haemostasis 2010;**8**(6):1433-5.

40. Erkens PMG, Gandara E, Wells PS, et al. Does the Pulmonary Embolism Severity Index accurately identify low risk patients eligible for outpatient treatment? Thrombosis research 2012;**129 (6)**:710-14.

41. Hariharan P, Takayesu JK, Kabrhel C. Association between the pulmonary embolism severity index (PESI) and short-term clinical deterioration. Thrombosis and haemostasis 2011;**105 (4)**:706-11.

42. Righini M, Roy PM, Meyer G, et al. The Simplified Pulmonary Embolism Severity Index (PESI): Validation of a clinical prognostic model for pulmonary embolism. Journal of Thrombosis and Haemostasis 2011;**9 (10)**:2115-17.

43. Sam A, Sanchez D, Gomez V, et al. The shock index and the simplified PESI for identification of low-risk patients with acute pulmonary embolism. European Respiratory Journal 2011;**37 (4)**:762-66.

44. Singanayagam A, Scally C, Al-Khairalla MZ, et al. Are biomarkers additive to pulmonary embolism severity index for severity assessment in normotensive patients with acute pulmonary embolism? Quarterly Journal of Medicine 2011;**104**(2):125-31.

45. Spirk D, Aujesky D, Husmann M, et al. Cardiac troponin testing and the simplified pulmonary embolism severity index the swiss venous thromboembolism registry (SWIVTER). Thrombosis and haemostasis 2011;**106 (5)**:978-84.

46. Vanni S, Nazerian P, Pepe G, et al. Comparison of two prognostic models for acute pulmonary embolism: Clinical vs. right ventricular dysfunction-guided approach. Journal of Thrombosis and Haemostasis 2011;**9 (10)**:1916-23.

47. Venetz C, Jimenez D, Mean M, et al. A comparison of the original and simplified pulmonary embolism severity index. Thrombosis and haemostasis 2011;**106 (3)**:423-28.

48. Labyk A, Ciurzynski M, Jankowski K, et al. Acute pulmonary embolism: analysis of consecutive 353 patients hospitalised in a single centre. A 3-year experience. Kardiologia polska 2012;**70**(1):15-22.

49. Lankeit M, Gomez V, Wagner C, et al. A strategy combining imaging and laboratory biomarkers in comparison with a simplified clinical score for risk stratification of patients with acute pulmonary embolism. Chest 2012;**141 (4)**:916-22.

50. Roca IC, Aursulesei V, Roca M, et al. [Comparative evaluation of prognostic scores in pulmonary embolism]. Revista Medico-Chirurgicala a Societatii de Medici Si Naturalisti Din Iasi 2012;**116**(1):69-74.

51. Soares TH, de Bastos M, de Carvalho BV, et al. Prognostic value of computed tomographic pulmonary angiography and the pulmonary embolism severity index in patients with acute pulmonary embolism. Blood Coagulation & Fibrinolysis 2013;**24**(1):64-70.

52. Becattini C, Casazza F, Forgione C, et al. Acute pulmonary embolism: external validation of an integrated risk stratification model. Chest 2013;**144**(5):1539-45.

53. Ferrer M, Morillo R, Elias T, et al. Validation of two clinical prognostic models in patients with acute symptomatic pulmonary embolism. Archivos de bronconeumologia 2013;**49**(10):427-31.

54. Ozsu S, Abul Y, Orem A, et al. Predictive value of troponins and simplified pulmonary embolism severity index in patients with normotensive pulmonary embolism. Multidiscip 2013;**8**(1):34.

55. Sanchez O, Trinquart L, Planquette B, et al. Echocardiography and pulmonary embolism severity index have independent prognostic roles in pulmonary embolism. European Respiratory Journal 2013;**42**(3):681-88.

56. Choi K-J, Cha S-I, Shin K-M, et al. Prognostic implications of computed tomographic right ventricular dilation in patients with acute pulmonary embolism. Thrombosis research 2014;**133**(2):182-86.

57. Ozsu S, Ozlu T, Şentürk A, et al. Combination and comparison of two models in prognosis of pulmonary embolism: Results from TUrkey Pulmonary Embolism Group (TUPEG) study. Thrombosis research 2014;**133**(6):1006-10.

58. Casazza F, Becattini C, Guglielmelli E, et al. Prognostic significance of free-floating right heart thromboemboli in acute pulmonary embolism Results from the Italian Pulmonary Embolism Registry. Thrombosis and haemostasis 2014;**111**(1):53-57.

59. Kabrhel C, Okechukwu I, Hariharan P, et al. Factors associated with clinical deterioration shortly after PE. Thorax 2014;**69**(9):835-42.

60. Lauque D, Maupas-Schwalm F, Bounes V, et al. Predictive value of the heart-type fatty acid-binding protein and the Pulmonary Embolism Severity Index in patients with acute pulmonary embolism in the emergency department. Academic Emergency Medicine 2014;**21**(10):1143-50.

61. Tong C, Zhang Z, Ma C, et al. [The value of simplified pulmonary embolism severity index and biomarkers in evaluating pulmonary embolism prognosis]. Zhonghua jie he he hu xi za zhi = Zhonghua jiehe he huxi zazhi = Chinese journal of tuberculosis and respiratory diseases 2014;**37**(2):104-8.

62. Fermann GJ, Erkens PM, Prins MH, et al. Treatment of pulmonary embolism with rivaroxaban: outcomes by simplified Pulmonary Embolism Severity Index score from a post hoc analysis of the EINSTEIN PE study. Academic Emergency Medicine 2015;**22**(3):299-307.

63. Fernandez C, Bova C, Sanchez O, et al. Validation of a Model for Identification of Patients at Intermediate to High Risk for Complications Associated With Acute Symptomatic Pulmonary Embolism. Chest 2015;**148**(1):211-18.

64. Kara H, Degirmenci S, Bayir A, et al. Pulmonary embolism severity index, age-based markers and evaluation in the emergency department. Acta Clinica Belgica 2015;**70**(4):259-64.

65. Mizuno A, Yamamoto T, Tanabe Y, et al. Pulmonary Embolism Severity Index and Simplified Pulmonary Embolism Severity Index Risk Scores Are Useful to Predict Mortality in Japanese Patients With Pulmonary Embolism. Circulation Journal 2015;**79**(4):889-91.

66. Bach AG, Taute BM, Baasai N, et al. 30-Day Mortality in Acute Pulmonary Embolism: Prognostic Value of Clinical Scores and Anamnestic Features. PLoS One 2016;**11**(2):e0148728.

67. Becattini C, Agnelli G, Lankeit M, et al. Acute pulmonary embolism: mortality prediction by the 2014 European Society of Cardiology risk stratification model. European Respiratory Journal 2016;**48**(3):780-6.

68. Cordeanu M, Gaertner S, Faller A, et al. Prognostic value of the simplified PESI score in comparison with the 2014 ESC risk model in pulmonary embolism. International journal of cardiology 2016;**220**:623-4.

69. Hobohm L, Hellenkamp K, Hasenfuss G, et al. Comparison of risk assessment strategies for not-high-risk pulmonary embolism. European Respiratory Journal 2016;**47**(4):1170-8.

70. Jimenez D, Lobo JL, Fernandez-Golfin C, et al. Effectiveness of prognosticating pulmonary embolism using the ESC algorithm and the Bova score. Thrombosis and haemostasis 2016;**115**(4):827-34.

71. Masotti L, Panigada G, Landini G, et al. Predictive ability of the new 2014 ESC prognostic model in acute pulmonary embolism. International journal of cardiology 2016;**202**:801-03.

72. Masotti L, Verdiani V, Cei M, et al. The predictive role of the Bova risk score in acute normotensive pulmonary embolism: A retrospective analysis on a real life cohort. Thrombosis research 2016;**137**:221-23.

73. Rozjabek HM, Coleman CI, Weeda ER, et al. Effect of vital sign measurement timing on Pulmonary Embolism Severity Index (PESI) and simplified PESI 30-day mortality risk determination. Thrombosis research 2016;**141**:8-10.

74. Vanni S, Nazerian P, Bova C, et al. Comparison of clinical scores for identification of patients with pulmonary embolism at intermediate–high risk of adverse clinical outcome: the prognostic role of plasma lactate. Internal and emergency medicine 2016:1-9.

75. Moores L, Aujesky D, Jimenez D, et al. Pulmonary Embolism Severity Index and troponin testing for the selection of low-risk patients with acute symptomatic pulmonary embolism. Journal of Thrombosis and Haemostasis 2010;**8 (3)**:517-22.

76. Singanayagam A, Chalmers JD, Scally C, et al. Right ventricular dilation on CT pulmonary angiogram independently predicts mortality in pulmonary embolism. Respiratory Medicine 2010;**104**(7):1057-62.

77. Jimenez D, Aujesky D, Moores L, et al. Combinations of prognostic tools for identification of high-risk normotensive patients with acute symptomatic pulmonary embolism. Thorax 2011;**66 (1)**:75-81.

78. Lankeit M, Jimenez D, Kostrubiec M, et al. Predictive value of the high-sensitivity troponin T assay and the simplified pulmonary embolism severity index in hemodynamically stable patients

with acute pulmonary embolism: A prospective validation study. Circulation 2011;**124 (24)**:2716-24.

79. Sanchez D, De Miguel J, Sam A, et al. The effects of cause of death classification on prognostic assessment of patients with pulmonary embolism. Journal of Thrombosis and Haemostasis 2011;**9 (11)**:2201-07.

80. Barra SNC, Paiva LV, Providência R, et al. Atrial fibrillation in acute pulmonary embolism: prognostic considerations. Emergency Medicine Journal 2014;**31**(4):308-12.

81. Lankeit M, Jiménez D, Kostrubiec M, et al. Validation of N-terminal pro-brain natriuretic peptide cut-off values for risk stratification of pulmonary embolism. European Respiratory Journal 2014;**43**(6):1669-77.

82. Hakemi EU, Alyousef T, Dang G, et al. The prognostic value of undetectable highly sensitive cardiac troponin I in patients with acute pulmonary embolism. Chest 2015;**147**(3):685-94.

83. Beer JH, Burger M, Gretener S, et al. Outpatient treatment of pulmonary embolism is feasible and safe in a substantial proportion of patients. Journal of Thrombosis and Haemostasis 2003;**1**(1):186-7.

84. Agterof MJ, Schutgens REG, Snijder RJ, et al. Out of hospital treatment of acute pulmonary embolism in patients with a low NT-proBNP level. Journal of Thrombosis and Haemostasis 2010;**8**(6):1235-41.

85. Otero R, Uresandi F, Jimenez D, et al. Home treatment in pulmonary embolism. Thrombosis research 2010;**126**(1):e1-5.

86. Aujesky D, Roy PM, Verschuren F, et al. Outpatient versus inpatient treatment for patients with acute pulmonary embolism: An international, open-label, randomised, non-inferiority trial. Lancet 2011;**378 (9785)**:41-48.

87. Meyer G, Vicaut E, Danays T, et al. Fibrinolysis for patients with intermediate-risk pulmonary embolism. New England Journal of Medicine 2014;**370**(15):1402-11.

88. Stamm JA, Long JL, Kirchner HL, et al. Risk Stratification in Acute Pulmonary Embolism: Frequency and Impact on Treatment Decisions and Outcomes. Southern Medical Journal 2014;**107**(2):72-78.

89. Ozsu S, Bektas H, Abul Y, et al. Value of Cardiac Troponin and sPESI in Treatment of Pulmonary Thromboembolism at Outpatient Setting. Lung 2015;**193**(4):559-65.

90. Bertoletti L, Le Gal G, Aujesky D, et al. Prognostic value of the Geneva prediction rule in patients with pulmonary embolism. Thrombosis research 2013;**132**(1):32-36.

91. Ng AC, Chow V, Yong AS, et al. Prognostic impact of the Charlson comorbidity index on mortality following acute pulmonary embolism. Respiration 2013;**85**(5):408-16.

92. Paiva LV, Providencia RC, Barra SN, et al. Cardiovascular risk assessment of pulmonary embolism with the GRACE risk score. The American journal of cardiology 2013;**111**(3):425-31.

93. Papaioannou AI, Kastanis A, Malli F, et al. Predicting short-term mortality in patients with pulmonary embolism: a simple model. American Journal of the Medical Sciences 2013;**345**(6):462-9.

94. Keller K, Coldewey M, Dippold W, et al. Simplified CRB-65 for risk stratification and predicting prognosis in acute pulmonary embolism. Phlebologie 2015;**44**(4):192-99.

95. Davies CWH, Wimperis J, Green ES, et al. Early discharge of patients with pulmonary embolism: a two-phase observational study. European Respiratory Journal 2007;**30**(4):708-14.

96. Zondag W, den Exter PL, Crobach MJT, et al. Comparison of two methods for selection of out of hospital treatment in patients with acute pulmonary embolism. Thrombosis and haemostasis 2013;**109**(1):47-52.

97. Zondag W, Vingerhoets LMA, Durian MF, et al. Hestia criteria can safely select patients with pulmonary embolism for outpatient treatment irrespective of right ventricular function. Journal of Thrombosis and Haemostasis 2013;**11**(4):686-92.

98. den Exter PL, Zondag W, Klok FA, et al. Efficacy and Safety of Outpatient Treatment Based on the Hestia Clinical Decision Rule With or Without NT-proBNP Testing in Patients With Acute Pulmonary Embolism: A Randomized Clinical Trial. American journal of respiratory and critical care medicine 2016.

99. Weeda ER, Kohn CG, Peacock WF, et al. External Validation of the Hestia Criteria for Identifying Acute Pulmonary Embolism Patients at Low Risk of Early Mortality. Clinical and Applied Thrombosis/Hemostasis 2016.

TABLES A4.5 (PATIENT CHARACTERISTICS)

A4.5.1.a: Prognostic Models - Construction studies (1): Patient characteristics.

NR: Not reported.

Author Year	Name and/ or acronym of the study model	Age: median, [IQR], Range (or mean ± SD)	Male sex (%)	History of VTE (%)	Risk factors for VTE other than cancer and history of VTE (%)	Cancer (%)	Chronic cardiac disease (%)	Chronic lung disease (%)	Chronic renal disease (%)	Cerebrovascular disease (%)	Clinically stable patients (%)
(Wicki, Perrier et al. 2000)[1]	Geneva prognostic score (GPS)	(67. 5 ± 16.7)	48.3	PE: 17.2, DVT: 26.7	NR	18.2	CHF: 34.8, CAD: 14.2	COPD: 14.9	NR	NR	NR
(Kostrubiec, Pruszczyk et al. 2005)[2]	No acronym (Polish model)	(62 ± 18)	35 (35)	NR	NR	13 (13)	CHF 17 (17), CAD 26 (26)	COPD 7 (7)	Renal failure 13 (13)	NR	All patients (100)
(Aujesky, Obrosky et al. 2005)[3]	PE severity index (PESI)	52.8 - 53.1% for age > 65	39.6 - 41.1	(5.5)	NR	19.9 - 19.0	CHF: 16.1 - 15.3	18.2 - 19.1	4.4 - 4.2	8.9 - 9.9	89.4 - 89.8
(Aujesky, Obrosky et al 2006)[4]	PE Prognostic algorithm	52.8 - 53.1% for age > 65	39.6 - 41.1	(5.5)	NR	19.9 - 19.0	CHF: 16.1 - 15.3	18.2 - 19.1	4.4 - 4.2	8.9 - 9.9	89.4 - 89.8
(Uresandi, Otero et al. 2007)[5]	No acronym (Spanish model)	(68) - 76.5% for age > 60	336 (49.34)	NR	Immobilisation > 4 d: 142 (20.8), surgery 89 (13.1)	(57+62)/681 (17.5)	NR	NR	NR	NR	NR
(Agterof, van Bladel et al 2009)[6]	No Acronym (Dutch model)	(59.6 ± 15.3)	218 (49.5)	69 (15.7)	NR	81 (18.4)	CHF 33 (7.5)	COPD 50 (11.4)	NR	NR	NR
(Volschan, Albuquerque et al 2009)[7]	EMEP (Estudo Multicentrico di Embolia Pulmonar)	73 [18 - 102]	245 (42.1)	102 (17.5)	Hip/ LL fracture 39 (6.7), surgery 59 (10.1), immobilisation 194 (33.3)	127 (21.8)	CHF 88 (15.1)	40 (6.9)	NR	33 (5.7) [stroke]	All patients (100)
(Yamaki, Nozaki et al 2009)[8]	No acronym (Japanese model)	(62.8 ± 15.9)	78 (38.4)	18 (8.9)	Many	30 (14.8)	CHF 26 (12.8)	NR	15 (7.4)	NR	All patients (100)

(Zhu, Wang et al 2009)[9]	No acronym (Chinese model)	(57.4 ± 14.1)	323 (62.1)	51 (9.8)	NR	12 (2.3)	CAD 66 (12.7)	COPD 43 (8.3)	NR	66 (12.7)	Unclear
(Jimenez, Aujesky et al 2010)[10]	PESI - sPESI (simplified PESI)	(age > 65): 67.4% (age > 80): 24.6%	(45.1)	NR	NR	24.0	CHF (6.9)	(7.4)	NR	NR	NR
(Sanchez, Trinquart et al. 2010)[11]	PREP (Facteurs PRonostiques dans l'Embolie Pulmonaire)	68 [52 - 77]	268 (47)	142 (25)	Major surgery, trauma: 70 (12), Seated travel: 60 (11)	87 (15)	CHF 27 (5), CAD 39 (7)	36 (6)	26 (5)	NR	529 (93)
(Agterof, Schutgens et al. 2011)[12]	UPS (Utrecht Prediction Score)	(56 ± 16.8)	96 (45.71)	41 (19.5)	NR	32 (15.2)	CHF 5 (2.4)	COPD 17 (8.1)	NR	NR	210 (100)
(Huang, Lin et al. 2011)[13]	No acronym	(71.3 ±14.8)	96 (64)	15 (10)	Recent major surgery 10 (6,7)	46 (30,7)	CHF 23 (15,3), CAD 25 (16,7)	COPD 21 (14)	NR	NR	Unclear 118 (78,7)
(Lankeit, Friesen et al 2013)[14 15]	Simple score FAST	68 [56–76]	56 (41)	42 (30.1)	Immobilisation 49 (36)	26 (19.1)	CHF 14 (10.3), CAD 17 (12.5)	20 (14.7)	GFR<60 ml/min/1.73 m2:36 (26.5)	NR	All patients (100)
(Jo, J., M. Lee, et al. 2013)[16]	SIRS-based criteria + others	(66.4 ± 13.3)	295 (44.2)	49 (7.3)	NR	181 (27.1)	75 (11.2%)	NR	96 (14.3)	NR	NR
(Bova, Sanchez et al 2014)[17]	No acronym	72 [60–80] (> 80): 675 (23)	1122 (39)	424 (15)	Recent surgery 311 (11) - Immobilisation 475 (16)	551 (19)	212 (7.4)	COPD 381 (13)	NR	NR	All patients (100)
(Jiménez, Kopecna et al 2014)[18]	eStiMaTe (PROTECT)	72 [59–80], (> 80): 184 (22)	416 (49)	121 (14)	Recent surgery 89 (10), immobilisation 167 (20)	144 (17)	51 (6.0)	108 (13)	NR	NR	All patients (100)
(Akgüllü, Ömürlü et al 2014)[19]	No acronym	(61.8 ± 11.8)	97 (47)	35 (17)	Smoking 89 (43.2)	43 (21)		58 (28)	NR	NR	NR
(Kundi, Balun et al 2015)[20]	No acronym	(60 ± 16)	294 (45.5)	NR	NR	NR	NR	NR	NR	NR	NR

(Maestre, Trujillo-Santos et al 2015)[21]	No acronym	67.25 (> 80): 4772 (25.5)	8796 (47)	2838 (15.17)	Immobility 3953 (21.13) Estrogen use 957 (5.11)	3897 (20.8)	1436 (7.7)	2386 (12.7)	Cl<30 1201 (6.4)	NR	(<90) : 589 (3.14)
(Vanni, Jiménez et al 2015)[22]	No acronym	(69 ± 16.5) (> 80): 124 (25)	242 (49)	64 (13)	NR	122 (25)	NR	44 (8.8)	NR	NR	All 496
(Ostovan, Ghaffari et al 2015)[23]	No acronym	(62.4 ± 17.2)	153 (51)		NR	14 (4.7)	NR	27.9 (9.3)	NR	NR	NR
(Xu, Chen et al 2016)[24]	No acronym	(62 ± 11)	141 (42.6)	49 (14.8)	NR Haematologic diseases: 78 (23.6)	83 (25.1)	NR	NR	51 (15.4)	217 (65.6)	NR

A4.5.1.b: Prognostic Models - Construction studies (2): Patient characteristics.

NR: NOT REPORTED. ALTERED MENTAL STATUS DEFINED AS DISORIENTATION, LETHARGY, STUPOR, OR COMA.

Author Year	Name and/ or acronym of the study model	Temperature (°C)	Heart rate (/mn)	Systolic blood pressure (mm Hg)	Respiratory rate (/ mn)	Altered mental status	Arterial oxygen saturation (%)	Initial treatment other than usual care
(Wicki, Perrier et al. 2000)[1]	Geneva prognostic score (GPS)	NR	(> 100): 125 (42.2%)	(< 100): 8 (2.7%)	(> 30): 57 (19.3%)	NR	NR	Decision by attending physician
(Kostrubiec, Pruszczyk et al. 2005)[2]	No acronym (Polish model)	NR	97± 20	127±19	NR	NR	91± 6	TL 19 (19%)
(Aujesky, Obrosky et al. 2005)[3]	PE severity index (PESI)	(< 36): 16.7 - 16.4%	(> 110): 29.2 - 30.0%	(< 100): 10.6 - 10.2 %	(< 30): 14.5 - 14.7	6.9 - 8.1%	(< 90): 8.0 - 7.8%	NR
(Aujesky, Obrosky et al 2006)[4]	PE Prognostic algorithm	(< 36): 16.7 - 16.4%	(> 110): 29.2 - 30.0%	(< 100): 10.6 - 10.2 %	(< 30): 14.5 - 14.7	6.9 - 8.1%	(< 90): 8.0 - 7.8%	NR
(Uresandi, Otero et al. 2007)[5]	No acronym (Spanish model)	NR	NR	NR	NR	NR	NR	NR
(Agterof, van Bladel et al 2009)[6]	No Acronym (Dutch model)	NR	(≥ 100/ mn): 148 (36.6)	(≤ 90): 14 (3.4%)	NR	NR	NR	TL 19 (4.3), IVC filter 2 (0.45), surgery 1 (0.22)
(Volschan, Albuquerque et al 2009)[7]	EMEP (Estudo Multicentrico di Embolia Pulmonar)	(> 37): 61 (10.5%)	(> 100/ mn): 232 (39.9)	NR	(> 20): 365 (62.5)	NR	NR	NR
(Yamaki, Nozaki et al 2009)[8]	No acronym (Japanese model)	NR	NR	NR	NR	NR	NR	NR
(Zhu, Wang et al 2009)[9]	No acronym (Chinese model)	NR	NR	NR	NR	NR	NR	NR

(Jimenez, Aujesky et al 2010)[10]	PESI - sPESI (simplified PESI)	(< 36): 9.5%	(≥ 110): 18.4%	(< 100): 8.9%	(≥ 30): 6.8%	0.2%	(< 90): 25.8%	Anticoagulants, IVC interrution, TL
(Sanchez, Trinquart et al. 2010)[11]	PREP (Facteurs PRonostiques dans l'Embolie Pulmonaire)	Median [IQR]: 37.1 [36.8 - 37.5]	89 [75 -101]	132 [120 - 148]	21 [18 - 26]	18 (3%)	NR	TL 31 (5), embolectomy 2 (<1), IVC filter 25 (4)
(Agterof, Schutgens et al. 2011)[12]	UPS (Utrecht Prediction Score)	NR	87.1 ± 18.1	NR	NR	NR	NR	TL 7 (3.3), embolectomy 1 (0.4)
(Huang, Lin et al. 2011)[13]	No acronym	36.6 ± 0.96	99.6 ± 21.8	128 ± 27.8	NR	NR	NR	TL 7 (4,7), embolectomy 2 (1,3)
(Lankeit, Friesen et al 2013)[14 15]	Simple score FAST	NR	(> 100/ mn): 53 (39.0)	NR	NR	NR	NR	NR
(Jo, J., M. Lee, et al. 2013)[16]	SIRS-based criteria + other criteria	(> 38.3 or < 36): 15 (2.2)	187 (28.0)	121.8 ± 20.6	(> 20): 248 (37.1)	65 (9.7)	NR	NR
(Bova, Sanchez et al 2014)[17]	No acronym	NR	(≥ 110): 533 (18)	(90 - 100): 156 (5.4)	NR	NR	(< 90%): 625 (22)	IVC filter: 63 (2.2)
(Jiménez, Kopecna et al 2014)[18]	eStiMaTe (PROTECT)	NR	(> 110): 176 (21)	(< 100): 34 (4.0)	NR	NR	(< 90): 185 (22)	IVC filter: 8 (0.9)
(Akgüllü, Ömürlü et al 2014)[19]	No acronym	NR	112 (54.4)		NR	NR	NR	Thrombolytic therapy 25 (12.1)
(Kundi, Balun et al 2015)[20]	No acronym	NR	NR	NR	NR	NR	NR	NR
(Maestre, Trujillo-Santos et al 2015)[21]	No acronym	< 36°2 676 (3.6)	(>110): 3693 (19.7)	(>100): 16663 (89) (<90): 589 (3.14)	NR	597 (3.2)	(< 90%): 3556 (19)	NR

(Vanni, Jiménez et al 2015)[22]	No acronym	NR	(>110): 83 (17)	(90-100): 37 (5.6)	NR	NR	(< 90%): 197 (40)	Filter: 21 (4.2)
(Ostovan, Ghaffari et al 2015)[23]	No acronym	NR	(>110) : 147 (49.1)	(<100): 53.1 (17.7)	NR	NR	(<90%): 182.4 (60.8)	NR
(Xu, Chen et al 2016)[24]	No acronym	NR	NR	NR	NR	NR	NR	NR

A4.5.2.a: Prognostic Models - External validation studies (1) including those that also updated the model: Patient characteristics.

NR: NOT REPORTED.

Author Year	Name and/ or acronym of the study model	Age median, [IQR], Range (or mean ± SD)	Male sex (%)	History of VTE (%)	Risk factors for VTE other than cancer and history of VTE (%)	Cancer (%)	Chronic cardiac disease (%)	Chronic lung disease (%)	Chronic renal disease (%)	Cerebrovascular disease (%)	Clinically stable patients (%)
(Nendaz, Bandelier et al. 2004)[25]	Geneva prognostic score (GPS)	(65.6 ± 18.3)	100 (45)	89 (40.1)	NR	34 (15.3)	CHF 26 (11.7)	COPD 16 (7.2)	NR	NR	218 (98.2)
(Aujesky, Perrier et al. 2007)[26]	PESI	64% for age > 65	382 (42)	NR	NR	109 (12)	CHF 134 (15)	75 (8)	NR	NR	874 (97.2)
(Jimenez, Yusen et al. 2007)[27]	GPS - PESI	67% for age > 65	(45.1)	(11. 0)	NR	(23.4)	CHF (8)	(10.5)	NR	NR	NR
(Donze, Le Gal et al. 2008)[28]	PESI	(64 ± 18)	158 (44)	116 (32)	Surgery 33 (9), OC 23 (6), HRT 16 (4)	33 (9)	22 (6)	42 (12)	NR	NR	NR
(Palmieri, Gallota et al 2008)[29]	PESI - cTnI - RVD	69.7% for age > 65	27 (30.3)	NR	NR	18 (20.2)	40 (44.9)	10 (11.2)	NR	NR	All (100)
(Toosi, Merlino et al. 2008)[30]	Shock Index (SI = HR/ SBP)	(58.9 ±17.7), Range 20 - 93	70 (45,2)	24 (15.5)	Surgery 28 (18.1), Major trauma 9 (5.8), OC 7 (4.5), HRT 9 (5.8), pregnancy 2 (1.3)	27 (17.4)	CAD or CHF 27 (17.4)	COPD 18 (11.6)	NR	Stroke 19 (12.2)	NR
(Bova, Pesavento et al. 2009)[31]	GPS + 5 prognostic markers (TELESIO)	(68.2 ± 17.5)	83 (41.3)	NR	Surgery or trauma 36 (17.9)	44 (21.9)	CHF 20 (10), CAD 14 (7)	20 (10)	NR	Stroke 7 (3.5)	All (100)
(Choi, Kwon et al. 2009)[32]	PESI	(60.4±16)	37 (41.1)	NR	Surgery 26 (28.9)	16 (17.8)	NR	Emphysema 9 (10)	NR	Stroke 10 (11.1)	NR

(Kukla, Bryniarski et al 2009)[33]	2008-ESC	(65.1 ± 15.3)	81 (39.5)	NR	Obesity 64 (31.2), immobilisation 57 (27.8)	15 (7.3)	23 (11.2)	NR	NR	NR	167 (81.5)
(Nordenholz, Ryan et al. 2009)[34]	PESI - Pulse oximetry	No AE: 53 [40–66], AE: 58 [41–72]	72 (43)	NR	NR	56 (33.33)	CHF 6 (3.6)	COPD 9 (5.4)	NR	NR	NR
(Subramaniam, Mandrekar et al 2009)[35]	Geneva prognostic score	58, [IQR NR], Range 16 - 96	239 (45.7)	75 (14.4)	NR	94 (18)	NR	NR	NR	NR	NR
(Chan CM, Woods C, Shorr AF. 2010 & 2012)[36 37]	PESI - PREP	(59.7 ± 17.2)	133 (44)	67 (22.2)	Recent orthopedic surgery 22 (7.3)	76 (25.2)	CHF 76 (25.2)	72 (23.8)	NR	31 (10.3)	NR
(Jakobsson, Jimenez et al 2010)[38]	Prognostic algorithm	60.7% for age ≥ 70	448 (45.6)	NR	NR	234 (23.8)	CHF 67 (6.8)	78 (7.9)	28 (2.8)	33 (3.4)	NR
(Jimenez, Aujesky et al 2010)[10]	PESI - sPESI (simplified PESI)	67.4% for age > 65 - 24.6% for age > 80	(45.1)	NR	NR	(24.0)	CHF (6.9)	(7.4)	NR	NR	NR
(Jimenez, Aujesky et al 2010)[10]	PESI - sPESI (simplified PESI)	68.2% for age > 65 - 23.5% for age > 80	45.9	NR	NR	-19.6	CHF (14.2)	-11.1	NR	NR	NR
(Vuilleumier, Le Gal et al 2010)[39]	NTproBNP vs GPS vs PESI	72 [21–94]	61 (42)	28 (19)	Oral contraceptive 9 (6), immobilisation 22 (15), surgery 9 (6), travel 10(7)	14 (10)	CAD 10 (7),	COPD 7(5)	GFR (Median IQR; Range) (72, 53–101; 26–210)	NR	All patients
(Erkens, Gandara et al 2011)[40]	PESI - sPESI	PESI low-risk (45.9 ± 17.0), high-risk (68.1 ± 11.7)	116 (47,7)	40 (16,5)	Surgery 33 (13,6)	103 (42,4)	CHF 13 (5,3), CAD 24 (9,9)	COPD 16 (6,6)	NR	Stroke 12(4,9)	NR
(Hariharan, Takayesu & Kabrhel 2011)[41]	PESI	(57 ± 17)	115 (47)	NR	NR	79 (32)	CHF 20 (8), CAD 25 (10)	COPD 18 (7)	2 (1)	Stroke - TIA 6 (2)	NR
(Righini, Roy et al 2011)[42]	sPESI	64 y	(44.0)	116 (32.5)	NR	(9.0)	NR	NR	NR	NR	NR

(Sam, Sanchez et al 2011)[43]	Shock Index (SI = HR/ SBP)	(69.3 ± 16.1) - 25% for age > 80	536 (44)	NR	NR	282 (23)	CHF 82 (7)	94 (8)	NR	NR	NR
(Singanayagam, Scally et al 2011)[44]	PESI - Biomarkers	55.4% for age > 65	*177* (43.1)	Not included	NR	*77* (18.8)	61 (14.9)	64 (15.5)	NR	NR	All
(Spirk, Aujesky et al 2011)[45]	sPESI - cTn	21% for age >80	195 (52.8)	Reported by subgroups	Reported by subgroups	78 (21)	CHF 34 (9)	39 (11)	NR	NR	340 (92.1)
(Vanni, Nazerian et al, 2011)[46]	PESI - 2008-ESC	73,3% for age > 65	223 (43,7%)	NR	NR	160 (31,4)	CHF (6,5)	CLD (15,9)	NR	NR	483/510 (94,7)
(Venetz, Jimenez et al 2011)[47]	sPESI - PESI	67 [52–77]	6227 (40.1)	(5.5)	NR	3046 (19.6)	2459 (15.8)	2868 (18.5)	(4.4 - 4.2)	(8.9 - 9.9)	(89.4 - 89.8)
(Labyk, Ciurzyński et al 2012)[48]	2008-ESC	(64.7 ± 18.12), Range 18–97	141 (39.9)	35 (9.9)	Surgery 39 (11), trauma 25 (7), contraception 5 (1.4), pregnancy/peripartum 2 (0.56)	42 (11.9)	IHD 82 (23.2), MI 19 (5.4), CHF 51 (14.4)	COPD 29 (8)	54 (15.3)	Stroke 10 (2.8)	330 (93.5)
(Lankeit, Gomez et al 2012)[49]	sPESI - 2008-ESC	74 [61 to 80], 22% for age > 80	227 (43)	NR	NR	82 (16)	CHF 36 (6.8)	44 (8.4)	NR	NR	484 (92)
(Roca, Aursulesei et al 2012)[50]	PESI - sPESI - SI	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
(Soares, de Bastos et al 2012)[51]	PESI - CT-RVD - CT-VOI	69 (71.9) for age > 40	45 (46.9)	NR	NR	11 (11.5)	3 (3.1)	7 (7.3)	NR	NR	92 (95.8)
(Becattini, Casazza et al 2013)[52]	2008-ESC (Integrated RSM)	(70 ± 15), Range 18-96	390 (45)	180 (21)	Trauma 95 (11), Surgery within 4 weeks 99 (11), OP therapy 45 (5)	168 (19)	CHF 52 (6), CAD 137 (16)	NR	NR	NR	1515 (100%, 869 (57.4) in analysis
(Ferrer, Morillo et al 2013)[53]	Spanish - sPESI	73 [60-80], 344 (24) for > 80	669 (46)	145 (10)	Recent surgery 142 (9.8), immobilisation 284 (20)	320 (22),metastatic 142 (9.8)	CHF 83 (5.7)	COPD 120 (8.3)	NR	NR	NR

(Jo, J., M. Lee, et al. 2013)[16]	SIRS-based criteria + others	(66.4 ± 13.3)	295 (44.2)	49 (7.3)	NR	181 (27.1)	75 (11.2%)	NR	96 (14.3)	NR	NR
(Ozsu, Abul et al 2013)[54]	sPESI - cTnT - hs-cTnT	70 [55-76], 13 (11) for > 80	52 (43)	NR	Surgery (18), Immobilisation (25)	28 (23)	CHF 19 (16)	COPD 9 (7)	NR	NR	All patients (100)
(Sanchez, Trinquart et al 2013)[55]	PESI - TTE-RVD - BNP - cTnI	67 (52–77)	247 (47)	134 (25)	Recent surgery 59 (11), immobilisation 18 (3)	77 (15)	25 (5)	33 (6)	NR	NR	All patients (100)
(Choi, Cha et al 2014)[56]	PESI - CT-RVD - NT-proBNP - cTnI	68 (NR)	362 (55.1)	24 (3.6)	Surgery or trauma 187 (28.5) immobilisation 237 (36.1)	156 (23.7)	48 (7.3)	61 (9.3)	9 (1.4)	52 (7.9)	633 (96.3)
(Dellas, Tschepe et al 2014)[15]	FAST - sPESI - 2008-ESC	70 (52–76)	119 (43.9)	DVT 87 (32.1), PE 41 (15.1)	Surgery 43 (15.9), Trauma 14 (5.2)	55 (20.3)	NR	NR	76/267 (28.5)	NR	All patients (100)
(Jiménez, Kopecna et al 2014) [18]	eStiMaTe (PROTECT) - Validation in PREP cohort	68 [52–78], 98 (19) for age > 80	246 (47)	134 (25)	Recent surgery 59 (11), immobilisation 18 (3)	77 (15)	25 (5)	33 (6)	NR	NR	All patients (100)
(Ozsu, Ozlu et a 2014)[57]	sPESI - 2008-ESC (TUPEG study)	67 [52–76]	484 (45)	NR	NR	113 (10)	CHF 72 (6)	COPD 71 (7)	NR	NR	957 (89)
(Casazza, Becattini et al 2014)[58]	Registry IPER	74 [18 – 97]	550 (43)	17 (1.4)	NR	NR	NR	NR	NR	NR	NR
(Kabrhel, Okechukwu et al 2014)[59]	No acronym	(59 ± 17)	152 (51)	NR	NR	107 (36)	38 (13)	48 (16)	8 (3)	20 (7)	All 298
(Lauque, Maupas-Schwalm et al 2014)[60]	No acronym	(69.3 ± 21.4)	68 (51.5)	NR	NR	13 (9.8)	5 (3.8)	7 (5.3)	NR	NR	NR
(Tong, Zhang et al 2014)[61]	No acronym	NR	68 (42)	NR	NR	NR	NR	NR	NR	NR	153 (94.4)

(Fermann, Erkens et al 2015)[62]	No acronym	(57.7 ± 17.2)	2556 (53)	944 (19.5)	Surgery/trauma: 813 (16.8) Estrogen therapy: 430 (8.9) Immobilization: 764 (15.8)	223 (4.6)	107 (2.2)	567 (21.5)	(< 50): 404 (8.4)	229 (4.7)	All 4832
(Fernández, Bova et al 2015)[63]	No acronym	72.5 [60 - 81] (>80): 572 (14.4)	1608 (40.6)	544 (14)	Surgery : 405 (10) Immobilisation : 687 (17)	720 (18)	279 (7)	474 (12)	NR	NR	1300 (96)
(Kara, Degirmenci et al 2015)[64]	No acronym	(63 ± 17) [20 – 80]	75 (43)	NR	Surgery : 31(18) Immobility : 30(17)	28 (16)	22 (13)	40 (23)	NR	9 (5)	NR
(Kundi, Balun et al 2015)[20]	No acronym	(60 ± 16)	294 (45.5)	NR	NR	NR	NR	NR	NR	NR	NR
(Maestre, Trujillo-Santos et al 2015)[21]	No acronym	67.25 (> 80): 4772 (25.5)	8796 (47)	2838 (15.17)	Immobility 3953 (21.13) Estrogen use 957 (5.11)	3897 (20.8)	1436 (7.7)	2386 (12.7)	Cl<30 1201 (6.4)	NR	(<90): 589 (3.14)
(Mizuno, Yamamoto et al 2015)[65]	Tokyo CCU Network	(63.9 ± 17.2) (>80): 64 (21.2)	127 (42.1)	NR	NR	11 (3.6)	10 (3.3)	9 (3)	NR	NR	NR
(Vanni, Jiménez et al 2015)[22]	No acronym	(69 ± 16.5) (> 80): 124 (25)	242 (49)	64 (13)	NR	122 (25)	NR	44 (8.8)	NR	NR	All 496
(Bach, Taute et al 2016)[66]	No acronym	65 [18 – 91]	178 (49)	NR	poor mobility : 65 (17.8)	111 (34)	NR	66 (18)	NR	NR	NR
(Becattini, Agnelli et al 2016)[67]	No acronym	(68 ± 16) [18 – 98]	417 (46)	NR	Recent surgery 78 (9) Recent trauma 46 (6)	174 (19)	NR	108 (12)	NR	NR	801 (89)
(Cordeanu, Gaertner et al 2016)[68]	REMOTEV Register	(65.9 ± 17.6)	49 (8)	NR	NR	(14)	NR	NR	NR	NR	NR
(Hobohm, Hellenkamp et al 2016)[69]	No acronym	70.5 [54 - 77]	179 (46.1)	122 (31.4)	Immobilisation, trauma or surgery: 121 (31.2)	60 (15.5)	64 (16.5)	53 (13.7)	118 (30.4)	NR	NR

(Jimenez, Lobo et al 2016)[70]	PROTECT	72 [59 – 80] (>80): 184 (21.7)	416 (49)	121 (14.3)	Surgery: 89(10.5) Immobilisation: 167 (19.7)	144 (17)	51 (6)	108 (12.7)	NR	NR	All 848
(Masotti, Panigada et al 2016)[71]	TUSCAN-PE	(75.3 ± 12.8)	129 (41.6)	NR	NR	NR	NR	NR	NR	NR	NR
(Masotti, Verdiani et al 2016)[72]	TUSCAN-PE	(75.8± 12.5)	105 (40.4)	NR	NR	NR	NR	NR	NR	NR	NR
(Ostovan, Ghaffari et al 2015)[23]	No acronym	(62.4 ± 17.2)	153 (51)	NR	NR	14 (4.7)		27.9 (9.3)		NR	NR
(Rozjabek, Coleman et al 2016)[73]	No acronym	(64.4 ± 16.5) (>80): 104 (18.2)	260 (45.4)	NR	NR	178 (31.1)	38 (6.6)	135 (23.6)		NR	NR
(Vanni, Nazerian et al 2016)[74]	No acronym	74 [64 – 81]	495 (49.8)	121 (12.2)	Immobilisation: 174 (17.5)	283 (28.4)	NR	NR	NR	NR	All

A4.5.2.b: Prognostic Models - External validation studies (2) including those that also updated the model: Patient characteristics.

NR: NOT REPORTED.

Author Year	Name and/ or acronym of the study model	Temperature (°C)	Heart rate (/mn)	Systolic blood pressure (mm Hg)	Respiratory rate (/ mn)	Altered mental status	Arterial oxygen saturation (%)	Initial treatment other than usual care
(Nendaz, Bandelier et al. 2004)[25]	GPS	NR	(> 100): 60 (27%)	(< 100): 4 (1.8%)	(> 30): 19 (8.8%)	NR	NR	UFH, LMWH
(Aujesky, Perrier et al. 2007)[26]	PESI	(< 36): 24 (3%)	(≥ 110): 173 (19%)	(< 100): 25 (3%)	(≥ 30): 112 (12%)	0 (0%)	(< 90): 132 (15%)	UFH, LMWH
(Jimenez, Yusen et al. 2007)[27]	GPS - PESI	(< 36): 6.2%	(> 110): 19.4%	(< 100): 8.7%	(> 30): 5%	0(0%)	(< 90): 23.7%	TL (hemodyn impairment) depending on physiscian
(Donze, Le Gal et al. 2008)[28]	PESI	(< 36): 8 (2%)	(≥ 110): 58 (16%)	(< 100): 14 (4%)	(≥ 30): 51 (14%)	13 (4%)	(< 90): 58 (16%)	TL 8
(Palmieri, Gallota et al 2008)[29]	PESI - cTnI - RVD	(< 36): none	(> 100): 37 (41.6%)	(< 100): 6 (6.7%)	(> 30): 42 (47.2%)	None	(< 90): 40 (44.9)	Usual care (anticogulants)
(Toosi, Merlino et al. 2008)[30]	Shock Index (SI = HR/ SBP)	NR	Reported by risk groups	Reported by risk groups	Reported by risk groups	NR	NR	Vasopressors 9, TL 11, embolectomy 5, CPR 9
(Bova, Pesavento et al. 2009)[31]	GPS + 5 prognostic markers (TELESIO)	NR	NR	NR	NR	NR	NR	TL 1
(Choi, Kwon et al. 2009)[32]	PESI	NR	NR	NR	NR	NR	NR	NR
(Kukla, Bryniarski et al 2009)[33]	2008-ESC	NR	NR	NR	NR	NR	NR	During hospitalisation: TL 20 (9.8), Surgery 15 (7.3) with 9 saddle PE

(Nordenholz, Ryan et al. 2009)[34]	PESI - Pulse oximetry	Continuous by subgroup	Continuous by subgroup	Continuous by subgroup	Continuous by subgroup	10 (5.9%)	(< 90): 18 (10.7%)	Heparin 166 (98.8%), IVC Filter 16 (9.5%)
(Subramaniam, Mandrekar et al 2009)[35]	GPS	NR	NR	NR	NR	NR	NR	NR
(Chan CM, Woods C, Shorr AF. 2010 & 2012)[36 37]	PESI - PREP	NR	NR	NR	NR	NR	NR	LMWH 226 (75%), UFH 65 (22%), TL 3 (1%), IVC filter 8 (2%)
(Jakobsson, Jimenez et al 2010)[38]	Prognostic algorithm	NR	(≥110): 179 (18.2%)	(< 100): 81 (8.2%)	NR	12 (1.2%)	(< 90): 249 (25.3%)	IVC filter, TL (2.7%) (depending on attending physician)
(Jimenez, Aujesky et al 2010)[10]	PESI - sPESI (simplified PESI)	(< 36): 9.5%	(≥ 110): 18.4%	(< 100): 8.9%	(≥ 30): 6.8%	0.2%	(< 90): 25.8%	Anticoagulants, IVC interrution, TL (depends on attending physician)
(Jimenez, Aujesky et al 2010) [10]	PESI - sPESI (simplified PESI)	(< 36): 9.3%	(≥ 110): 23.4%	(< 100): 7.0%	NR	NR	(< 90): 24.4%	Anticoagulants, IVC interrution, TL (depends on attending physician)
(Vuilleumier, Le Gal et al 2010)[39]	NTproBNP vs GPS vs PESI	NR	(Median IQR; Range): 92 (80–101;50–180)	(Median IQR; Range):140 (120–151; 90–230)	NR	NR	NR	NR
(Erkens, Gandara etal, 2011)[40]	PESI - sPESI	(< 36): 11 (4,5%)	(> 110): 57 (23,5%)	(< 100): 15 (6,2%)	(≥ 30): 16 (6,6%)	5 (2,06%)	(< 90): 34 (14%)	LMWH 209 (86%), UFH 32 (13,2%), TL 2 (0,8%)
(Hariharan, Takayesu & Kabrhel, 2011)[41]	PESI	Highest ºF: 98.6 [98.1–99.2]	Highest 94 [81–111]	Lowest: 108 [97–124]	Highest 20 [20–24]	NR	Lowest 95% [93%-97%]	NR
(Righini, Roy et al 2011)[42]	sPESI	NR	NR	(< 100): 4%	NR	NR	NR	TL: 8 (2%)
(Sam, Sanchez et al 2011)[43]	Shock Index (SI = HR/ SBP)	(< 36): 126 (10%)	(≥ 110): 226 (19%) - (92.5 ± 19.5)	(< 100): 103 (8%) - (128.8 ± 25.7)	(≥ 30): 86 (7%)	17 (1%)	(< 90): 300 (25%)	TL 38 (3%), IVC filter 22 (1.2%)

(Singanayagam, Scally et al, 2011)[44]	PESI - Biomarkers	NR	(> 110): 113 (27.4%)	NR	> 30/ mn: 69 (16.8)	NR	(< 90): 33 (8.1%)	Standard treatment
(Spirk, Aujesky et al 2011)[45]	sPESI - cTn	NR	(> 110): 113 (32%)	(< 100): 31 (8%)	NR	NR	(< 90): 116 (35%)	By subgroups. Parenteral anticoagulation in 95 - 99 %
(Vanni, Nazerian et al, 2011)[46]	PESI - 2008-ESC	(< 36): 5,8%	(≥110): 22,2%	(< 100): 6,5%	(> 30): 6,7%	17 (3,3%)	(< 90): 26,2%	UFH - LMWH - OAC, TL 40 (7,8%)
(Venetz, Jimenez et al 2011)[47]	sPESI - PESI	(< 36): 2575 (16.6%)	(> 110): 2742 (17.7%)	(< 100): 1624 (10.5%)	(< 30): 2261 (14.6%)	1131 (7.3%)	(< 90): 1235 (8.0%)	NR
(Labyk, Ciurzyński et al 2012)[48]	2008-ESC	NR	NR	NR	NR	NR	NR	TL (High risk 9, Intermediate risk > 13, low-risk 2), embolectomy 1
(Lankeit, Gomez et al 2012)[49]	sPESI - 2008-ESC	(< 36): 77 (15%)	(> 110): 131 (25%)	(< 100): 69 (13%)	(≥ 30): 47 (8.9%)	12 (2.3%)	(< 90): 134 (25%)	Anticoagulants (89,5%), TL 47 (9%), IVC filter 8 (1,5%)
(Roca, Aursulesei et al 2012)[50]	PESI - sPESI - SI	NR	NR	NR	NR	NR	NR	NR
(Soares, de Bastos et al 2012)[51]	PESI - CT-RVD - CT-VOI	0 (0) for < 36° C	(>110): 11 (11.5)	(<90): 2 (2.1)	(>30): (5.2)	3 (3.1)	(<90): 9 (9.4)	Unclear
(Becattini, Casazza et al 2013)[52]	2008-ESC (Integrated RSM)	NR	98 ± 21	131 ± 21	NR	NR	NR	TL 87 (10)
(Ferrer, Morillo et al 2013)[53]	Spanish - sPESI	NR	(> 110): 285 (20)	(<100): 118 (8.1)	NR	NR	(<90): 359 (25)	TL 64 (4), Filter 28 (1.8)
(Jo, J., M. Lee, et al. 2013)[16]	SIRS-based criteria + other criteria	(> 38.3 or < 36): 15 (2.2)	187 (28.0)	121.8 ± 20.6	(> 20): 248 (37.1)	65 (9.7)	NR	NR

(Ozsu, Abul et al 2013)[54]	sPESI - cTnT - hs-cTnT	NR	(> 110): 30 (25)	(< 100): 14 (12)	NR	NR	(< 90): 21 (19)	NR
(Sanchez, Trinquart et al 2013)[55]	PESI - TTE-RVD - BNP - cTnI	NR	(> 110): 68 (13), 88 (75–100)	(< 100): 6 (1.1), 134 (120–150)	NR	7 (1)	(< 90): 35 (6.6)	IVC filter: 22 (4.1)
(Choi, Cha et al 2014)[56]	PESI - CT-RVD - NT-proBNP - cTnI	NR	(> 110): 106 (16.1)	(< 90): 24 (3.6)	NR	NR	NR	TLs 40 (6.1)
(Dellas, Tschepe et al 2014)[15]	FAST - sPESI - 2008-ESC	NR	88 (74–106)	NR	NR	NR	NR	Anticoagulants (81.5), Recanalisation treatment 50 (18.5)
(Jiménez, Kopecna et al 2014)[18]	eStiMaTe (PROTECT) - Validation in PREP cohort	NR	(> 110): 68 (13)	(< 100): 6 (1.1)	NR	7 (1)	(< 90): 35 (6.6)	IVC filter: 22 (4.1)
(Ozsu, Ozlu et a 2014)[57]	sPESI - 2008-ESC (TUPEG study)	NR	95 [85–110]	120 [106–130]	22 [18–25]	NR	92 [88 - 95]	TL 108 (10)
(Casazza, Becattini et al 2014)[58]	IPER Registry	NR	NR	NR	NR	NR	NR	172 (13.5)
(Kabrhel, Okechukwu et al 2014)[59]	No acronym	NR	NR	NR	NR	NR	NR	NR
(Lauque, Maupas-Schwalm et al 2014)[60]	No acronym	NR	NR	NR	NR	NR	NR	NR
(Tong, Zhang et al 2014)[61]	No acronym	NR	NR	NR	NR	NR	NR	NR
(Fermann, Erkens et al 2015)[62]	No acronym	NR	(> 100): 398 (8)	(< 100): 120 (2.5)	NR	NR	(< 90): 118 (2.4)	Rivaroxaban, standard therapy

(Fernández, Bova et al 2015)[63]	No acronym	NR	(> 110): 450 (11.4) 765 (19)	(90-100): 139 (3.5) 253 (6)	NR	NR	(< 90): 923 (23)	NR
(Kara, Degirmenci et al 2015)[64]	No acronym	NR	Survival (158) : 99 ± 24 Death (15) : 122 ± 25	Survival (158) :109 ±17 Death (15) : 90 ±14	NR	NR	NR	NR
(Kundi, Balun et al 2015)[20]	No acronym	NR			NR	NR	NR	NR
(Maestre, Trujillo-Santos et al 2015)[21]	No acronym	(< 36°2): 676 (3.6)	(>110): 3693 (19.7)	(>100): 16663 (89) (<90): 589 (3.14)	NR	597 (3.2)	(< 90%): 3556 (19)	NR
(Mizuno, Yamamoto et al 2015)[65]	Tokyo CCU Network	(<36): 49 (16.2)	(>110): 85 (28.1)	(<100): 51 (16.9)	(>30): 37 (12.3)	30 (9.9)	(<90%): 57 (18.9)	NR
(Vanni, Jiménez et al 2015)[22]	No acronym		(>110): 83 (17)	(90-100): 37 (5.6)	NR	NR	(< 90%): 197 (40)	Filter: 21 (4.2)
(Bach, Taute et al 2016)[66]	No acronym	37.0 (36.9–37.5)	107 (90–130)	109 (100–111)	23 (21–31)		92 (87–98)	
(Becattini, Agnelli et al 2016)[67]	No acronym	NR	NR	NR	NR	NR	NR	87 (11)
(Cordeanu, Gaertner et al 2016)[68]	REMOTEV register	NR	NR	NR	NR	NR	NR	DOA (66) VKA (19) LMWH/ antiXa (15.5)
(Hobohm, Hellenkamp et al 2016)[69]	No acronym	NR	(> 134): (34.5)		NR	NR	(<90%): 89 (26.9)	
(Jimenez, Lobo et al 2016)[70]	PROTECT	NR	(< 111): 176 (20.7)	90–100 34 (4.0)	NR	NR	(< 90%): 185 (21.8)	Filter: 8 (0.9)

(Masotti, Panigada et al 2016)[71]	TUSCAN-PE	NR	NR	NR	NR	NR	NR	NR
(Masotti, Verdiani et al 2016)[72]	TUSCAN-PE	NR	NR	NR	NR	NR	NR	NR
(Ostovan, Ghaffari et al 2015)[23]	No acronym	NR	(>110) : 147 (49.1)	(<100): 53.1 (17.7)	NR	NR	(<90%): 182.4 (60.8)	NR
(Rozjabek, Coleman et al 2016)[73]	No acronym	(<36): 145 (25.3)	(>110): 124 (21.6)	(<100): 27 (4.7)	13 (2.3)	29 (5.1)	(<90%): 25 (4.4)	NR
(Vanni, Nazerian et al 2016)[74]	No acronym	NR	(>110): 213 (21.4)	(90-100): 57 (5.7)	NR	NR	(< 90%): 344 (34.6)	NR

A4.5.3.A: PROGNOSTIC MODELS – UPDATE STUDIES (1): PATIENT CHARACTERISTICS.

NR: NOT REPORTED

Author Year	Name and/ or acronym of the study model	Age: median, [IQR], Range (or mean ± SD)	Male sex (%)	History of VTE (%)	Risk factors for VTE other than cancer and history of VTE (%)	Cancer (%)	Chronic cardiac disease (%)	Chronic lung disease (%)	Chronic renal disease (%)	Cerebrovascular disease (%)	Clinically stable patients (%)
(Palmieri, Gallota et al 2008)[29]	PESI + cTnI + RVD	69.7% for age > 65	27 (30.3)	NR	NR	18 (20.2)	40 (44.9)	10 (11.2)	NR	NR	All
(Toosi, Merlino et al. 2008)[30]	Shock Index (SI = HR/ SBP)	(58.9 ±17.7), Range 20 - 93	70 (45,2)	24 (15.5)	Surgery 28 (18.1), Major trauma 9 (5.8), OC 7 (4.5), HRT 9 (5.8), pregnancy 2 (1.3)	27 (17.4)	CAD or CHF 27 (17.4)	COPD 18 (11.6)	NR	Stroke 19 (12.2)	NR
(Moores, Aujesky et al. 2010)[75]	PESI + cTn	74% for age > 65	245 (43)	59 (10)	Surgery 51 (9), Immobility ≥ 4 d 117 (21)	93 (16)	CHF 50 (9)	48 (8)	NR	NR	All
(Singanayagam, Chalmers et al 2010)[76]	PESI - CT-RVD	55.4% for age > 65	*N* (43)	Not included	NR	*N* (18.8)	CHF (14.9)	Chronic lung disease (15.4)	NR	NR	NR
(Jimenez, Aujesky et al 2011)[77]	PESI - RVD, cTnI, US-DVT	74 (65 to 82), 74% for age > 65	254 (43)	59 (10)	52 (8.8)	95 (16)	51 (8.6)	51 (8.6)	NR	NR	All
(Lankeit, Jimenez et al 2011)[78]	sPESI - hscTnT	71 [55–79]	266 (51)	115 (21.9)	Immobilisation 14 d: 131 (25.0)	85 (16.2)	CHF: 61 (11.6)	67 (12.8)	175 (33.3)	NR	All
(Sanchez, de Miguel et al 2011)[79]	sPESI - cTnI	69 ± 16	579 (44,8)	128 (9.9)	Surgery: 127 (9.8), immobilsation 262 (20)	301 (23)	85 (6.6)	101 (7.8)	NR	NR	Unclear
(Singanayagam, Scally et al, 2011)[44]	PESI - Biomarkers	55.4% for age > 65	*177* (43.1)	Not included	NR	*77* (18.8)	61 (14.9)	64 (15.5)	NR	NR	All

(Spirk, Aujesky et al 2011)[45]	sPESI - cTn	21% for age > 80	195 (52.8)	Reported by subgroups	Reported by subgroups	78 (21)	CHF 34 (9)	39 (11)	NR	NR	340 (92.1)
(Jo, J., M. Lee, et al. 2013)[16]	PESI - SIRS-based criteria + others	66.4 (± 13.3)	295 (44.2)	49 (7.3)	NR	181 (27.1)	75 (11.2%)	NR	96 (14.3)	NR	NR
(Ozsu, Abul et al 2013)[54]	sPESI - cTnT - hs-cTnT	70 [55-76], 13 (11) for > 80	52 (43)	NR	Surgery (18), Immobilisation (25)	28 (23)	CHF 19 (16)	COPD 9 (7)	NR	NR	All patients (100)
(Sanchez, Trinquart et al 2013)[55]	PESI - TTE-RVD - BNP - cTnI	67 (52–77)	247 (47)	134 (25)	Recent surgery 59 (11), immobilisation 18 (3)	77 (15)	25 (5)	33 (6)	NR	NR	All patients (100)
(Barra, Paiva et al 2014)[80]	sPESI - AF	70.1±15.8	57 (40.1)	63 (23.3)	NR	60 (22.2)	CHF 63 (23.3), history AF 57 (21.1)	NR	NR	45 (16.7)	NR
(Choi, Cha et al 2014)[56]	PESI - CT-RVD - NT-proBNP - cTnI	68 (not provided)	362 (55.1)	24 (3.6)	Surgery or trauma 187 (28.5), immobilisation 237 (36.1)	156 (23.7)	48 (7.3)	61 (9.3)	9 (1.4)	52 (7.9)	633 (96.3)
(Lankeit, Jiménez et al 2014)[81]	sPESI - NTproBNP - TTE-RVD	70 (54–78)	326 (47.4)	153 (22.3)	Trauma Major surgery 117 (17.0), Immobilisation 198 (28.8)	113 (16.4)	CHF 68 (9.9)	87 (12.6)	222 (30.8)	NR	All (100)
(Akgüllü, Ömürlü et al 2014)[19]	No acronym	(61.8 ± 11.8)	97 (47)	35 (17)	Smoking: 89 (43.2)	43 (21)		58 (28)	NR	NR	NR
(Lauque, Maupas-Schwalm et al 2014)[60]	No acronym	(69.3 ± 21.4)	68 (51.5)	NR	NR	13 (9.8)	5 (3.8)	7 (5.3)	NR	NR	NR
(Hakemi, Alyousef et al 2015)[82]	No acronym	(56 ± 13)	151 (51)	NR	Postoperative: 16 (5) Sepsis: 13 (4)	68 (23)	28 (9)	29 (10)	21 (7)	NR	NR
(Vanni, Jiménez et al 2015)[22]	No acronym	(69 ± 16.5 (> 80): 124 (25)	242 (49)	64 (13)	NR	122 (25)	NR	44 (8.8)	NR	NR	All 496

(Vanni, Nazerian et al 2016)[74]	No acronym	74 [64 – 81]	495 (49.8)	121 (12.2)	Immobilisation: 174 (17.5)	283 (28.4)	NR	NR	NR	NR	All

A4.5.3.b: Prognostic models – Update studies (2): Patient characteristics.

NR: NOT REPORTED

Author Year	Name and/ or acronym of the study model	Temperature (°C)	Heart rate (/mn)	Systolic blood pressure (mm Hg)	Respiratory rate (/ mn)	Altered mental status	Arterial oxygen saturation (%)	Initial treatment other than usual care
(Palmieri, Gallota et al 2008)[29]	PESI + cTnI + RVD	(< 36): none	(> 100): 37 (41.6%)	(< 100): 6 (6.7%)	(> 30): 42 (47.2%)	None	(< 90): 40 (44.9)	Usual care (anticogulants)
(Toosi, Merlino et al. 2008)[30]	Shock Index (SI = HR/ SBP)	NR	Reported by risk groups	Reported by risk groups	Reported by risk groups	NR	NR	Vasopressors 9, TL 11, embolectomy 5, CPR 9
(Moores, Aujesky et al. 2010)[75]	PESI + cTn	NR	(≥ 100): 232 (41%)	(< 120): 187 (33%)	NR	NR	(PO2 < 60): 301 (53)	Parenteral anticoagulant, rescue TL, inotropic, IVC filter
(Singanayagam, Chalmers et al 2010)[76]	PESI - CT-RVD	NR	(> 110): (27.4%)	(<100): (11.5%)	(³ 30): (16.8%)	Confusion: (3.1%)	(< 90): (8.2%)	Thrombolysis 1.2%
(Jimenez, Aujesky et al 2011)[77]	PESI - RVD, cTnI, US-DVT	(<36): 134 (23%)	(> 110): 135 (23%)	(< 120): 192 (32%)	(≥ 30): 52 (8.8%)	4 (0.7%)	(< 90): 211 (36)	Standard treatment
(Lankeit, Jimenez et al 2011)[78]	sPESI - hscTnT	NR	90 (80–107) - (≥ 110): 117 (22.3%)	130 (115–147) - (90-100): 25 (4.8%)	NR	NR	(< 90): 96 (20.6)	Decision made by the clinician, TL 36 (6.8)
(Sanchez, de Miguel et al 2011)[79]	sPESI - cTnI	(< 36): 141 (11%)	(> 110): 246 (19)	(< 100): 109 (8.4%)	(≥ 30): 90 (7.0%)	14 (1.1%)	(< 90): 320 (24.8)	Anticoagulants 1247, TL 44 (3)
(Singanayagam, Scally et al, 2011)[44]	PESI - Biomarkers	NR	(> 110): 113 (27.4%)	NR	(> 30): 69 (16.8)	NR	(< 90): 33 (8.1)	Standard treatment
(Spirk, Aujesky et al 2011)[45]	sPESI - cTn	NR	(≥ 110): 113/358 (32%)	(< 100): 31 (8%)	NR	NR	(< 90): 116/330 (35)	Reported by subgroups (parenteral anticoagulation in 95 - 99%)
(Jo, J., M. Lee, et al.	PESI - SIRS-based	(> 38.3 or < 36): 15 (2.2)	187 (28.0)	121.8 ± 20.6	(> 20): 248 (37.1)	65 (9.7)	NR	NR

2013)[16]	criteria + others							
(Ozsu, Abul et al 2013)[54]	sPESI - cTnT - hs-cTnT	NR	(> 110): 30 (25)	(< 100): 14 (12)	NR	NR	(< 90): 21 (19)	NR
(Sanchez, Trinquart et al 2013)[55]	PESI - TTE-RVD - BNP - cTnI	NR	(> 110): 68 (13), 88 (75–100)	(< 100): 6 (1.1), 134 (120–150)	NR	7 (1)	(< 90): 35 (6.6)	IVC filter: 22 (4.1)
(Barra, Paiva et al 2014)[80]	sPESI - AF	NR	NR	NR	NR	NR	NR	NR
(Choi, Cha et al 2014)[56]	PESI - CT-RVD - NT-proBNP - cTnI	NR	(> 110): 106 (16.1)	(< 90): 24 (3.6)	NR	NR	NR	TLs 40 (6.1)
(Lankeit, Jiménez et al 2014)[81]	sPESI - NTproBNP - TTE-RVD	NR	90 (80–108), tachycardia 161 (23.4)	130 (115–147), hypotension 29 (4.2)	NR	NR	(< 90): 128 (22.0)	Early recanalisation (TL, Surgery) 64 (9.3), IVC filter 4 (0.6)
(Akgüllü, Ömürlü et al 2014)[19]	No acronym	NR	112 (54.4)	NR	NR	NR	NR	Thrombolytic therapy 25 (12.1)
(Lauque, Maupas-Schwalm et al 2014)[60]	No acronym	NR	NR	NR	NR	NR	NR	NR
(Hakemi, Alyousef et al 2015)[82]	No acronym	(< 36) : 2 (1)	99 ± 20 (> 110): 95 (32)	129 ± 23 (<100): 24 (8)	21 ± 6 (>30): 10 (3)	NR	95 ± 4 (< 90%): 23 (8)	NR
(Vanni, Jiménez et al 2015)[22]	No acronym	NR	(>110): 83 (17)	(90-100): 37 (5.6)	NR	NR	(< 90%): 197 (40)	Filter: 21 (4.2)
(Vanni, Nazerian et al 2016)[74]	No acronym	NR	(>110): 213 (21.4)	(90-100): 57 (5.7)	NR	NR	(< 90%): 344 (34.6)	NR

A4.5.4.a: Prognostic models – Impact studies (1): Patients characteristics.

NR: NOT REPORTED.

Author Year	Name and/ or acronym of the study model	Age: median, [IQR], Range (or mean ± SD)	Male sex (%)	History of VTE (%)	Risk factors for VTE other than cancer and history of VTE (%)	Cancer (%)	Chronic cardiac disease (%)	Chronic lung disease (%)	Chronic renal disease (%)	Cerebrovascular disease (%)	Clinically stable patients (%)
(Beer, Burger et al 2003)[83]	GPS - Management study (Out-of-hospital treatment)	69, range 18-96	NR	NR	NR	NR	NR	NR	NR	NR	NR
(Agterof, Schutgens et al, 2010)[84]	NTproBNP - Management study (Out-of-hospital treatment)	53.4 ± 14.3	74 (48.7)	23 (15.1)	NR	20 (13.2)	cardiac failure 1 (0.7)	COPD 8 (5.3)	NR	NR	All
(Otero, Uresandi et al, 2010)[85]	Spanish model - RCT (Early discharge group)	60 ±17.5	36 (50)	NR	Surgery 8 (11), immobilisation 8 (11.1)	3 (4.2)	NR	NR	NR	NR	All
(Otero, Uresandi et al, 2010)[85]	Spanish model - RCT (Hospitalisation group)	61.5 ± 16	29 (48)	NR	Surgery 10 (17), immobilisation 5 (8.3)	3 (5)	NR	NR	NR	NR	All
(Aujesky, Roy et al, 2011)[86]	PESI - OTPE - RCT (Outpatient group)	47 ± 16	84 (49)	31 (18)	Bed rest 14 (8), surgery 13 (8), oestrogen 39 (23), thrombophilia 7 (4)	1 (1)	2 (1)	7 (4)	Not included GFR 110 (38)	Not included	All
(Aujesky, Roy et al, 2011)[86]	PESI - OTPE - RCT (Inpatient group)	49 ± 15	85 (51)	40 (24)	Bed rest 14 (8), surgery 13 (8), oestrogen 39 (23), thrombophilia 7 (4)	3 (2)	2 (1)	6 (4)	Not included GFR 110 (34)	Not included	All
(Meyer, Vicaut et al 2014)[87]	2008-ESC - PEITHO - RCT (Tenecteplase + heparin)	70.0 [59.0–77.0] (66.5±14.7)	242 (47.8)	126 (24.9)	Surgery or major trauma 31 (6.1), immobilisation 55 (10.9), oestrogen 30 (5.9)	41 (8.1)	21 (4.2)	26 (5.1)	NR	NR	All
(Meyer, Vicaut et al 2014)[87]	2008-ESC - PEITHO - RCT (Placebo + heparin)	[70.0 (57.0–78.0] (65.8±15.9)	231 (46.3)	147 (29.5)	Surgery or major trauma 27 (5.4), immobilisation 56 (11.2), oestrogen 33 (6.6)	32 (6.4)	26 (5.2)	34 (6.8)	NR	NR	All

(Stamm, Long et al 2014)[88]	PESI - 2008-ESC - Risk stratified group	62 ± 17	275 (52)	NR	NR	95 (18)	CHF (10), MI (19)	COPD (21)	NR	NR	NR
(Stamm, Long et al 2014)[88]	PESI - 2008-ESC - Non risk stratified group	58 ± 18	191 (53)	NR	NR	155 (43)	CHF (3), MI (13)	COPD (19)	NR	NR	NR
(Ozsu, Bektas et al 2015)[89]	No acronym	71 [58 – 80] (>80): 48 (23)	82 (40)	12 (6)	Immobility: 104 (51) Surgery: 23 (12)	55 (27)	NR	NR	NR	NR	NR

A4.5.4.b: Prognostic models – Impact studies (2): Patients characteristics.

NR: NOT REPORTED.

Author Year	Name and/ or acronym of the study model	Temperature (°C)	Heart rate (/mn)	Systolic blood pressure (mm Hg)	Respiratory rate (/ mn)	Altered mental status	Arterial oxygen saturation (%)	Initial treatment other than usual care
(Beer, Burger et al 2003)[83]	GPS - Management study (Out-of-hospital treatment)	NR	NR	NR	NR	NR	NR	None (All LMWH)
(Agterof, Schutgens et al, 2010)[84]	NTproBNP - Management study (Out-of-hospital treatment)	NR	82.3 ± 14.9	144 ± 21.2	NR	NR	97.1 ± 1.9%	Usual care
(Otero, Uresandi et al, 2010)[85]	Spanish model - RCT (Early discharge group)	NR	(> 100): 14 (19%)	(< 90) : 0 (0)	NR	NR	PaO2 < 60 mmHg: 9 (17)	LMWH, OAC starting on day 10
(Otero, Uresandi et al, 2010)[85]	Spanish model - RCT (Hospitalisation group)	NR	(> 100): 13 (22%)	(< 90): 1 (1.7)	NR	NR	PaO2 < 60 mmHg:11 (27.5)	LMWH, OAC starting on day 10
(Aujesky, Roy et al, 2011)[86]	PESI - OTPE - RCT (Outpatient group)	36·9 ± 0·6	86 ± 14	136 ± 18	19 ± 4	NR	96 ± 2	Enoxaparin - OAC Duration LMWH 11·5 (12·8)
(Aujesky, Roy et al, 2011)[86]	PESI - OTPE - RCT (Inpatient group)	36·9 ± 0·6	85 ± 15	136 ± 18	19 ± 4	NR	96 ± 2	Enoxaparin - OAC Duration LMWH 8·9 (10·1)
(Meyer, Vicaut et al 2014)[87]	2008-ESC - PEITHO - RCT (Tenecteplase + heparin)	NR	94.5±17.1	130.8±18.3	21.8±5.8	NR	Oxygen supply 436 (86.2)	NR
(Meyer, Vicaut et al 2014)[87]	2008-ESC - PEITHO - RCT (Placebo + heparin)	NR	92.3±16.7	131.3±18.5	21.6±5.7	NR	Oxygen supply 421 (84.4)	NR
(Stamm, Long et al 2014)[88]	PESI - 2008-ESC - Risk stratified group	98.5 ± 1.2 °F	89.4 ± 18.0	127 ± 21	20.3 ± 4.6	NR	96.5 ± 4.3	Thrombolysis (3), IVC filter (20), ICU (17)

(Stamm, Long et al 2014)[88]	PESI - 2008-ESC - Non risk stratified group	98.6 ± 1.1 °F	86.9 ± 18.1	128 ± 20	19.6 ± 3.8	NR	96.6 ± 2.6	Thrombolysis (0), IVC filter (13), ICU (3)
(Ozsu, Bektas et al 2015)[89]	No acronym	NR	(>110): 46 (23)	NR	22 (20 - 26)	NR	94 (91–96) (<90%): 41 (21)	

A4.5.5.A: OTHER MODELS (1): PATIENT CHARACTERISTICS.

NR: not reported. Types 2 and 3 models are different from prognostic models (type1). Type 2 Models: model variables originally not specific to PE or to its prognosis. Type 3 Models: models using hospital criteria checklists.

Author Year	Name and/ or acronym of the study model	Age: median, [IQR], Range (or mean ± SD)	Male sex (%)	History of VTE (%)	Risk factors for VTE other than cancer and history of VTE (%)	Cancer (%)	Chronic cardiac disease (%)	Chronic lung disease (%)	Chronic renal disease (%)	Cerebrovascular disease (%)	Clinically stable patients (%)
Type 2											
(Bertoletti, Le Gal et al 2013)[90]	RGS - SGS - PESI	(64±17.9) - 196 (54.9) for age > 65	157 (44)	116 (32.5)	Recent surgery or fracture 41 (11.5)	33 (9.2)	CHF 20/303 (6.6)	17 (4.8)	NR	Neuro deficiency 16/303 (5.3)	NR
(Ng, Chow et al 2013)[91]	CCI-based model	71.6 [57.6–80.4]	457 (45, 42–48)	NR	NR	NR	NR	NR	NR	NR	NR
(Paiva, Providencia et al 2013)[92]	GRACE, GPS, sPESI, SI, 2008ESC	70.3 ± 15.6	85 (41.3)	NR	NR	42 (20.4)	NR	NR	NR	NR	NR
(Papaioannou, Kastanis et al. 2013)[93]	No acronym (includes CCI)	(68.6 ± …)	40 (40)	NR	NR	7 (7)	CHF 10 (10)	15 (15)	NR	11 (11)	All patients (100)
(Keller, Coldewey et al 2015)[94]	No acronym	(68.5 ± 15.3)	64.9 ± 15.0	43 (23.6)	Surgery/ trauma in last 3 months: **33 (**18.1)	37 (20.3)	NR	NR	NR	NR	175 (96.2)
(Bach, Taute et al 2016)[66]	No acronym	65 [18 – 91]	178 (49)	NR	Poor mobility : 65 (17.8)	111 (34)	NR	66 (18)	NR	NR	NR
Type3											
(Davies, Wimperis et al 2007)[95]	Davies criteria	59, range 19–91	109 (48.4)	N NR	NR	NR	NR	NR	NR	NR	NR
(Davies, Wimperis et al 2007)[95]	Davies criteria	58, range 18–85	86 (54.8)	N NR	NR	NR	NR	NR	NR	NR	NR

(Zondag, den Exter et al 2013)[96]	sPESI - Hestia criteria	43 (9) for age > 80, (58)	257 (55)	N NR (25)	Recent surgery or immobilisation (9)	69 (15)	CardioPulmonary 47 (10)	CardioPulmonary 47 (10)	NR	NR	440 (94)
(Zondag, Vingerhoets et al 2013)[97]	sPESI - CT-RVD	58 ± 17	268 (54)	Same cohort	Same cohort	Same cohort	13 (2.6)	32 (6.5%)	NR	NR	Same cohort
(den Exter, Zondag et al 2016)[98]	Hestia versus Hestia – NT-proBNP	(54 ± 15)	297 (54)	PE: 86 (15.6) DVT:58 (10.5)	Immobilization or recent surgery: 72 (13.1) Estrogen use: 95 (17.3)	37 (6.7)	4 (0.7)	23 (4.2)	NR	NR	All 550
(Weeda, Kohn et al 2016)[99]	No acronym	(64.1 ± 16.9) (> 80): 106 (18.4)	NR	NR	NR	113 (19.6)	NR	157 (27.2)	(Creatinine clearance < 30): 20 (3.5)	NR	492 (85)

A4.5.5.B: OTHER MODELS (2): PATIENT CHARACTERISTICS.

NR: not reported. Types 2 and 3 models are different from prognostic models (type1). Type 2 Models: model variables originally not specific to PE or to its prognosis. Type 3 Models: models using hospital criteria checklists.

Author Year	Name and/ or acronym of the study model	Temperature (°C)	Heart rate (/mn)	Systolic blood pressure (mm Hg)	Respiratory rate (/ mn)	Altered mental status	Arterial oxygen saturation (%)	Initial treatment other than usual care
Type 2								
(Bertoletti, Le Gal et al 2013)[90]	RGS - SGS - PESI	NR	NR	NR	NR	NR	NR	NR
(Ng, Chow et al 2013)[91]	CCI-based model	NR	NR	NR	NR	NR	NR	NR
(Paiva, Providencia et al 2013)[92]	GRACE – GPS - sPESI - SI - 2008ESC	NR	101.29 ± 21.30	122.62 ± 23.36	26.43 ± 8.67	NR	90.49 ± 6.66	TL: 19 (9.2)
(Papaioannou, Kastanis et al. 2013)[93]	No acronym (includes CCI)	NR	NR	NR	NR	NR	NR	NR
(Keller, Coldewey et al 2015)[94]	No acronym	NR	93.8	143.63	NR	NR	NR	NR
(Bach, Taute et al 2016)[66]	No acronym	37.0 (36.9–37.5)	107 (90–130)	109 (100–111)	23 (21–31)	NR	92 (87–98)	NR
Type3								
(Davies, Wimperis et al 2007)[95]	Davies criteria	NR	NR	NR	NR	NR	NR	sc Tinzaparin 175 IU/Kg OD x median 7.0, range 1–26
(Davies, Wimperis et al 2007)[95]	Davies criteria	NR	NR	NR	NR	NR	NR	sc Tinzaparin 175 IU/Kg OD x median 7.0, range 3–46

(Zondag, den Exter et al 2013)[96]	sPESI - Hestia criteria	NR	(>110): 76 (16)	(<100): 18 (4)	NR	NR	(< 90): 33 (7)	TL 5 (1), the other treaments NR
(Zondag, Vingerhoets et al 2013)[97]	sPESI - CT-RVD	NR	91 ± 19	138 ± 24	NR	NR	Same cohort	TL 16
(den Exter, Zondag et al 2016)[98]	Hestia versus Hestia – NT-proBNP (patients at low-risk)	NR	82.5 ± 15	138 ± 25	NR	NR	NR	NR
(Weeda, Kohn et al 2016)[99]	No acronym	NR	NR	NR	NR	NR	(<90): 320 (55.5)	Thrombolytic:30 (5.2)

REFERENCES

1. Wicki J, Perrier A, Perneger TV, et al. Predicting adverse outcome in patients with acute pulmonary embolism: A risk score. Thrombosis and haemostasis 2000;**84 (4)**:548-52.

2. Kostrubiec M, Pruszczyk P, Bochowicz A, et al. Biomarker-based risk assessment model in acute pulmonary embolism. European heart journal 2005;**26 (20)**:2166-72.

3. Aujesky D, Obrosky DS, Stone RA, et al. Derivation and validation of a prognostic model for pulmonary embolism. American journal of respiratory and critical care medicine 2005;**172 (8)**:1041-46.

4. Aujesky D, Obrosky DS, Stone RA, et al. A prediction rule to identify low-risk patients with pulmonary embolism. Archives of internal medicine 2006;**166 (2)**:169-75.

5. Uresandi F, Otero R, Cayuela A, et al. A clinical prediction rule for identifying short-term risk of adverse events in patients with pulmonary thromboembolism. [Spanish]. Archivos de bronconeumologia 2007;**43 (11)**:617-22.

6. Agterof MJ, Van Bladel ER, Schutgens REG, et al. Risk stratification of patients with pulmonary embolism based on pulse rate and D-dimer concentration. Thrombosis and haemostasis 2009;**102 (4)**:683-87.

7. Volschan A, Albuquerque D, Tura BR, et al. Predictors of hospital mortality in hemodynamically stable patients with pulmonary embolism. [Portuguese, Spanish, English]. Arquivos brasileiros de cardiologia 2009;**93 (2)**:135-40.

8. Yamaki T, Nozaki M, Sakurai H, et al. Presence of Lower Limb Deep Vein Thrombosis and Prognosis in Patients with Symptomatic Pulmonary Embolism: Preliminary Report. European Journal of Vascular and Endovascular Surgery 2009;**37 (2)**:225-31.

9. Zhu L, Wang C, Yang Y-h, et al. [Prognostic value of right ventricular dysfunction and derivation of a prognostic model for patients with acute pulmonary thromboembolism]. Chung-Hua Liu Hsing Ping Hsueh Tsa Chih Chinese Journal of Epidemiology 2009;**30**(2):184-8.

10. Jimenez D, Aujesky D, Moores L, et al. Simplification of the pulmonary embolism severity index for prognostication in patients with acute symptomatic pulmonary embolism. Archives of internal medicine 2010;**170 (15)**:1383-89.

11. Sanchez O, Trinquart L, Caille V, et al. Prognostic factors for pulmonary embolism: The PREP study, a prospective multicenter cohort study. American journal of respiratory and critical care medicine 2010;**181 (2)**:168-73.

12. Agterof MJ, Schutgens RE, Moumli N, et al. A prognostic model for short term adverse events in normotensive patients with pulmonary embolism. American Journal of Hematology 2011;**86 (8)**:646-49.

13. Huang CM, Lin YC, Lin YJ, et al. Risk stratification and clinical outcomes in patients with acute pulmonary embolism. Clinical Biochemistry 2011;**44**(13):1110-5.

14. Lankeit M, Friesen D, Schafer K, et al. A simple score for rapid risk assessment of non-high-risk pulmonary embolism. Clin 2013;**102**(1):73-80.

15. Dellas C, Tschepe M, Seeber V, et al. A novel H-FABP assay and a fast prognostic score for risk assessment of normotensive pulmonary embolism. Thrombosis and haemostasis 2014;**111**(5):996-1003.

16. Jo J, Lee M, Lee J, et al. Leukocytes and systemic inflammatory response syndrome as prognostic factors in pulmonary embolism patients. BMC Pulmonary Medicine 2013;**13**(1):74.

17. Bova C, Sanchez O, Prandoni P, et al. Identification of intermediate-risk patients with acute symptomatic pulmonary embolism. European Respiratory Journal 2014;**44**(3):694-703.

18. Jiménez D, Kopecna D, Tapson V, et al. Derivation and Validation of Multimarker Prognostication for Normotensive Patients with Acute Symptomatic Pulmonary Embolism. American journal of respiratory and critical care medicine 2014;**189**(6):718-26.

19. Akgüllü Ç, Ömürlü İK, Eryılmaz U, et al. Predictors of early death in patients with acute pulmonary embolism. The American journal of emergency medicine 2015;**33**(2):214-21.

20. Kundi H, Balun A, Cicekcioglu H, et al. The relation between platelet-to-lymphocyte ratio and Pulmonary Embolism Severity Index in acute pulmonary embolism. Heart & Lung: The Journal of Acute and Critical Care 2015;**44**(4):340-43.

21. Maestre A, Trujillo-Santos J, Riera-Mestre A, et al. Identification of Low-Risk Patients with Acute Symptomatic Pulmonary Embolism for Outpatient Therapy. Annals of the American Thoracic Society 2015;**12**(8):1122-9.

22. Vanni S, Jimenez D, Nazerian P, et al. Short-term clinical outcome of normotensive patients with acute PE and high plasma lactate. Thorax 2015;**70**(4):333-8.

23. Ostovan MA, Ghaffari S, Pourafkari L, et al. Modification of Simplified Pulmonary Embolism Severity Index and its Prognostic Value in Patients with Acute Pulmonary Embolism. Heart, Lung and Circulation 2016;**25**(2):184-90.

24. Xu NL, Xue H, Chen YS, et al. [Establishment and evaluation of a prognostic model for acute pulmonary embolism]. Zhonghua jie he he hu xi za zhi = Zhonghua jiehe he huxi zazhi = Chinese journal of tuberculosis and respiratory diseases 2016;**39**(4):304-10.

25. Nendaz MR, Bandelier P, Aujesky D, et al. Validation of a risk score identifying patients with acute pulmonary embolism, who are at low risk of clinical adverse outcome. Thrombosis and haemostasis 2004;**91 (6)**:1232-36.

26. Aujesky D, Perrier A, Roy PM, et al. Validation of a clinical prognostic model to identify low-risk patients with pulmonary embolism. Journal of internal medicine 2007;**261 (6)**:597-604.

27. Jimenez D, Yusen RD, Otero R, et al. Prognostic models for selecting patients with acute pulmonary embolism for initial outpatient therapy. Chest 2007;**132**(1):24-30.

28. Donze J, Le Gal G, Fine MJ, et al. Prospective validation of the Pulmonary Embolism Severity Index: A clinical prognostic model for pulmonary embolism. Thrombosis and haemostasis 2008;**100 (5)**:943-48.

29. Palmieri V, Gallotta G, Rendina D, et al. Troponin I and right ventricular dysfunction for risk assessment in patients with nonmassive pulmonary embolism in the Emergency Department in combination with clinically based risk score. Internal and emergency medicine 2008;**3 (2)**:131-38.

30. Toosi MS, Merlino JD, Leeper KV. Prognostic Value of the Shock Index Along With Transthoracic Echocardiography in Risk Stratification of Patients With Acute Pulmonary Embolism. American Journal of Cardiology 2008;**101 (5)**:700-05.

31. Bova C, Pesavento R, Marchiori A, et al. Risk stratification and outcomes in hemodynamically stable patients with acute pulmonary embolism: a prospective, multicentre, cohort study with three months of follow-up. Journal of Thrombosis and Haemostasis 2009;**7**(6):938-44.

32. Choi WH, Sung UK, Yoon JJ, et al. The pulmonary embolism severity index in predicting the prognosis of patients with pulmonary embolism. Korean Journal of Internal Medicine 2009;**24 (2)**:123-27.

33. Kukla P, Bryniarski L, Dlugopolski R, et al. Acute pulmonary embolism registry in the Malopolska region - clinical course. Kardiologia polska 2009;**67**(7):735-41.

34. Nordenholz K, Ryan J, Atwood B, et al. Pulmonary embolism risk stratification: Pulse oximetry and pulmonary embolism severity index. Journal of Emergency Medicine 2011;**40 (1)**:95-102.

35. Subramaniam RM, Mandrekar J, Blair D, et al. The Geneva prognostic score and mortality in patients diagnosed with pulmonary embolism by CT pulmonary angiogram. Journal of medical imaging and radiation oncology 2009;**53 (4)**:361-65.

36. Chan CM, Woods C, Shorr AF. The validation and reproducibility of the pulmonary embolism severity index. Journal of Thrombosis and Haemostasis 2010;**8 (7)**:1509-14.

37. Chan CM, Woods CJ, Shorr AF. Comparing the pulmonary embolism severity index and the prognosis in pulmonary embolism scores as risk stratification tools. J Hosp Med 2012;**7**(1):22-27.

38. Jakobsson C, Jimenez D, Gomez V, et al. Validation of a clinical algorithm to identify low-risk patients with pulmonary embolism. Journal of Thrombosis and Haemostasis 2010;**8**(6):1242-7.

39. Vuilleumier N, Le Gal G, Cornily JC, et al. Is N-terminal pro-brain natriuretic peptide superior to clinical scores for risk stratification in non-massive pulmonary embolism? Journal of Thrombosis and Haemostasis 2010;**8**(6):1433-5.

40. Erkens PMG, Gandara E, Wells PS, et al. Does the Pulmonary Embolism Severity Index accurately identify low risk patients eligible for outpatient treatment? Thrombosis research 2012;**129 (6)**:710-14.

41. Hariharan P, Takayesu JK, Kabrhel C. Association between the pulmonary embolism severity index (PESI) and short-term clinical deterioration. Thrombosis and haemostasis 2011;**105 (4)**:706-11.

42. Righini M, Roy PM, Meyer G, et al. The Simplified Pulmonary Embolism Severity Index (PESI): Validation of a clinical prognostic model for pulmonary embolism. Journal of Thrombosis and Haemostasis 2011;**9 (10)**:2115-17.

43. Sam A, Sanchez D, Gomez V, et al. The shock index and the simplified PESI for identification of low-risk patients with acute pulmonary embolism. European Respiratory Journal 2011;**37 (4)**:762-66.

44. Singanayagam A, Scally C, Al-Khairalla MZ, et al. Are biomarkers additive to pulmonary embolism severity index for severity assessment in normotensive patients with acute pulmonary embolism? Quarterly Journal of Medicine 2011;**104**(2):125-31.

45. Spirk D, Aujesky D, Husmann M, et al. Cardiac troponin testing and the simplified pulmonary embolism severity index the swiss venous thromboembolism registry (SWIVTER). Thrombosis and haemostasis 2011;**106 (5)**:978-84.

46. Vanni S, Nazerian P, Pepe G, et al. Comparison of two prognostic models for acute pulmonary embolism: Clinical vs. right ventricular dysfunction-guided approach. Journal of Thrombosis and Haemostasis 2011;**9 (10)**:1916-23.

47. Venetz C, Jimenez D, Mean M, et al. A comparison of the original and simplified pulmonary embolism severity index. Thrombosis and haemostasis 2011;**106 (3)**:423-28.

48. Labyk A, Ciurzynski M, Jankowski K, et al. Acute pulmonary embolism: analysis of consecutive 353 patients hospitalised in a single centre. A 3-year experience. Kardiologia polska 2012;**70**(1):15-22.

49. Lankeit M, Gomez V, Wagner C, et al. A strategy combining imaging and laboratory biomarkers in comparison with a simplified clinical score for risk stratification of patients with acute pulmonary embolism. Chest 2012;**141 (4)**:916-22.

50. Roca IC, Aursulesei V, Roca M, et al. [Comparative evaluation of prognostic scores in pulmonary embolism]. Revista Medico-Chirurgicala a Societatii de Medici Si Naturalisti Din Iasi 2012;**116**(1):69-74.

51. Soares TH, de Bastos M, de Carvalho BV, et al. Prognostic value of computed tomographic pulmonary angiography and the pulmonary embolism severity index in patients with acute pulmonary embolism. Blood Coagulation & Fibrinolysis 2013;**24**(1):64-70.

52. Becattini C, Casazza F, Forgione C, et al. Acute pulmonary embolism: external validation of an integrated risk stratification model. Chest 2013;**144**(5):1539-45.

53. Ferrer M, Morillo R, Elias T, et al. Validation of two clinical prognostic models in patients with acute symptomatic pulmonary embolism. Archivos de bronconeumologia 2013;**49**(10):427-31.

54. Ozsu S, Abul Y, Orem A, et al. Predictive value of troponins and simplified pulmonary embolism severity index in patients with normotensive pulmonary embolism. Multidiscip 2013;**8**(1):34.

55. Sanchez O, Trinquart L, Planquette B, et al. Echocardiography and pulmonary embolism severity index have independent prognostic roles in pulmonary embolism. European Respiratory Journal 2013;**42**(3):681-88.

56. Choi K-J, Cha S-I, Shin K-M, et al. Prognostic implications of computed tomographic right ventricular dilation in patients with acute pulmonary embolism. Thrombosis research 2014;**133**(2):182-86.

57. Ozsu S, Ozlu T, Şentürk A, et al. Combination and comparison of two models in prognosis of pulmonary embolism: Results from TUrkey Pulmonary Embolism Group (TUPEG) study. Thrombosis research 2014;**133**(6):1006-10.

58. Casazza F, Becattini C, Guglielmelli E, et al. Prognostic significance of free-floating right heart thromboemboli in acute pulmonary embolism Results from the Italian Pulmonary Embolism Registry. Thrombosis and haemostasis 2014;**111**(1):53-57.

59. Kabrhel C, Okechukwu I, Hariharan P, et al. Factors associated with clinical deterioration shortly after PE. Thorax 2014;**69**(9):835-42.

60. Lauque D, Maupas-Schwalm F, Bounes V, et al. Predictive value of the heart-type fatty acid-binding protein and the Pulmonary Embolism Severity Index in patients with acute pulmonary embolism in the emergency department. Academic Emergency Medicine 2014;**21**(10):1143-50.

61. Tong C, Zhang Z, Ma C, et al. [The value of simplified pulmonary embolism severity index and biomarkers in evaluating pulmonary embolism prognosis]. Zhonghua jie he he hu xi za zhi = Zhonghua jiehe he huxi zazhi = Chinese journal of tuberculosis and respiratory diseases 2014;**37**(2):104-8.

62. Fermann GJ, Erkens PM, Prins MH, et al. Treatment of pulmonary embolism with rivaroxaban: outcomes by simplified Pulmonary Embolism Severity Index score from a post hoc analysis of the EINSTEIN PE study. Academic Emergency Medicine 2015;**22**(3):299-307.

63. Fernandez C, Bova C, Sanchez O, et al. Validation of a Model for Identification of Patients at Intermediate to High Risk for Complications Associated With Acute Symptomatic Pulmonary Embolism. Chest 2015;**148**(1):211-18.

64. Kara H, Degirmenci S, Bayir A, et al. Pulmonary embolism severity index, age-based markers and evaluation in the emergency department. Acta Clinica Belgica 2015;**70**(4):259-64.

65. Mizuno A, Yamamoto T, Tanabe Y, et al. Pulmonary Embolism Severity Index and Simplified Pulmonary Embolism Severity Index Risk Scores Are Useful to Predict Mortality in Japanese Patients With Pulmonary Embolism. Circulation Journal 2015;**79**(4):889-91.

66. Bach AG, Taute BM, Baasai N, et al. 30-Day Mortality in Acute Pulmonary Embolism: Prognostic Value of Clinical Scores and Anamnestic Features. PLoS One 2016;**11**(2):e0148728.

67. Becattini C, Agnelli G, Lankeit M, et al. Acute pulmonary embolism: mortality prediction by the 2014 European Society of Cardiology risk stratification model. European Respiratory Journal 2016;**48**(3):780-6.

68. Cordeanu M, Gaertner S, Faller A, et al. Prognostic value of the simplified PESI score in comparison with the 2014 ESC risk model in pulmonary embolism. International journal of cardiology 2016;**220**:623-4.

69. Hobohm L, Hellenkamp K, Hasenfuss G, et al. Comparison of risk assessment strategies for not-high-risk pulmonary embolism. European Respiratory Journal 2016;**47**(4):1170-8.

70. Jimenez D, Lobo JL, Fernandez-Golfin C, et al. Effectiveness of prognosticating pulmonary embolism using the ESC algorithm and the Bova score. Thrombosis and haemostasis 2016;**115**(4):827-34.

71. Masotti L, Panigada G, Landini G, et al. Predictive ability of the new 2014 ESC prognostic model in acute pulmonary embolism. International journal of cardiology 2016;**202**:801-03.

72. Masotti L, Verdiani V, Cei M, et al. The predictive role of the Bova risk score in acute normotensive pulmonary embolism: A retrospective analysis on a real life cohort. Thrombosis research 2016;**137**:221-23.

73. Rozjabek HM, Coleman CI, Weeda ER, et al. Effect of vital sign measurement timing on Pulmonary Embolism Severity Index (PESI) and simplified PESI 30-day mortality risk determination. Thrombosis research 2016;**141**:8-10.

74. Vanni S, Nazerian P, Bova C, et al. Comparison of clinical scores for identification of patients with pulmonary embolism at intermediate–high risk of adverse clinical outcome: the prognostic role of plasma lactate. Internal and emergency medicine 2016:1-9.

75. Moores L, Aujesky D, Jimenez D, et al. Pulmonary Embolism Severity Index and troponin testing for the selection of low-risk patients with acute symptomatic pulmonary embolism. Journal of Thrombosis and Haemostasis 2010;**8 (3)**:517-22.

76. Singanayagam A, Chalmers JD, Scally C, et al. Right ventricular dilation on CT pulmonary angiogram independently predicts mortality in pulmonary embolism. Respiratory Medicine 2010;**104**(7):1057-62.

77. Jimenez D, Aujesky D, Moores L, et al. Combinations of prognostic tools for identification of high-risk normotensive patients with acute symptomatic pulmonary embolism. Thorax 2011;**66 (1)**:75-81.

78. Lankeit M, Jimenez D, Kostrubiec M, et al. Predictive value of the high-sensitivity troponin T assay and the simplified pulmonary embolism severity index in hemodynamically stable patients with acute pulmonary embolism: A prospective validation study. Circulation 2011;**124 (24)**:2716-24.

79. Sanchez D, De Miguel J, Sam A, et al. The effects of cause of death classification on prognostic assessment of patients with pulmonary embolism. Journal of Thrombosis and Haemostasis 2011;**9 (11)**:2201-07.

80. Barra SNC, Paiva LV, Providência R, et al. Atrial fibrillation in acute pulmonary embolism: prognostic considerations. Emergency Medicine Journal 2014;**31**(4):308-12.

81. Lankeit M, Jiménez D, Kostrubiec M, et al. Validation of N-terminal pro-brain natriuretic peptide cut-off values for risk stratification of pulmonary embolism. European Respiratory Journal 2014;**43**(6):1669-77.

82. Hakemi EU, Alyousef T, Dang G, et al. The prognostic value of undetectable highly sensitive cardiac troponin I in patients with acute pulmonary embolism. Chest 2015;**147**(3):685-94.

83. Beer JH, Burger M, Gretener S, et al. Outpatient treatment of pulmonary embolism is feasible and safe in a substantial proportion of patients. Journal of Thrombosis and Haemostasis 2003;**1**(1):186-7.

84. Agterof MJ, Schutgens REG, Snijder RJ, et al. Out of hospital treatment of acute pulmonary embolism in patients with a low NT-proBNP level. Journal of Thrombosis and Haemostasis 2010;**8**(6):1235-41.

85. Otero R, Uresandi F, Jimenez D, et al. Home treatment in pulmonary embolism. Thrombosis research 2010;**126**(1):e1-5.

86. Aujesky D, Roy PM, Verschuren F, et al. Outpatient versus inpatient treatment for patients with acute pulmonary embolism: An international, open-label, randomised, non-inferiority trial. Lancet 2011;**378 (9785)**:41-48.

87. Meyer G, Vicaut E, Danays T, et al. Fibrinolysis for patients with intermediate-risk pulmonary embolism. New England Journal of Medicine 2014;**370**(15):1402-11.

88. Stamm JA, Long JL, Kirchner HL, et al. Risk Stratification in Acute Pulmonary Embolism: Frequency and Impact on Treatment Decisions and Outcomes. Southern Medical Journal 2014;**107**(2):72-78.

89. Ozsu S, Bektas H, Abul Y, et al. Value of Cardiac Troponin and sPESI in Treatment of Pulmonary Thromboembolism at Outpatient Setting. Lung 2015;**193**(4):559-65.

90. Bertoletti L, Le Gal G, Aujesky D, et al. Prognostic value of the Geneva prediction rule in patients with pulmonary embolism. Thrombosis research 2013;**132**(1):32-36.

91. Ng AC, Chow V, Yong AS, et al. Prognostic impact of the Charlson comorbidity index on mortality following acute pulmonary embolism. Respiration 2013;**85**(5):408-16.

92. Paiva LV, Providencia RC, Barra SN, et al. Cardiovascular risk assessment of pulmonary embolism with the GRACE risk score. The American journal of cardiology 2013;**111**(3):425-31.

93. Papaioannou AI, Kastanis A, Malli F, et al. Predicting short-term mortality in patients with pulmonary embolism: a simple model. American Journal of the Medical Sciences 2013;**345**(6):462-9.

94. Keller K, Coldewey M, Dippold W, et al. Simplified CRB-65 for risk stratification and predicting prognosis in acute pulmonary embolism. Phlebologie 2015;**44**(4):192-99.

95. Davies CWH, Wimperis J, Green ES, et al. Early discharge of patients with pulmonary embolism: a two-phase observational study. European Respiratory Journal 2007;**30**(4):708-14.

96. Zondag W, den Exter PL, Crobach MJT, et al. Comparison of two methods for selection of out of hospital treatment in patients with acute pulmonary embolism. Thrombosis and haemostasis 2013;**109**(1):47-52.

97. Zondag W, Vingerhoets LMA, Durian MF, et al. Hestia criteria can safely select patients with pulmonary embolism for outpatient treatment irrespective of right ventricular function. Journal of Thrombosis and Haemostasis 2013;**11**(4):686-92.

98. den Exter PL, Zondag W, Klok FA, et al. Efficacy and Safety of Outpatient Treatment Based on the Hestia Clinical Decision Rule With or Without NT-proBNP Testing in Patients With Acute Pulmonary Embolism: A Randomized Clinical Trial. American journal of respiratory and critical care medicine 2016.

99. Weeda ER, Kohn CG, Peacock WF, et al. External Validation of the Hestia Criteria for Identifying Acute Pulmonary Embolism Patients at Low Risk of Early Mortality. Clinical and Applied Thrombosis/Hemostasis 2016.

TABLES A4.6 (POPULATION EVENT RATES)

Table A4.6: Population event rates

Outcome	Haemodynamic status	N of studies	In-hospital			N of studies	30-day			N of studies	3-month		
				0.95 CI				0.95 CI				0.95 CI	
All-cause mortality	Both stable &	15	0.05	0.03	0.07	10	0.07	0.05	0.09	2	0.04	0.03	0.06
	Stable	5	0.04	0.00	0.12	9	0.07	0.05	0.09	1	0.09	0.05	0.13
	Not reported	11	0.07	0.05	0.09	11	0.06	0.04	0.08	6	0.07	0.05	0.09
	Unclear					2	0.05	0.03	0.07	3	0.06	0.03	0.09
	Overall	31	0.06	0.04	0.07	32	0.07	0.05	0.08	12	0.06	0.05	0.08
PE-related mortality	Both stable &	4	0.04	0.03	0.05	5	0.04	0.03	0.05	1	0.03	0.01	0.08
	Stable	3	0.01	0.00	0.04	5	0.04	0.02	0.06				
	Not reported	2	0.02	0.01	0.03	1	0.02	0.1	0.04	5	0.01	0.00	0.02
	Unclear					1	0.08	0.04	0.13	1	0.04	0.02	0.07
	Overall	9	0.03	0.02	0.04	12	0.04	0.03	0.05	7	0.01	0.00	0.03

VTE recurrence	**Both stable & Stable**	3	0.00	0.00	0.02	4	0.01	0.00	0.02				
	Not reported	2	0.00	0.00	0.00	1	0.01	0.00	0.02	2	0.01	0.00	0.02
	Unclear									2	0.03	0.02	0.05
	Overall									1	0.00	0.00	0.02
		5	0.00	0.00	0.01	5	0.01	0.00	0.01	5	0.01	0.00	0.03
Death VTE Major bleeding	**Both stable & Stable**	1	0.04	0.03	0.06								
	Not reported	1	0.05	0.03	0.09					1	0.09	0.06	0.14
	Unclear	2	0.03	0.03	0.03	1	0.04	0.03	0.07				
	Overall									1	0.10	0.07	0.14
		4	0.04	0.03	0.06	1	0.04	0.03	0.07	2	0.09	0.07	0.12

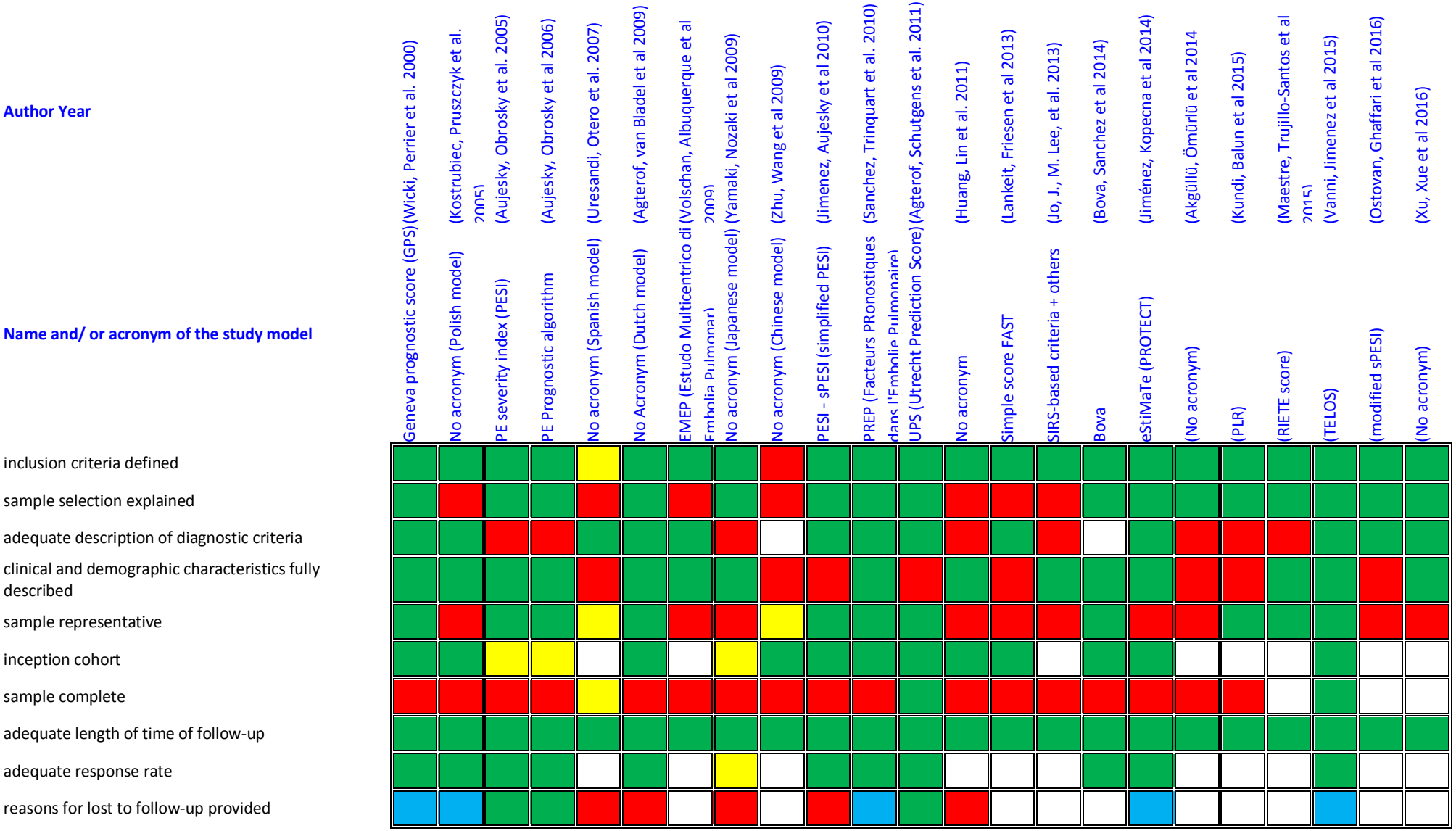
Outcome	**Haemodynamic status**	**N of studies**	**In-hospital**			**N of studies**	**30-day**			**N of studies**	**3-month**		
				0.95 CI				**0.95 CI**				**0.95 CI**	
Death Adverse outcome	**Both stable & Stable**	3	0.07	0.03	0.13	2	0.07	0.06	0.10				
	Not reported	4	0.09	0.02	0.20	1	0.21	0.14	0.30				
	Unclear	2	0.04	0.03	0.05								
	Overall												
		9	0.07	0.04	0.11	3	0.12	0.05	0.20	0			
Adverse outcome	**Both stable & Stable**	3	0.17	0.09	0.27								
	Not reported					1	0.06	0.04	0.09				
	Unclear												
	Overall												
		3	0.17	0.09	0.27	1	0.06	0.04	0.09	0			
Major bleeding	**Both stable & Stable**	3	0.02	0.00	0.04	3	0.02	0.01	0.02				
	Not reported	1	0.02	0.01	0.04					1	0.02	0.01	0.05
	Unclear	3	0.02	0.00	0.03	2	0.03	0.02	0.04	2	0.04	0.02	0.06
	Overall									1	0.01	0.00	0.02
		7	0.02	0.01	0.03	5	0.02	0.01	0.03	4	0.02	0.01	0.04
Fatal bleeding	**Both stable & Stable**	1	0.01	0.00	0.03	1	0.00	0.00	0.01				
	Not reported									1	0.01	0.00	0.03
	Unclear	1	0.00	0.00	0.01								
	Overall									1	0.00	0.00	0.01
		2	0.00	0.00	0.01	1	0.00	0.00	0.01	2	0.00	0.00	0.01

Not accounted for in the analysis of population event rates studies that included only specific risk groups. Cohorts that were used by more than one study were included once.

FIGURES A4.1 (STUDY QUALITY)

Figure A4.1.1: Study Quality - Model Construction studies

Yes (in green): meets the criteria - No (in red): does not meet the criteria - Unclear (in yellow): not clearly reported - Not applicable (in blue) - Not reported (unfilled)



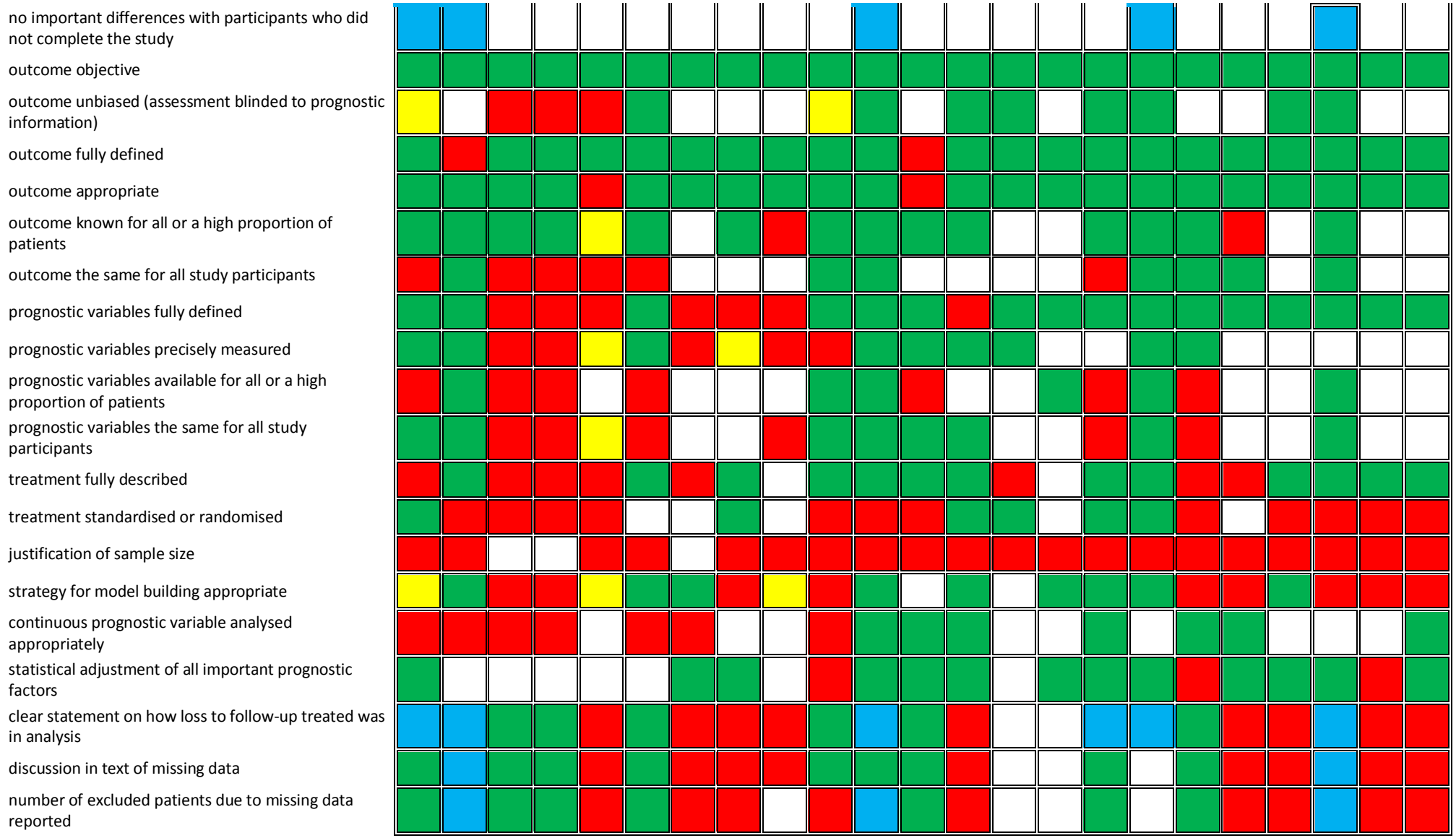

no important differences with participants who did not complete the study
outcome objective
outcome unbiased (assessment blinded to prognostic information)
outcome fully defined
outcome appropriate
outcome known for all or a high proportion of patients
outcome the same for all study participants
prognostic variables fully defined
prognostic variables precisely measured
prognostic variables available for all or a high proportion of patients
prognostic variables the same for all study participants
treatment fully described
treatment standardised or randomised
justification of sample size
strategy for model building appropriate
continuous prognostic variable analysed appropriately
statistical adjustment of all important prognostic factors
clear statement on how loss to follow-up treated was in analysis
discussion in text of missing data
number of excluded patients due to missing data reported

Figure A4.1.2: Summary of Study Quality in Model Construction Studies

Yes (in green): meets the criteria - No (in red): does not meet the criteria - Unclear (in yellow): not clearly reported - Not applicable (in blue) - Not reported (in violet)

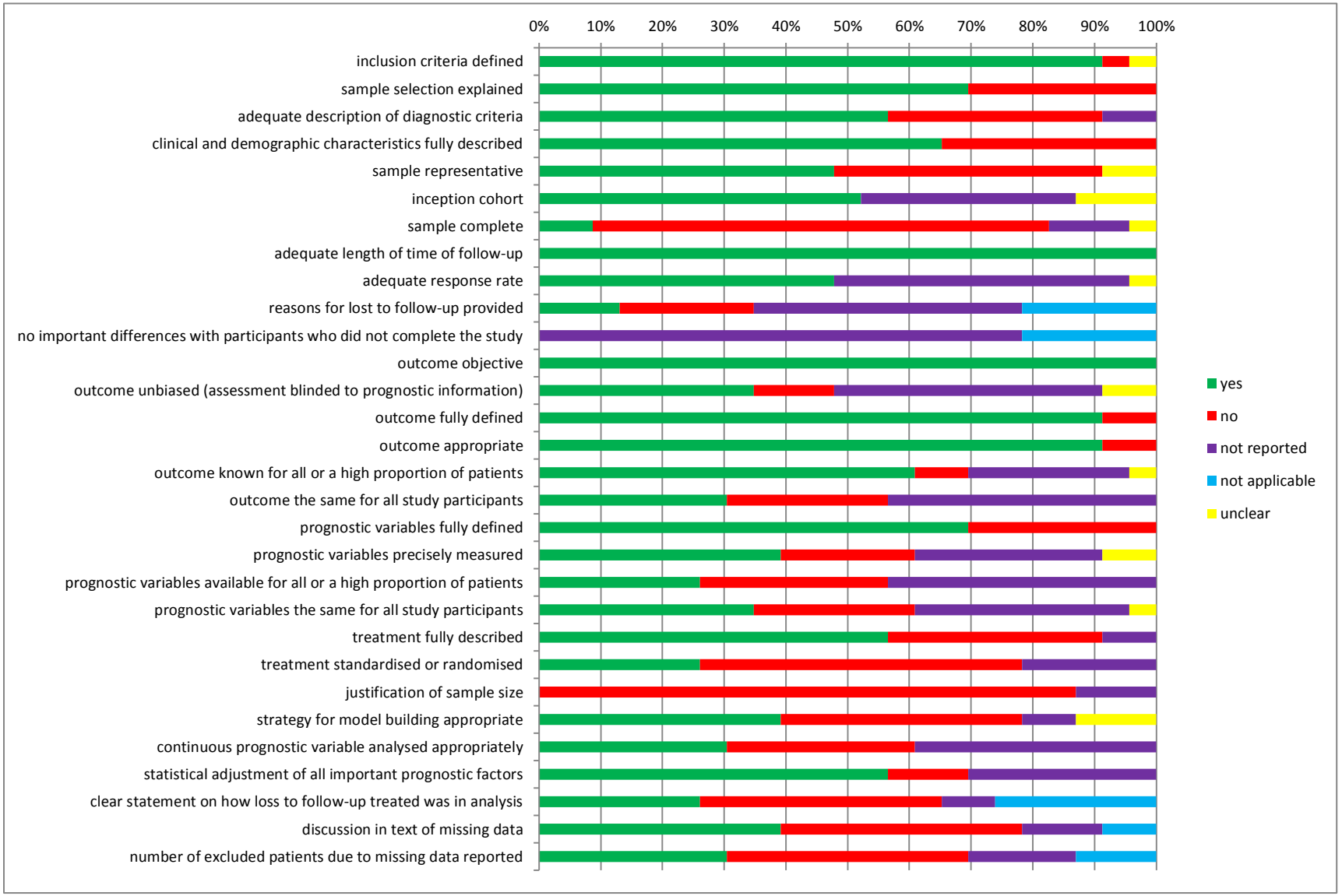
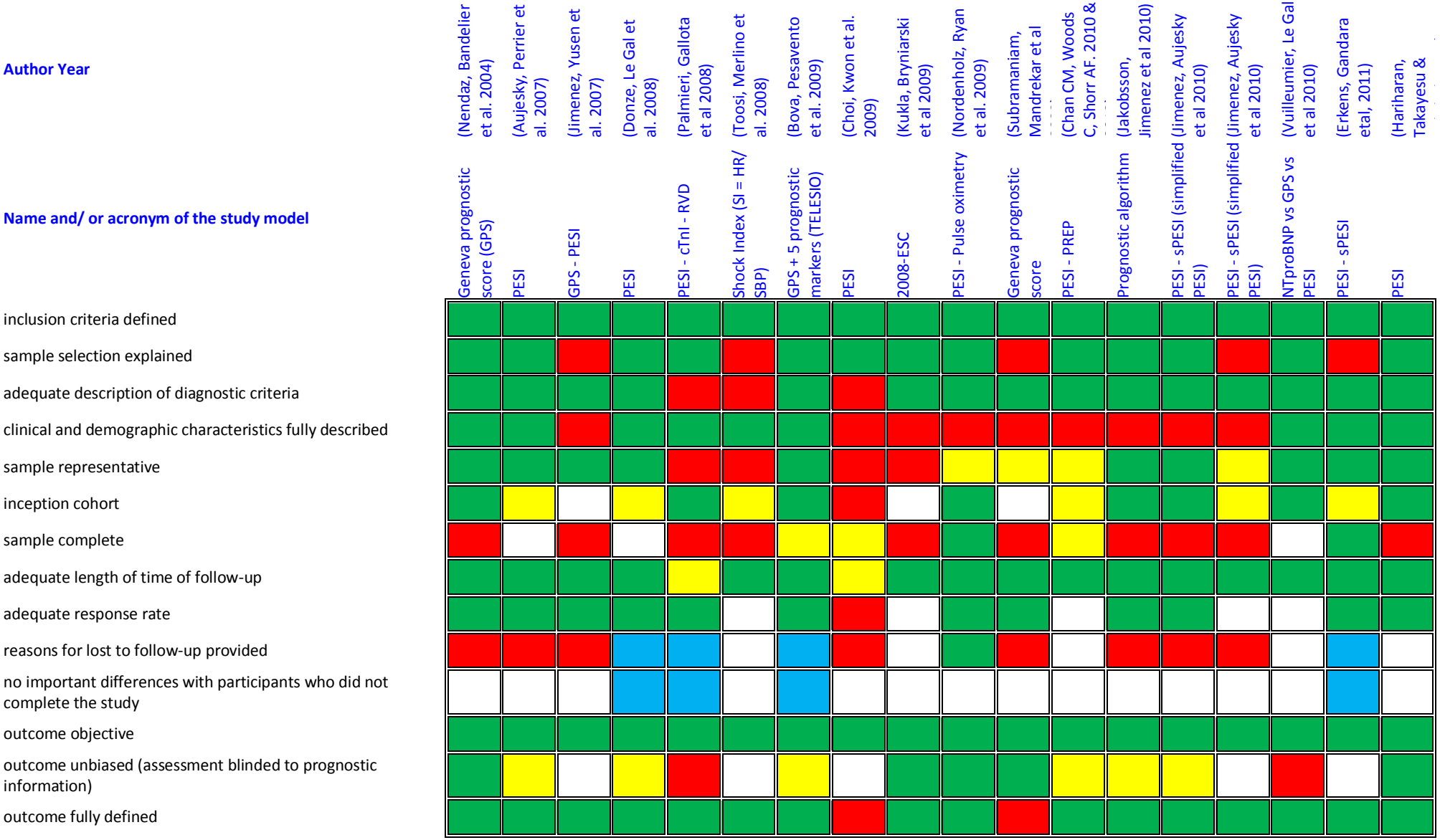


Figure A4.1.3a: Study Quality - External Validation Studies (1)

Yes (in green): meets the criteria - No (in red): does not meet the criteria - Unclear (in yellow): not clearly reported - Not applicable (in blue) - Not reported (unfilled)



outcome appropriate

outcome known for all or a high proportion of patients

outcome the same for all study participants

prognostic variables fully defined

prognostic variables precisely measured

prognostic variables available for all or a high proportion of patients

prognostic variables the same for all study participants

treatment fully described

treatment standardised or randomised

justification of sample size

strategy for model building appropriate

continuous prognostic variable analysed appropriately

statistical adjustment of all important prognostic factors

clear statement on how loss to follow-up treated was in analysis

discussion in text of missing data

number of excluded patients due to missing data reported

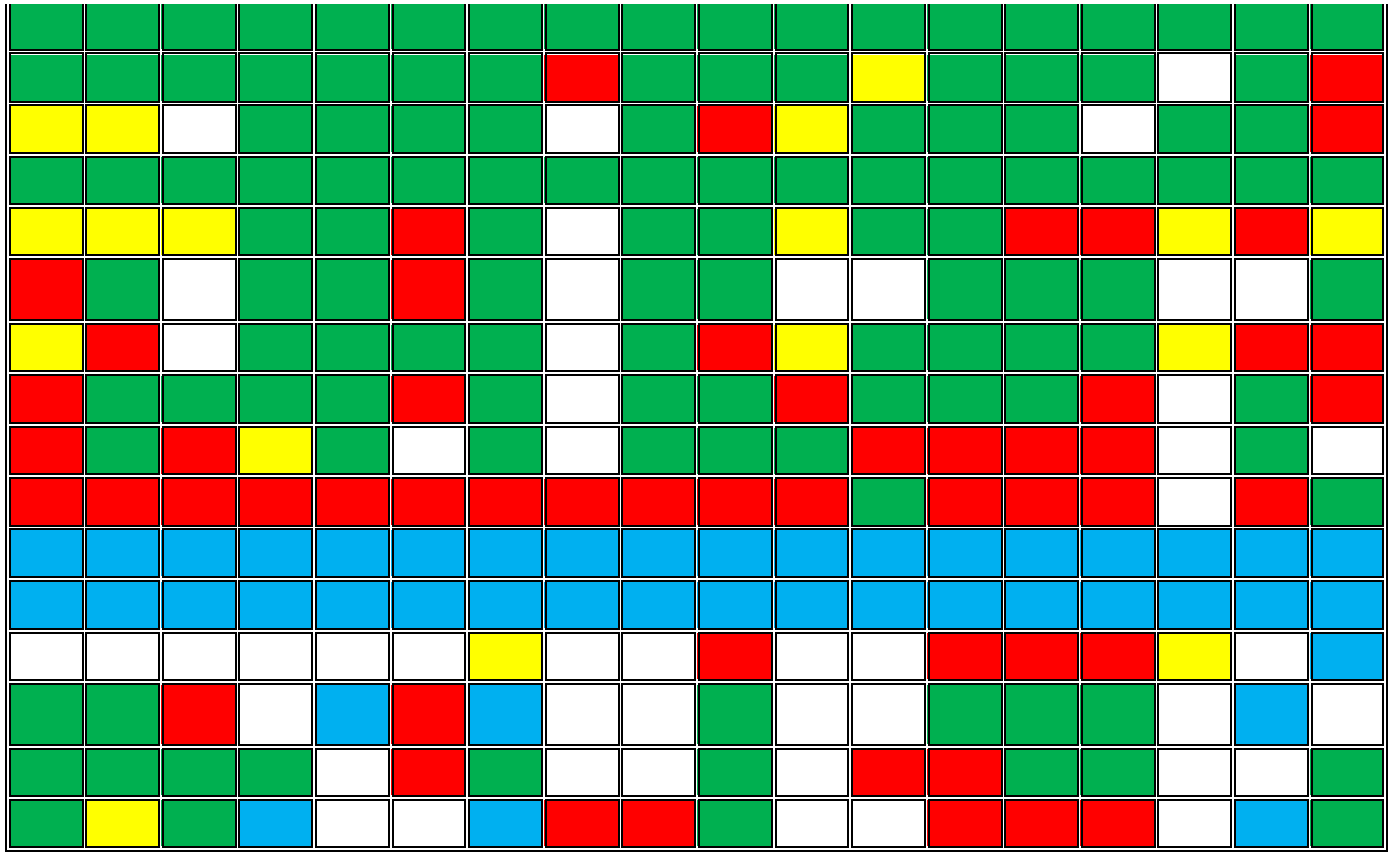
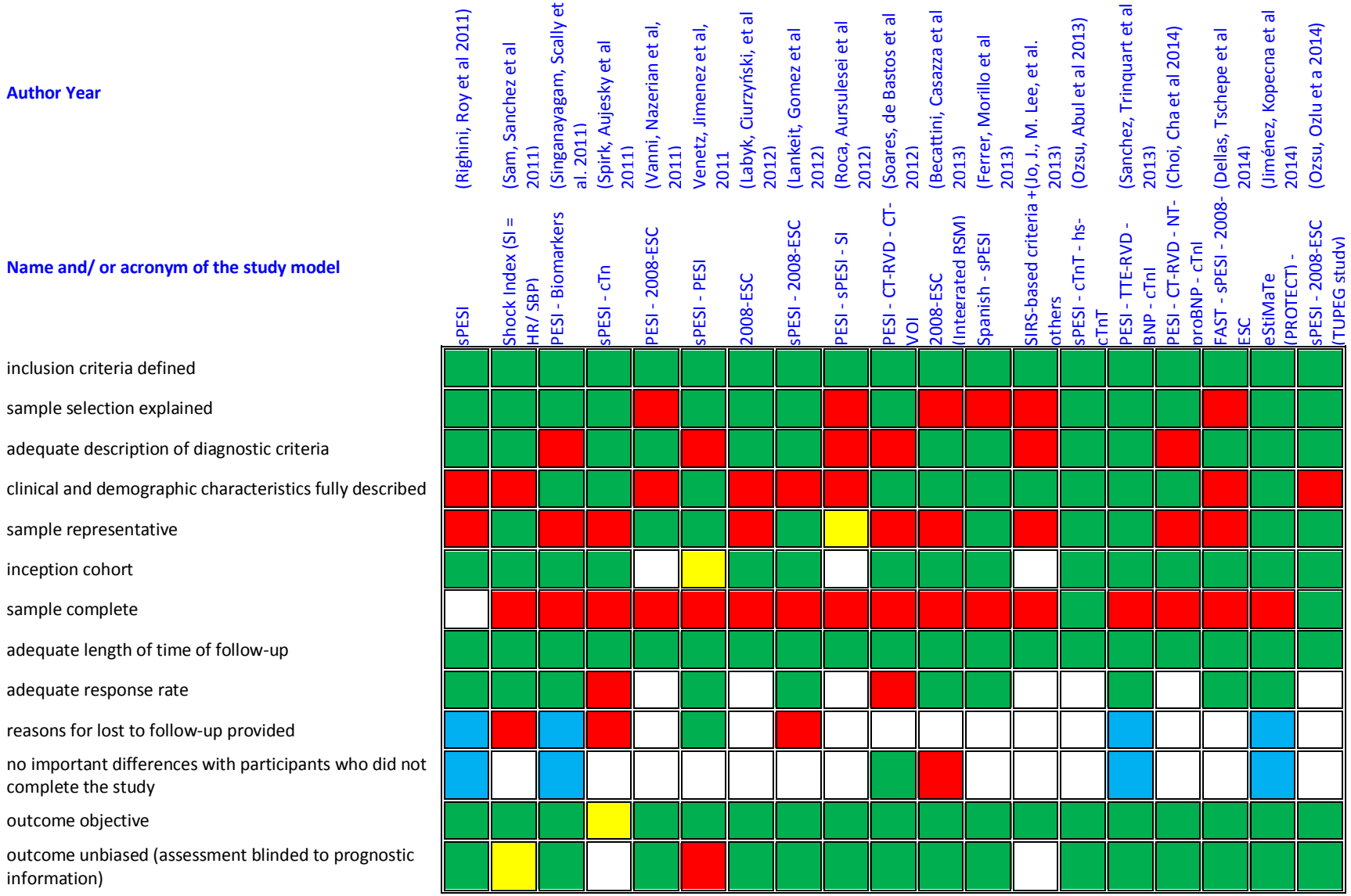


Figure A4.1.3b: Study Quality - External Validation Studies (2)

Yes (in green): meets the criteria - No (in red): does not meet the criteria - Unclear (in yellow): not clearly reported - Not applicable (in blue) - Not reported (unfilled)



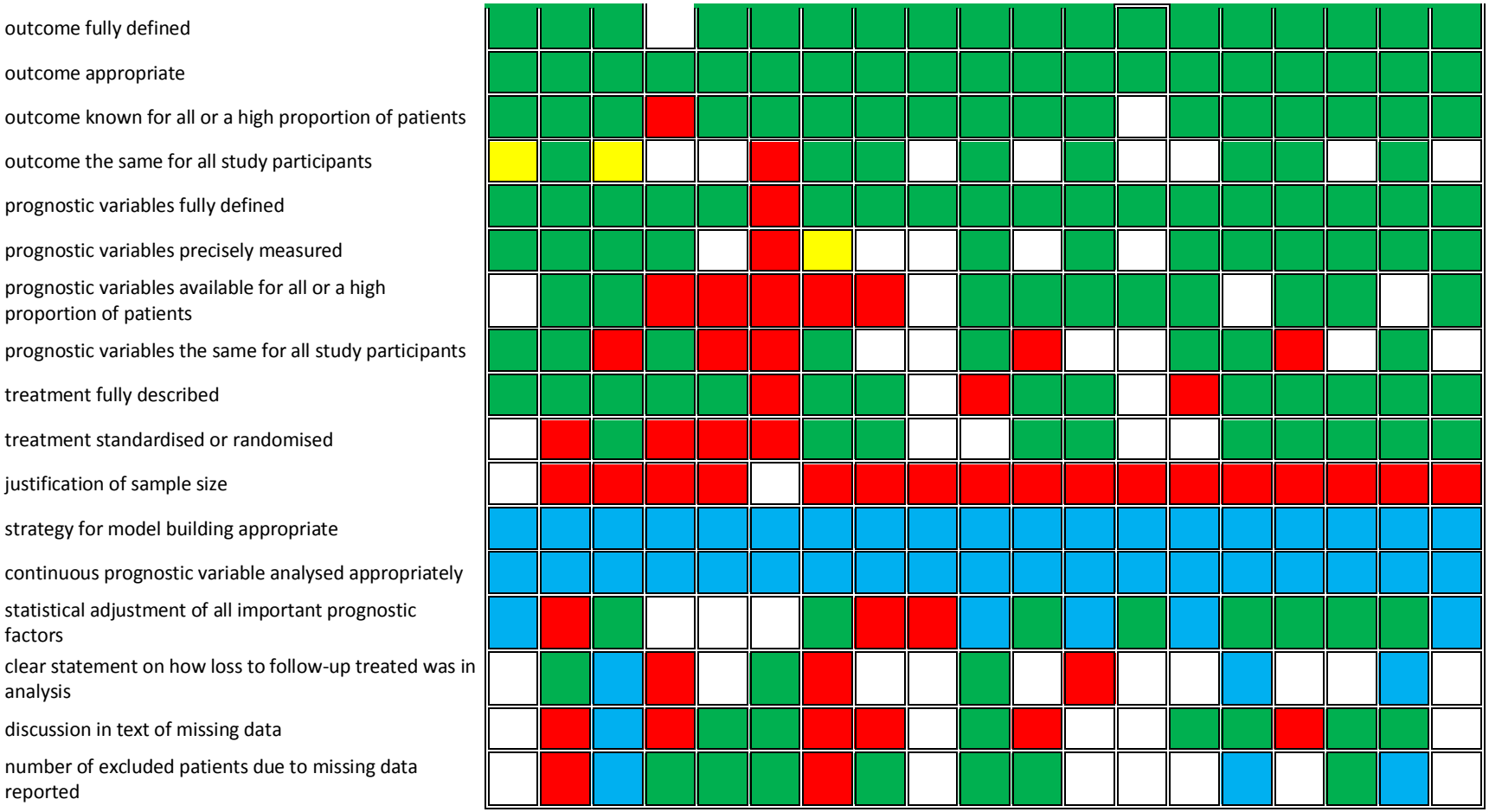
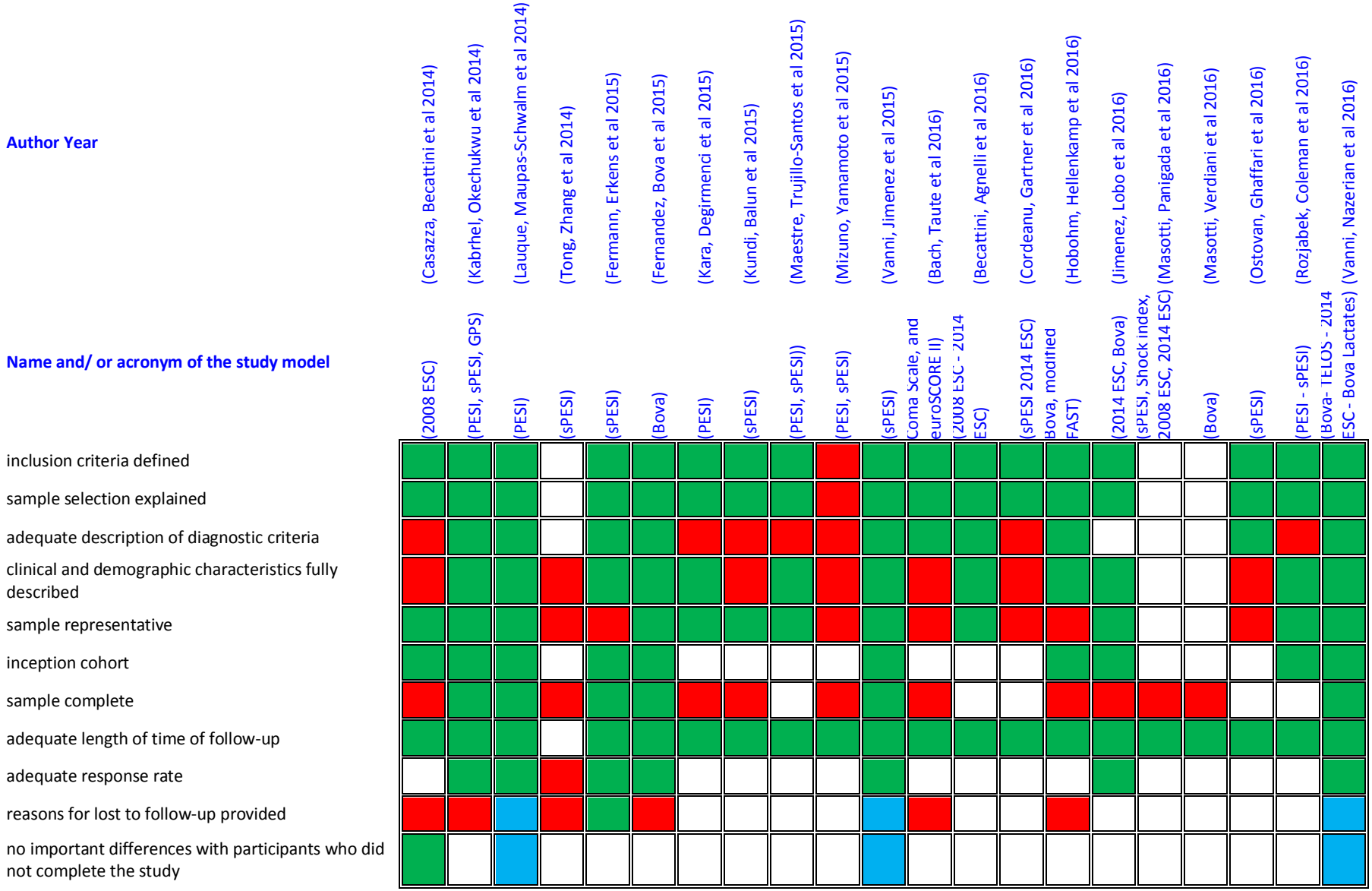

outcome fully defined
outcome appropriate
outcome known for all or a high proportion of patients
outcome the same for all study participants
prognostic variables fully defined
prognostic variables precisely measured
prognostic variables available for all or a high proportion of patients
prognostic variables the same for all study participants
treatment fully described
treatment standardised or randomised
justification of sample size
strategy for model building appropriate
continuous prognostic variable analysed appropriately
statistical adjustment of all important prognostic factors
clear statement on how loss to follow-up treated was in analysis
discussion in text of missing data
number of excluded patients due to missing data reported

Figure A4.1.3c: Study Quality - External Validation Studies (3)

Yes (in green): meets the criteria - No (in red): does not meet the criteria - Unclear (in yellow): not clearly reported - Not applicable (in blue) - Not reported (unfilled)



outcome objective

outcome unbiased (assessment blinded to prognostic information)

outcome fully defined

outcome appropriate

outcome known for all or a high proportion of patients

outcome the same for all study participants

prognostic variables fully defined

prognostic variables precisely measured

prognostic variables available for all or a high proportion of patients

prognostic variables the same for all study participants

treatment fully described

treatment standardised or randomised

justification of sample size

strategy for model building appropriate

continuous prognostic variable analysed appropriately

statistical adjustment of all important prognostic factors

clear statement on how loss to follow-up treated was in analysis

discussion in text of missing data

number of excluded patients due to missing data reported

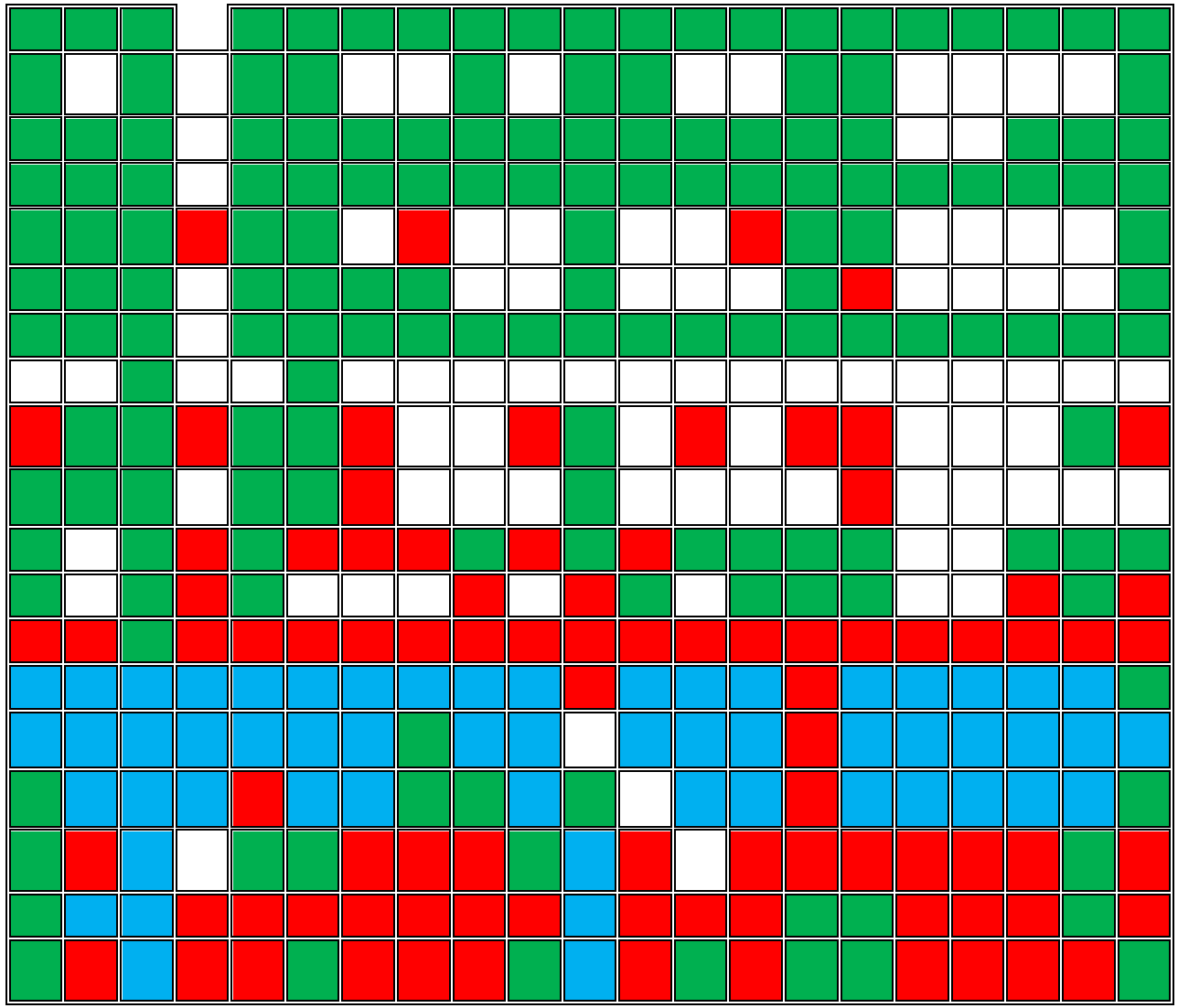


Figure A4.1.4: Summary of Study Quality in External Validation Studies

Yes (in green): meets the criteria - No (in red): does not meet the criteria - Unclear (in yellow): not clearly reported - Not applicable (in blue) - Not reported (in violet)

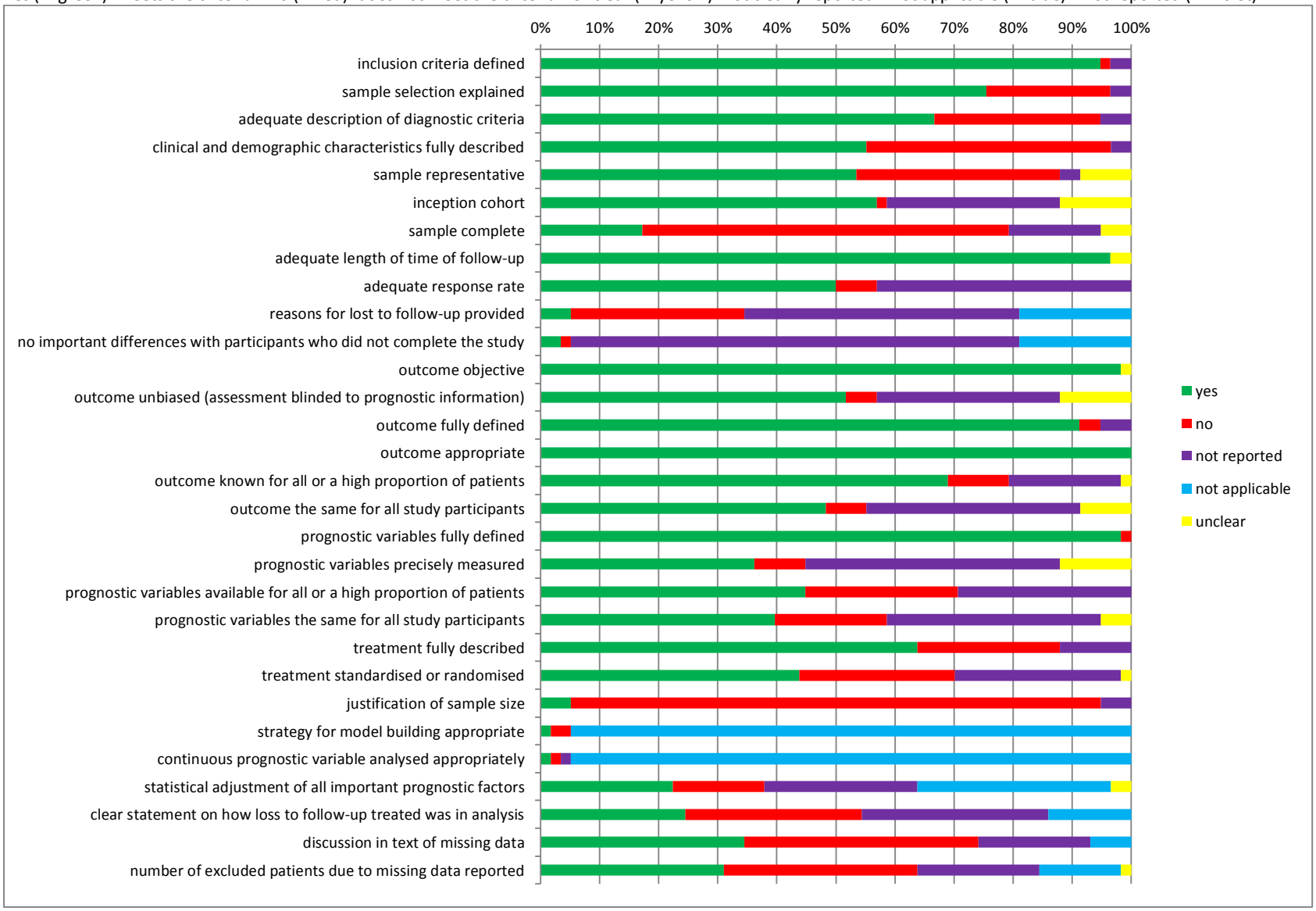
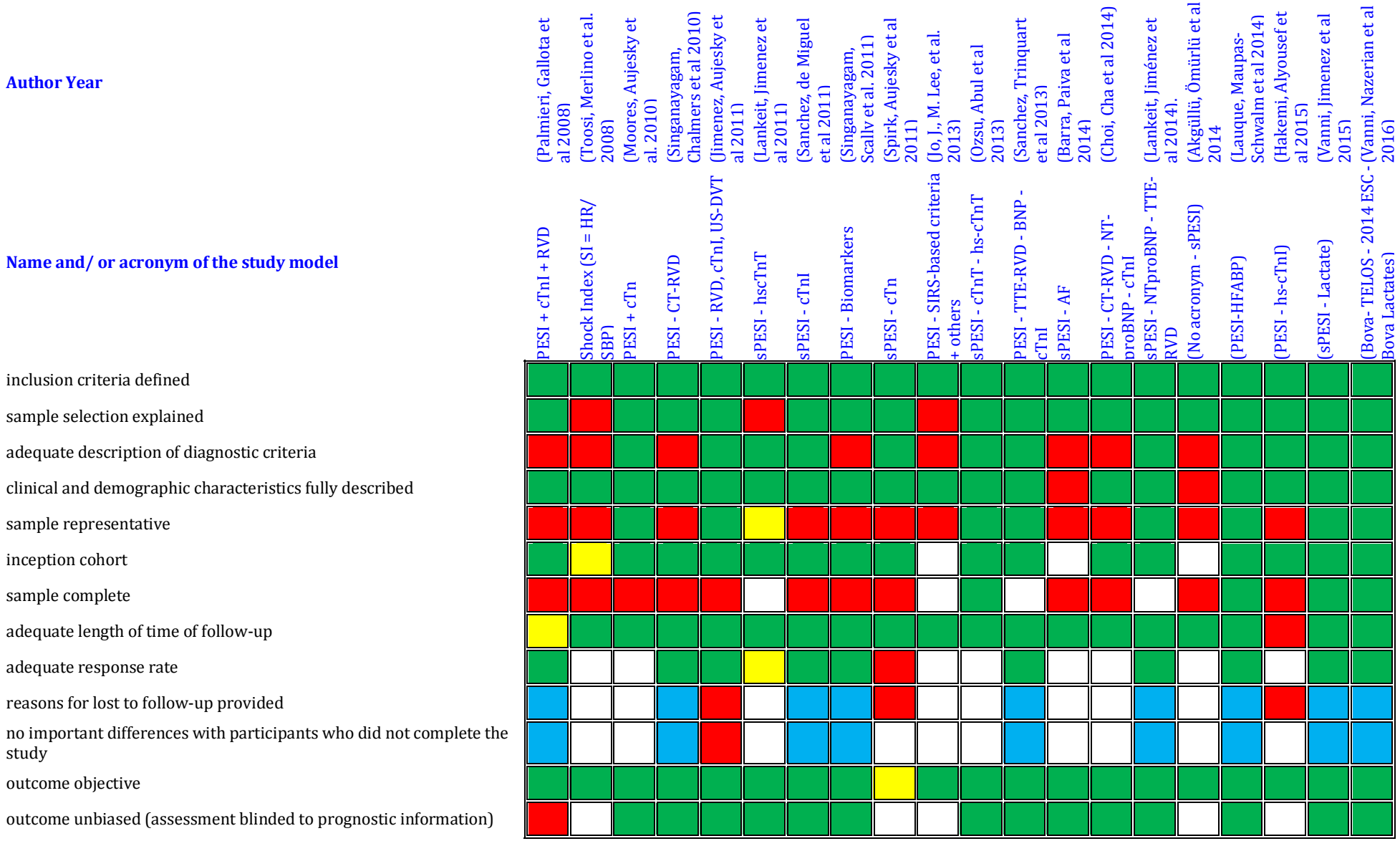


Figure A4.1.5: Study Quality - Update Studies

Yes (in green): meets the criteria - No (in red): does not meet the criteria - Unclear (in yellow): not clearly reported - Not applicable (in blue) - Not reported (in violet)



outcome fully defined

outcome appropriate

outcome known for all or a high proportion of patients

outcome the same for all study participants

prognostic variables fully defined

prognostic variables precisely measured

prognostic variables available for all or a high proportion of patients

prognostic variables the same for all study participants

treatment fully described

treatment standardised or randomised

justification of sample size

strategy for model building appropriate

continuous prognostic variable analysed appropriately

statistical adjustment of all important prognostic factors

clear statement on how loss to follow-up treated was in analysis

discussion in text of missing data

number of excluded patients due to missing data reported

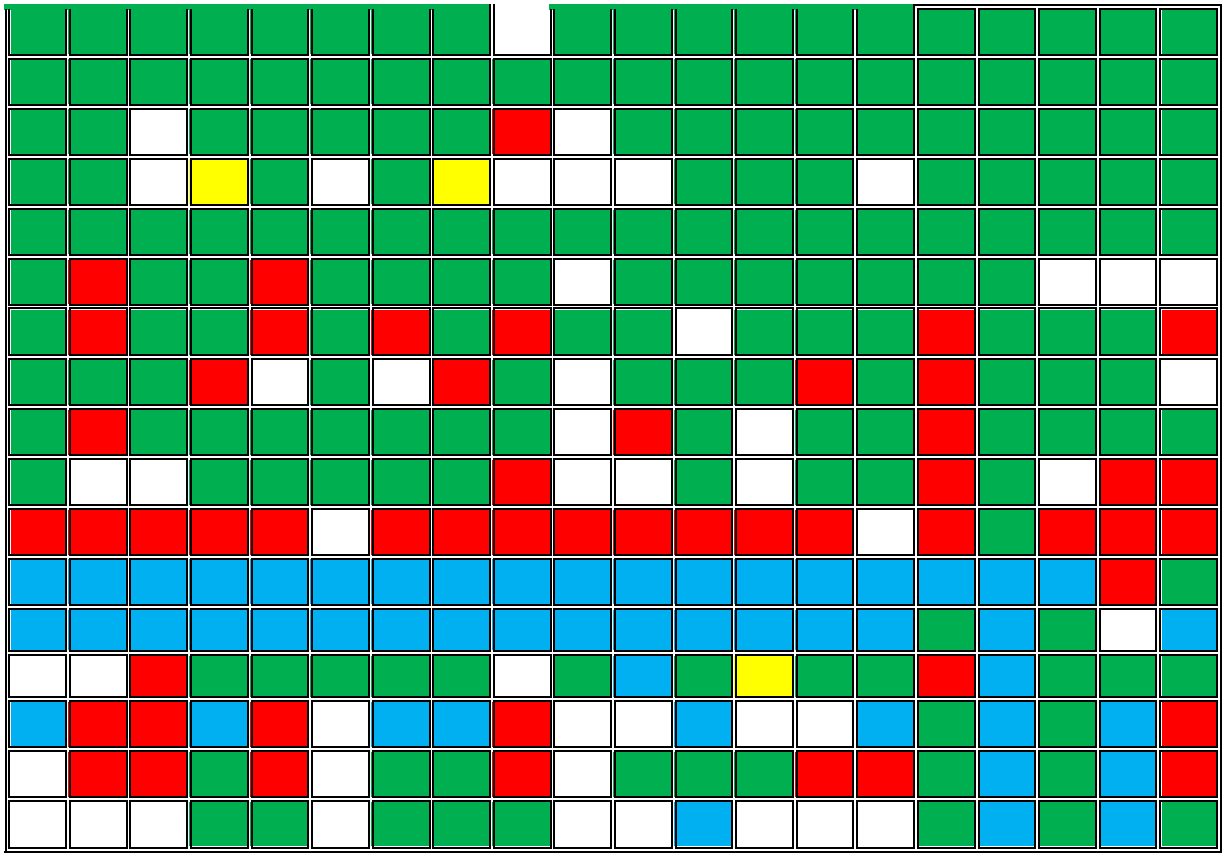


Figure A4.1.6: Summary of Study Quality in Update Studies

Yes (in green): meets the criteria - No (in red): does not meet the criteria - Unclear (in yellow): not clearly reported - Not applicable (in blue) - Not reported (unfilled)

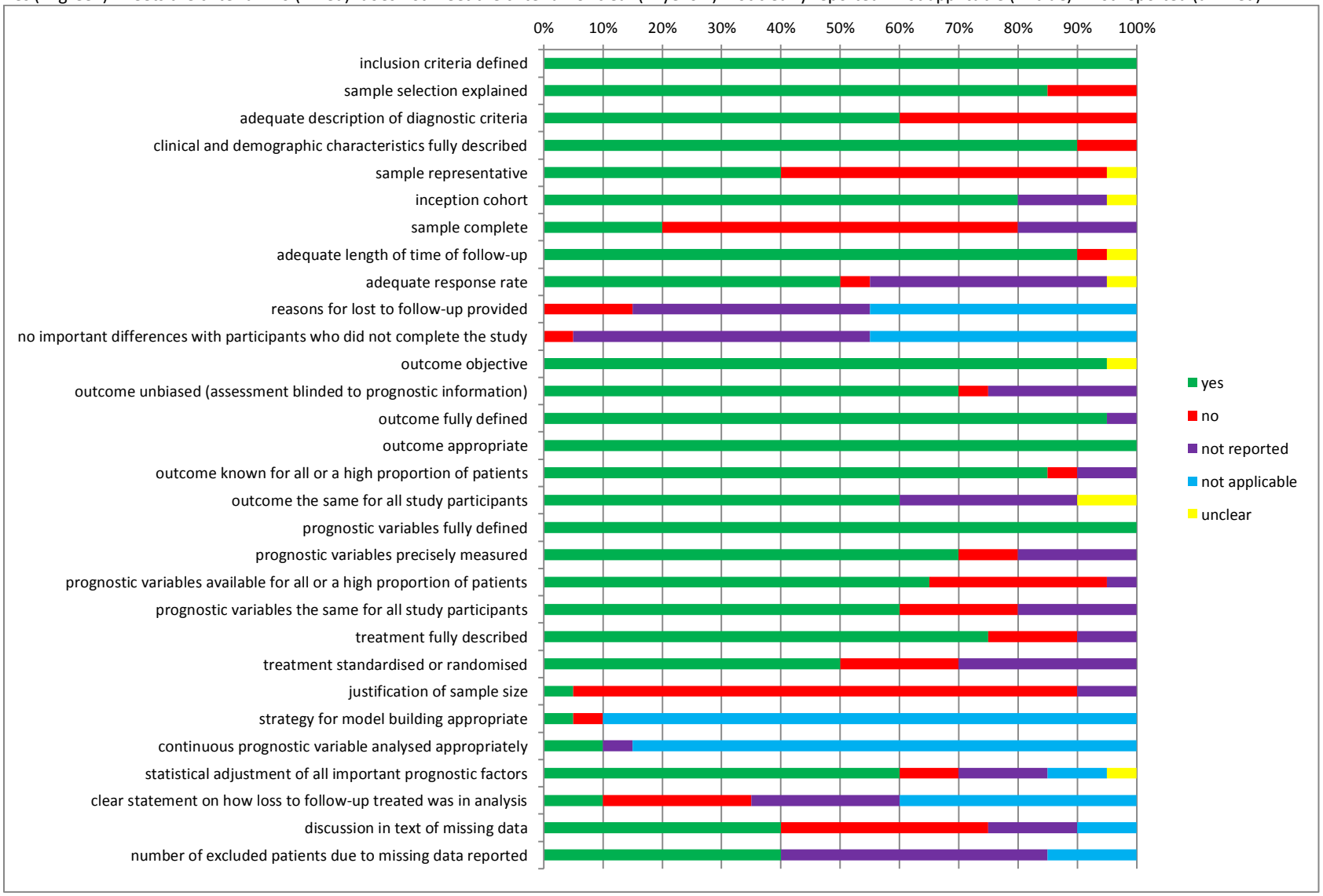
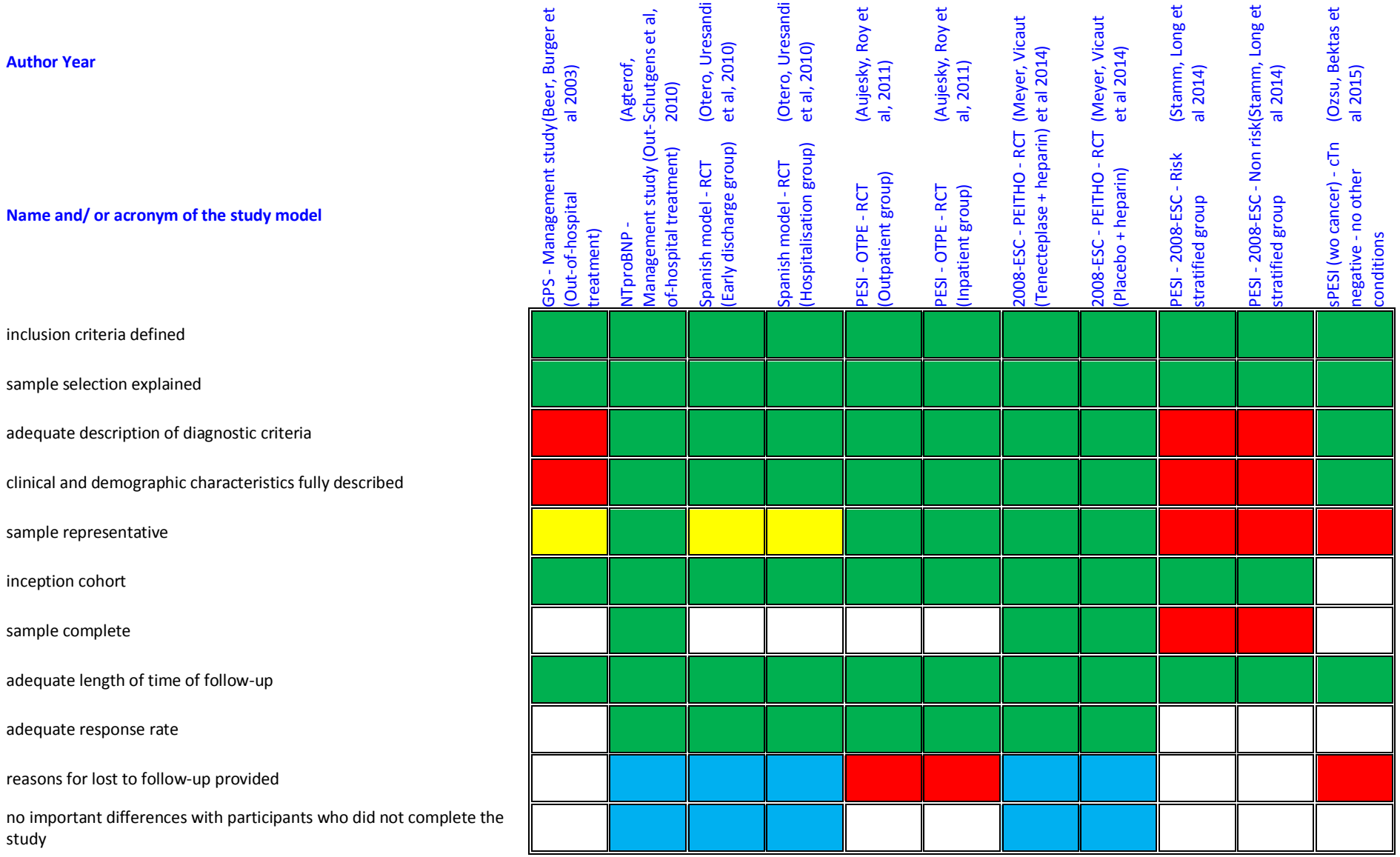


Figure A4.1.7: Study Quality - Impact studies

Yes (in green): meets the criteria - No (in red): does not meet the criteria - Unclear (in yellow): not clearly reported - Not applicable (in blue) - Not reported (unfilled)



outcome objective

outcome unbiased (assessment blinded to prognostic information)

outcome fully defined

outcome appropriate

outcome known for all or a high proportion of patients

outcome the same for all study participants

prognostic variables fully defined

prognostic variables precisely measured

prognostic variables available for all or a high proportion of patients

prognostic variables the same for all study participants

treatment fully described

treatment standardised or randomised

justification of sample size

strategy for model building appropriate

continuous prognostic variable analysed appropriately

statistical adjustment of all important prognostic factors

clear statement on how loss to follow-up treated was in analysis

discussion in text of missing data

number of excluded patients due to missing data reported

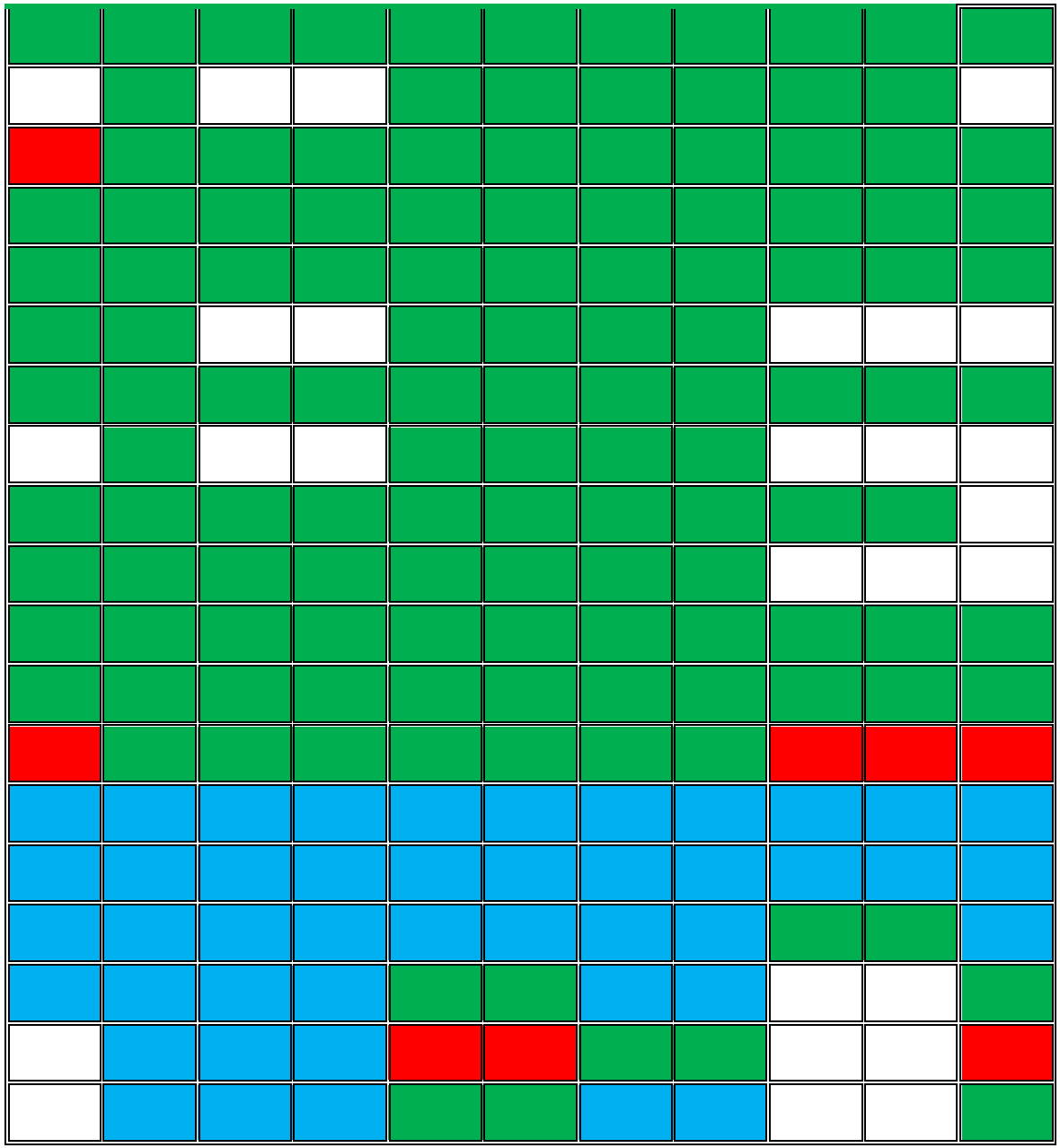


Figure A4.1.8: Summary of Study Quality in Impact studies

Yes (in green): meets the criteria - No (in red): does not meet the criteria - Unclear (in yellow): not clearly reported - Not applicable (in blue) - Not reported (in violet)

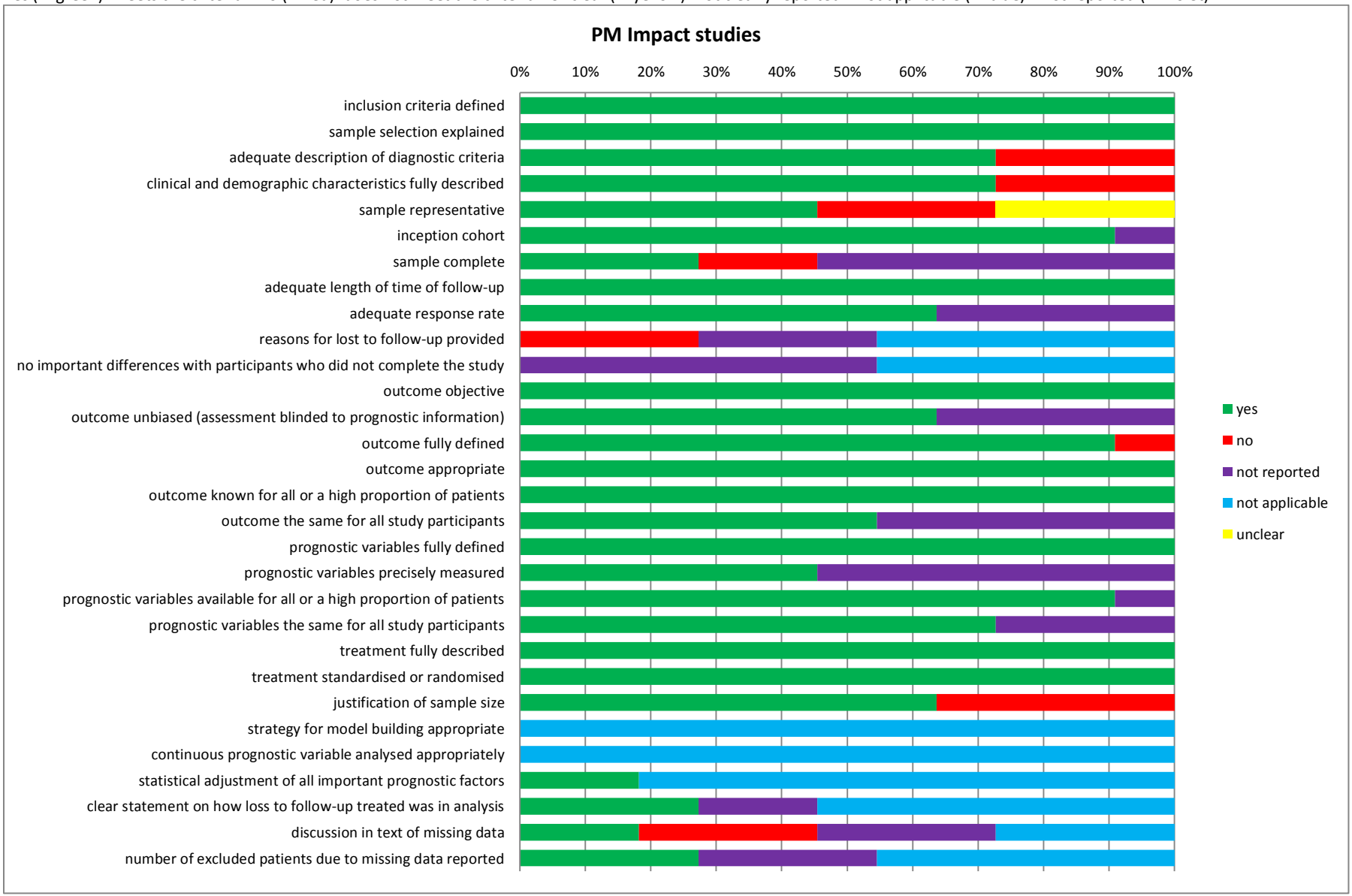


Figure A4.1.9: Study Quality - Type 2 model Studies

Yes (in green): meets the criteria - No (in red): does not meet the criteria - Unclear (in yellow): not clearly reported - Not applicable (in blue) - Not reported (in violet)

Author Year	(Bertoletti, Le Gal et al 2013)	(Ng, Chow et al 2013)	(Paiva, Providencia et al 2013)	(Papaioannou, Kastanis et al. 2013)	Keller, Coldewey et al 2015	Bach, Taute et al 2016
Name and/ or acronym of the study model	RGS - SGS - PESI	CCI-based model	GRACE, GPS, sPESI, SI, 2008ESC	No acronym (includes CCI)	sCRB-65	APACHE II, PESI, sPESI, GCS, euroSCORE II.
inclusion criteria defined						
sample selection explained						
adequate description of diagnostic criteria						
clinical and demographic characteristics fully described						
sample representative						
inception cohort						
sample complete						
adequate length of time of follow-up						
adequate response rate						
reasons for lost to follow-up provided						
no important differences with participants who did not complete the study						
outcome objective						
outcome unbiased (assessment blinded to prognostic information)						
outcome fully defined						
outcome appropriate						
outcome known for all or a high proportion of patients						
outcome the same for all study participants						
prognostic variables fully defined						

prognostic variables precisely measured						
prognostic variables available for all or a high proportion of patients						
prognostic variables the same for all study participants						
treatment fully described						
treatment standardised or randomised						
justification of sample size						
strategy for model building appropriate						
continuous prognostic variable analysed appropriately						
statistical adjustment of all important prognostic factors						
clear statement on how loss to follow-up treated was in analysis						
discussion in text of missing data						
number of excluded patients due to missing data reported						

Figure A4.1.10: Summary of Study Quality in Type 2 model Studies

Yes (in green): meets the criteria - No (in red): does not meet the criteria - Unclear (in yellow): not clearly reported - Not applicable (in blue) - Not reported (unfilled)

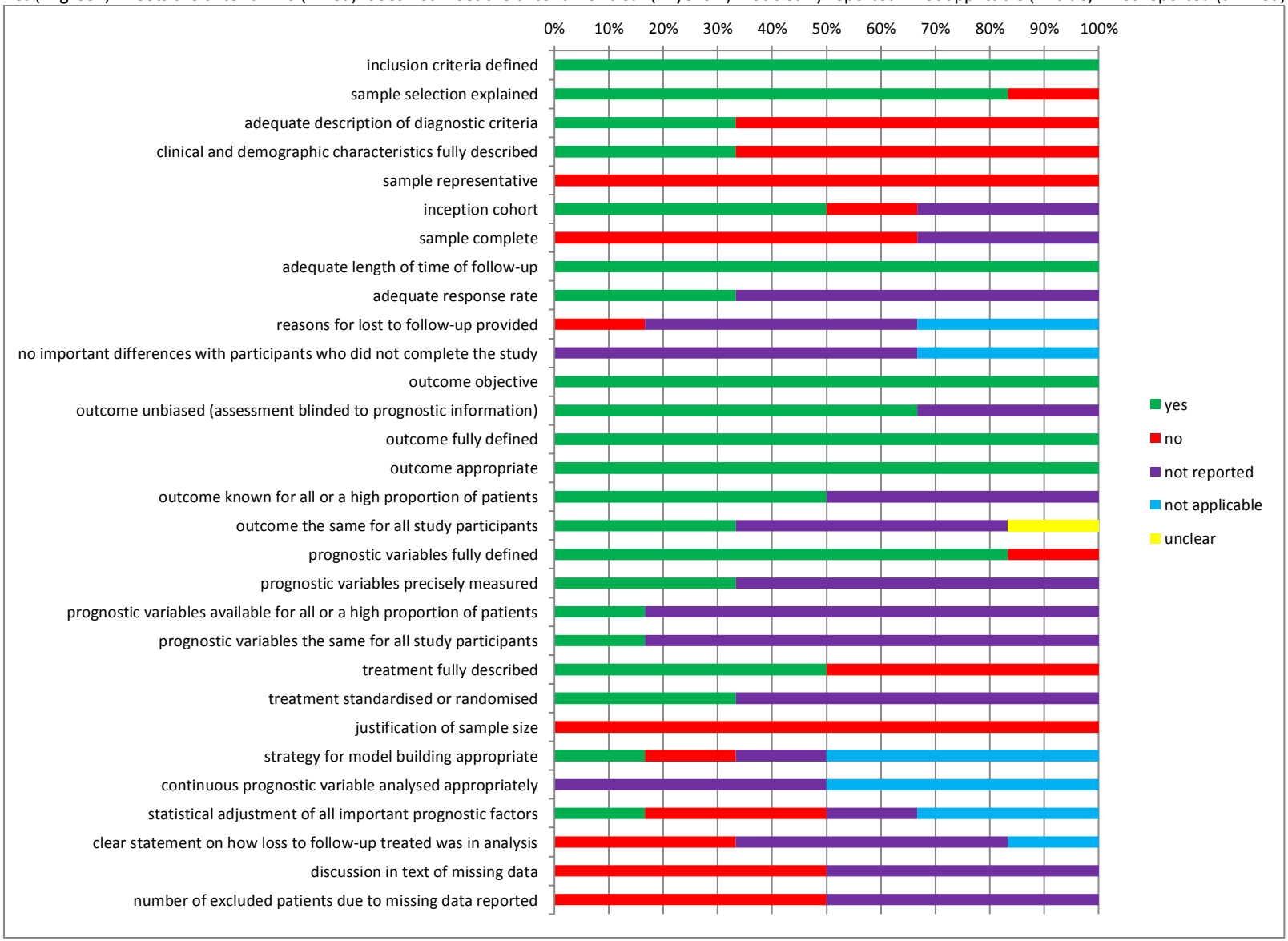


Figure A4.1.11: Study Quality - Type 3 model studies

Yes (in green): meets the criteria - No (in red): does not meet the criteria - Unclear (in yellow): not clearly reported - Not applicable (in blue) - Not reported (unfilled)

Author Year	(Davies, Wimperis et al 2007)	(Davies, Wimperis et al 2007)	(Zondag, den Exter et al 2013)	(Zondag, Vingerhoets et al 2013)	(den Exter, Zondag et al 2016)	(Weeda, Kohn et al 2016)
Name and/ or acronym of the study model	Davies criteria	Davies criteria	sPESI - Hestia criteria	sPESI - CT-RVD	(Hestia-NTproBNP versus Hestia)	(Hestia)
inclusion criteria defined						
sample selection explained						
adequate description of diagnostic criteria						
clinical and demographic characteristics fully described						
sample representative						
inception cohort						
sample complete						
adequate length of time of follow-up						
adequate response rate						
reasons for lost to follow-up provided						
no important differences with participants who did not complete the study						
outcome objective						
outcome unbiased (assessment blinded to prognostic information)						
outcome fully defined						
outcome appropriate						
outcome known for all or a high proportion of patients						
outcome the same for all study participants						
prognostic variables fully defined						

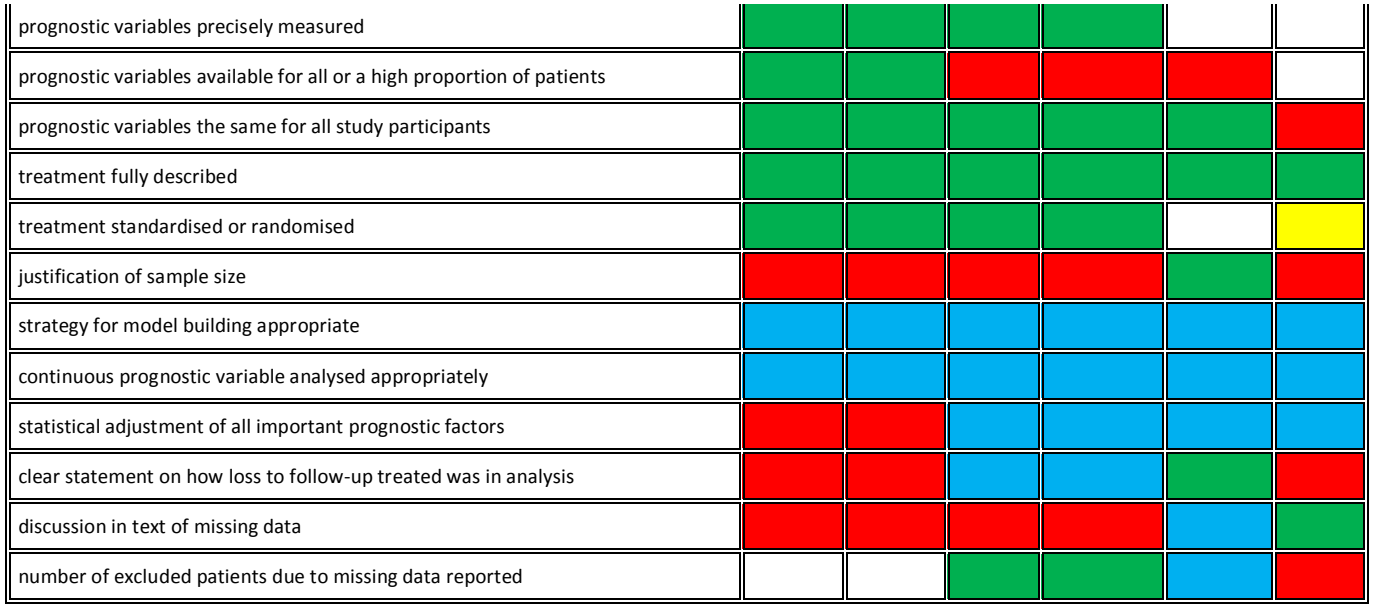
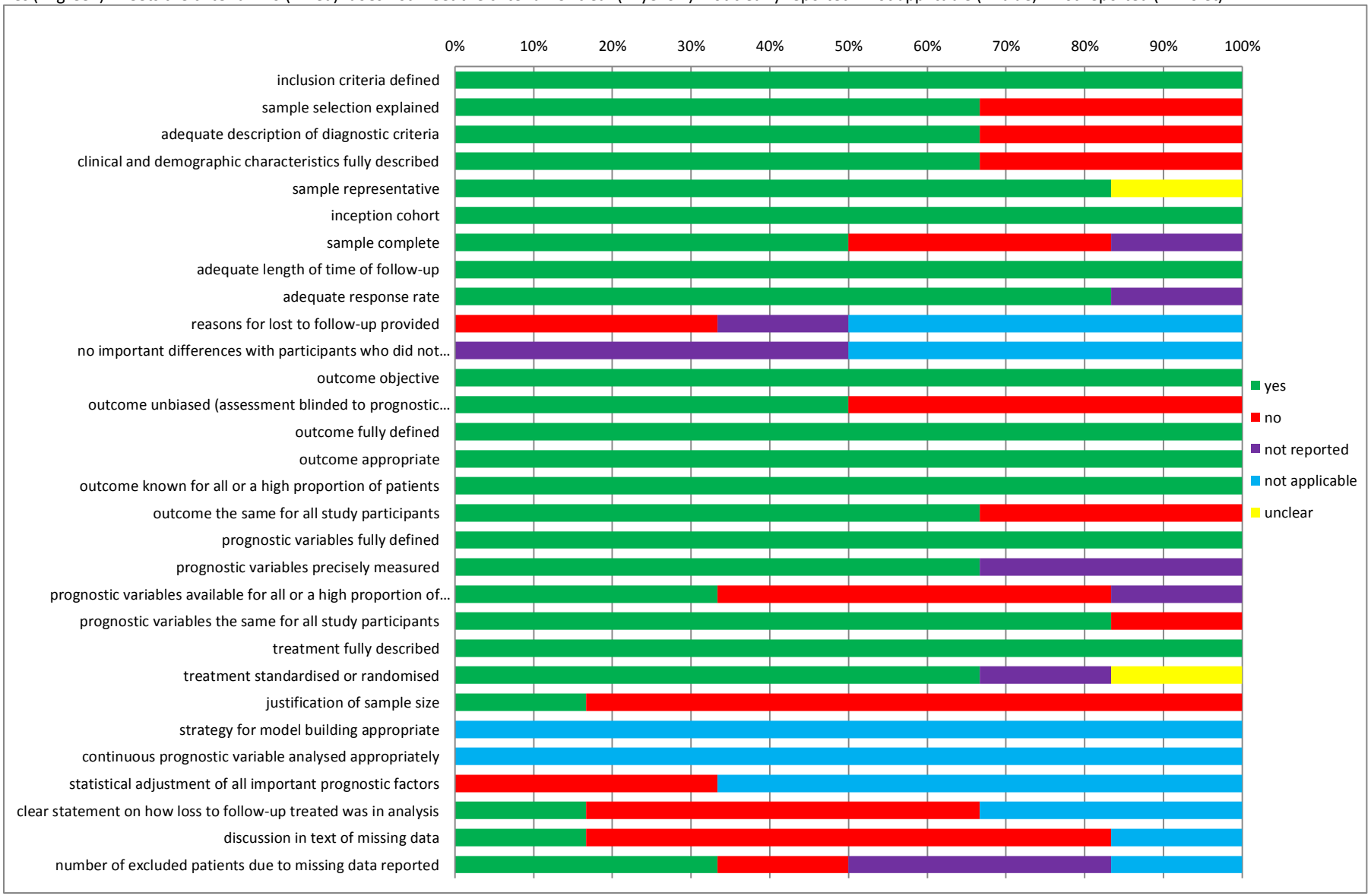

prognostic variables precisely measured
prognostic variables available for all or a high proportion of patients
prognostic variables the same for all study participants
treatment fully described
treatment standardised or randomised
justification of sample size
strategy for model building appropriate
continuous prognostic variable analysed appropriately
statistical adjustment of all important prognostic factors
clear statement on how loss to follow-up treated was in analysis
discussion in text of missing data
number of excluded patients due to missing data reported

Figure A4.1.12: Summary of Study Quality in Type 3 model studies

Yes (in green): meets the criteria - No (in red): does not meet the criteria - Unclear (in yellow): not clearly reported - Not applicable (in blue) - Not reported (in violet)

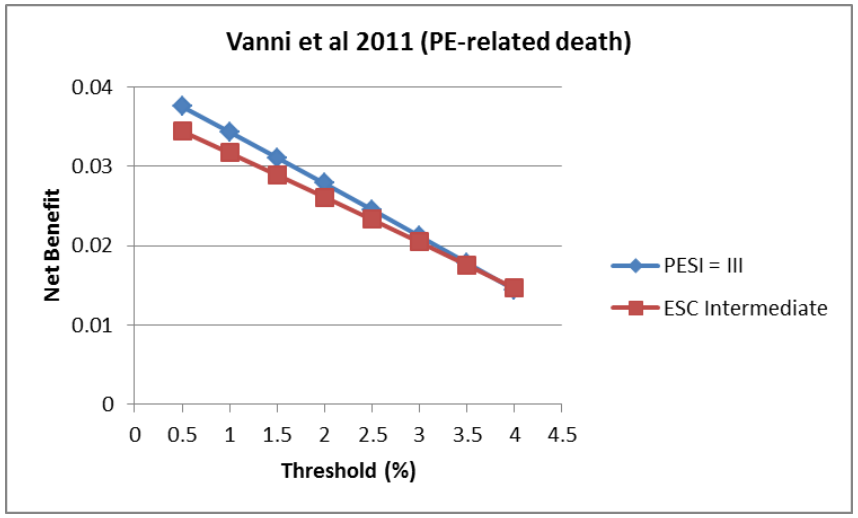


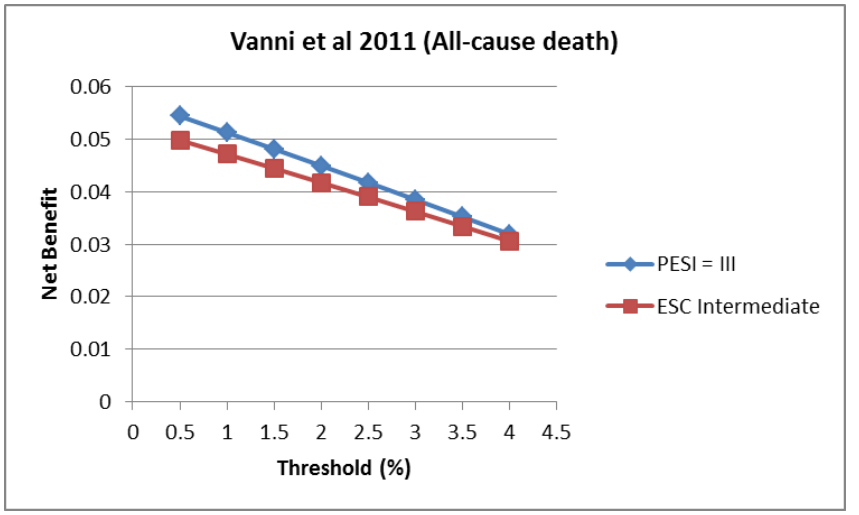
Appendices A5 - Net Benefit of Prognostic Models in Acute Pulmonary Embolism in Direct Comparison Studies.

TABLES AND FIGURES A5.1 TO A5.23 (COMPETING MODELS)

A5.1: PESI - 2008 ESC

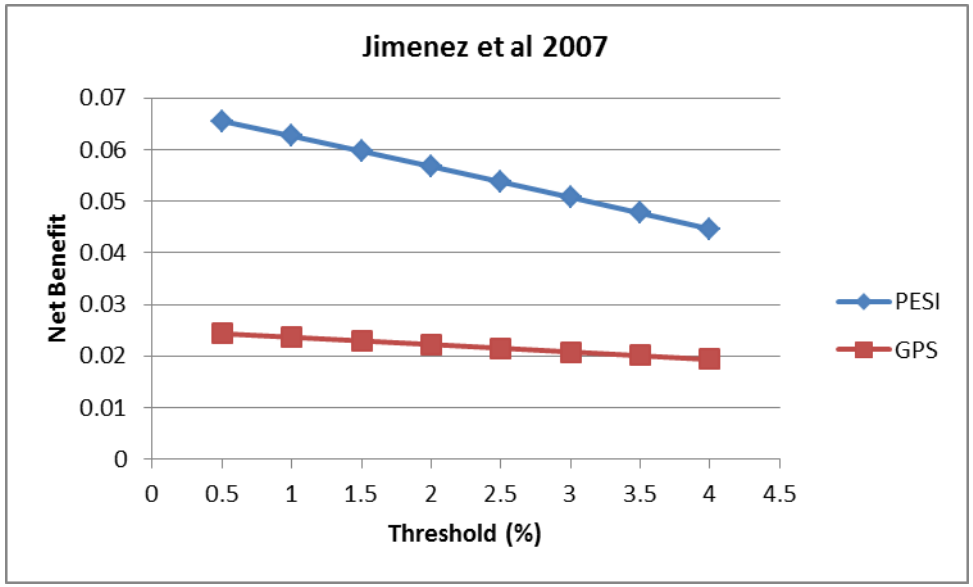
Vanni, Nazerian et al. 2011[1] **(Model - Cut-off)**	**Development phase** **Type of study**	**Patients**	**Time-point** **Outcome**	**Sample size**	**Population event rate**	**Proportion (95% CI)** **High-risk** **Low-risk**	**Event rate (95% CI)** **High-risk** **Low-risk**	**Overall** **Net Reclassification** **Improvement**
(PESI ≥ III)	External validation Retrospective	Stable	In-hospital PE-related death	418	0.04	67 (62.3-71.3) 33 (28.7-37.7)	6.1 (3.8-9.5) 0.7 (0.1-5)	
(2008 ESC Intermediate)				458		57.6 (53.1 – 62.1) 42.4 (37.9 – 46.9)	6.4 (4.0 – 10.1) 1.0 (0.3 – 4.0)	NRI (2008 ESC – PESI) = 0.045
(PESI ≥ III)			In-hospital All-cause death	418	0.065	67 (62.3-71.3) 33 (28.7-37.7)	8.6 (5.6-12.5) 2.2 (0.4-6.2)	
(2008 ESC Intermediate)				458		57.6 (53.1 – 62.1) 42.4 (37.9 – 46.9)	9.1 (5.9-13.2) 2.6 (0.8-5.9)	NRI (2008 ESC – PESI) = 0.034





A5.2: PESI - GPS

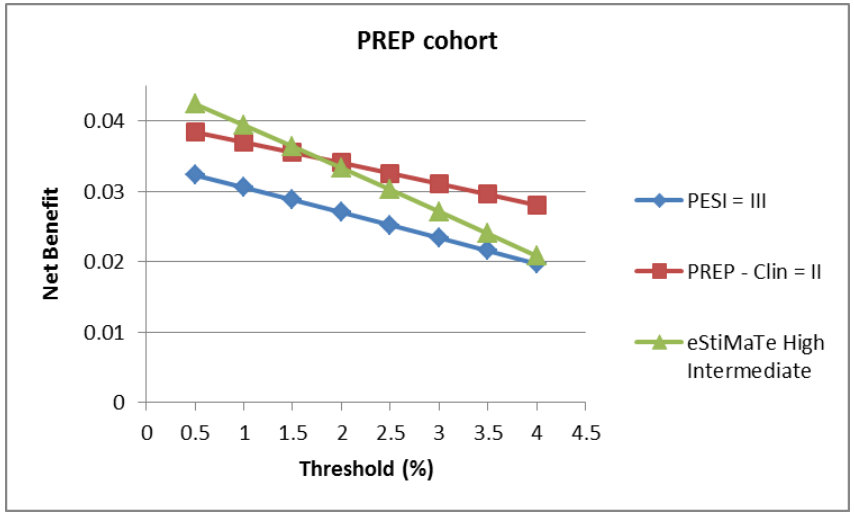
Jimenez, Yusen et al. 2007[2] **(Model - Cut-off)**	**Development phase** **Type of study**	**Patients**	**Time-point** **Outcome**	**Sample size**	**Population event rate**	**Proportion (95% CI)** **High-risk** **Low-risk**	**Event rate (95% CI)** **High-risk** **Low-risk**	**Overall** **Net Reclassification Improvement**
(PESI ≥ III)	External validation Retrospective	Not reported	30-day. All-cause death	599	0.072	63.9 (60-67.8) 36.1 (32.2-40)	10.7 (7.8-14.2) 0.9 (0.1-3.3)	
(GPS ≥ 3)						16.2 (13.3-19.4) 83.8 (80.6-86.7)	15.5 (8.9-24.2) 5.6 (3.7-8)	NRI (GPS – PESI)= - 0.137



A5.3: PESI - PREP - eStiMaTe (PREP cohort)

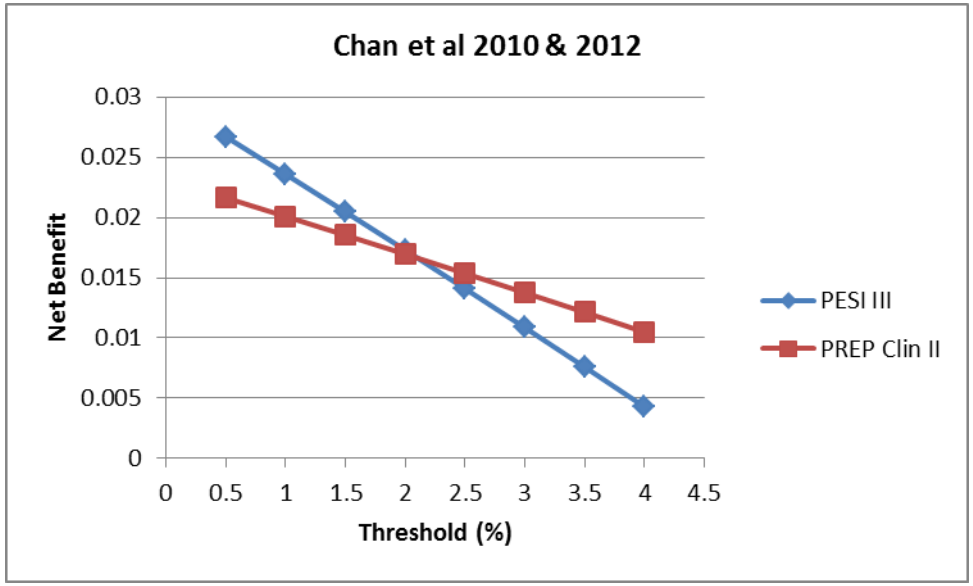
Sanchez, Trinquart et al. 2010[3] **(Model - Cut-off)**	**Development phase** **Type of study**	**Patients**	**Time-point** **Outcome**	**Sample size**	**Population event rate**	**Proportion (95% CI)** **High-risk** **Low-risk**	**Event rate (95% CI)** **High-risk** **Low-risk**	**Overall** **Net Reclassification Improvement**
(PESI ≥ III)[4]	External validation Retrospective	Stable	30-day Adverse outcome	529	0.05	37.8 (33.8-42) 62.2 (58-66.2)	9 (5.7-13.8) 2.1 (1-4.4)	
(PREP - Clin ≥ II)[3]	Derivation Prospective	Stable	30-day Death VTE	477	0.05	32.3 (28.2-36.6) 67.7 (63.4-71.8)	12.3 (8-18.5) 2.5 (1.2-4.9)	NRI (PREP - PESI)= 0.102
(eStiMaTe High Intermediate)[5]	External validation Retrospective	Stable	30-day Adverse outcome	529	0.05	63.5 (59.3-37.5) 36.5 (32.5-40.7)	7.1 (4.8-10.4) 0.3 (0-4)	NRI (eStiMaTe - PESI)= 0.023 NRI (eStiMaTe - PREP)= - 0.079

PREP model (Sanchez, Trinquart et al. 2010)[3], PESI model (Sanchez, Trinquart et al 2013)[4] and eStiMaTe PROTECT model[5] (Jiménez, Kopecna et al 2014)



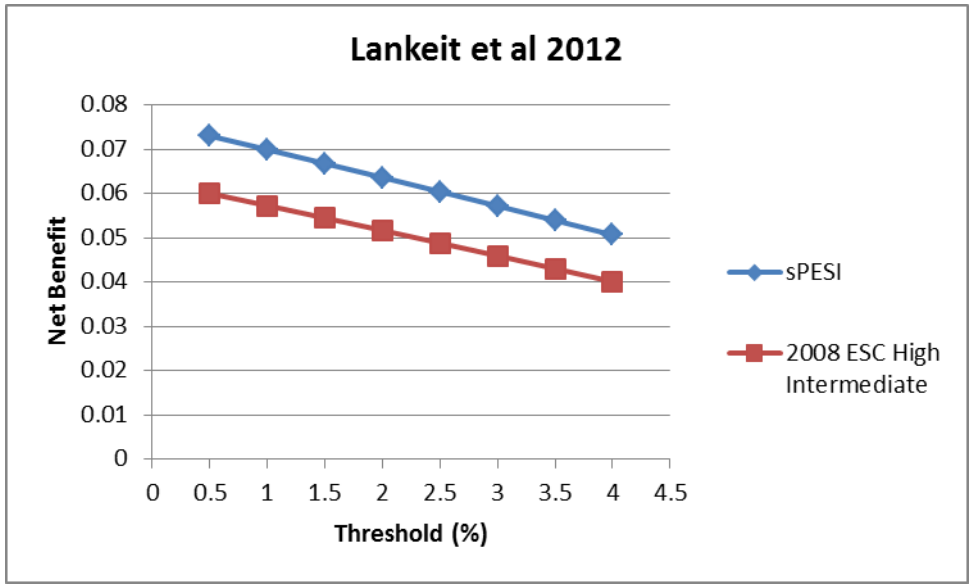
A5.4: PESI - PREP

Chan CM, Woods C, Shorr AF. 2010[6] and 2012[7] **(Model - Cut-off)**	**Development phase** **Type of study**	**Patients**	**Time-point** **Outcome**	**Sample size**	**Population event rate**	**Proportion (95% CI)** **High-risk** **Low-risk**	**Event rate (95% CI)** **High-risk** **Low-risk**	**Overall** **Net Reclassification Improvement**
(PESI ≥ III)	External validation Retrospective	Both stable and unstable	30-day All-cause death	302	0.03	64.2 (58.5-69.6) 35.8 (30.4-41.5)	4.6 (2.1-8.6) 0 (0-0.3)	
(PREP Clin ≥ II)						32.8 (27.5-38.4) 67.2 (61.6-72.5)	7.1 (2.9-14) 1 (0.1-3.5)	NRI (PREP – PESI)= 0.095



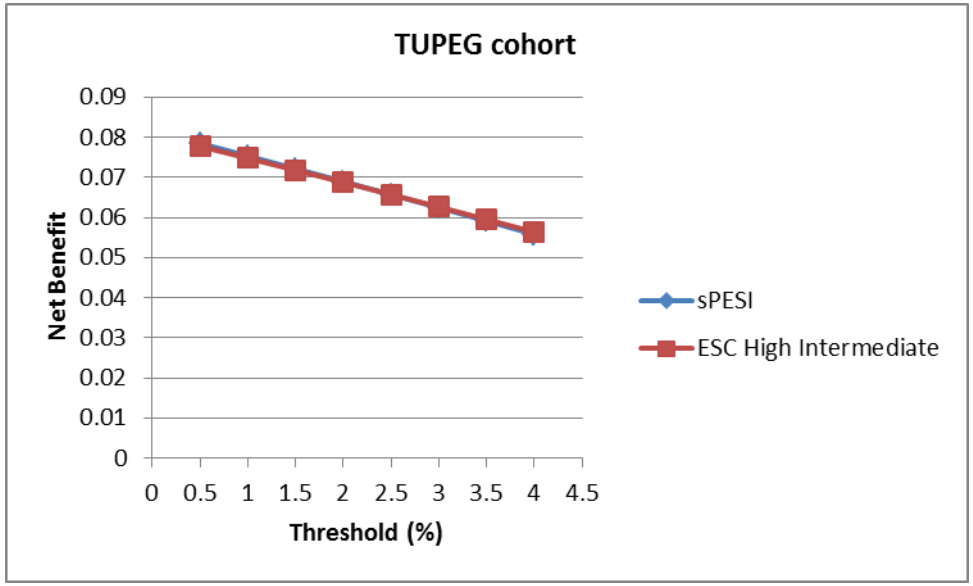
A5.5: sPESI – 2008 ESC

Lankeit, Gomez et al. 2012[8] **(Model - Cut-off)**	**Development phase** **Type of study**	**Patients**	**Time-point** **Outcome**	**Sample size**	**Population event rate**	**Proportion (95% CI)** **High-risk** **Low-risk**	**Event rate (95% CI)** **High-risk** **Low-risk**	**Overall** **Net Reclassification Improvement**
(sPESI ≥ 1)	Derivation External validation Prospective & Retrospective	Both stable and unstable	30-day All-cause death	526	0.076	68.6 (64.5-72.6) 31.4 (27.4-37.5)	11.1 (8-14.8) 0 (0-2.2)	
(2008 ESC High Intermediate)						60.6 (56.3-64.8) 39.4 (35.2-43.7)	10.3 (7.2-14.2) 3.4 (1.4-6.8)	NRI (2008 ESC – sPESI)= - 0.103



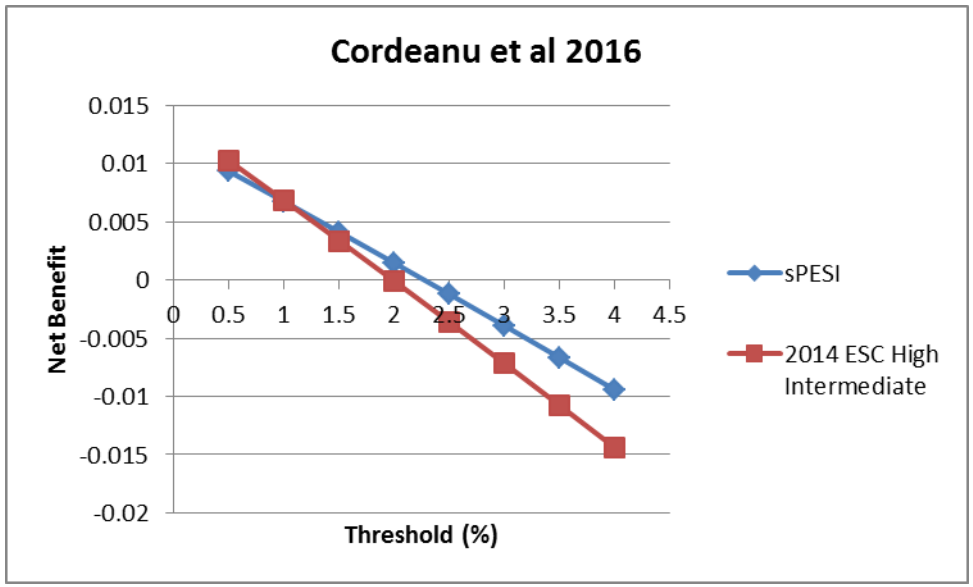
A5.6: sPESI – 2008 ESC (TUPEG cohort)

Ozsu, Ozlu et a 2014[9] **(Model - Cut-off)**	**Development phase Type of study**	**Patients**	**Time-point Outcome**	**Sample size**	**Population event rate**	**Proportion (95% CI) High-risk Low-risk**	**Event rate (95% CI) High-risk Low-risk**	**Overall Net Reclassification Improvement**
(sPESI ≥ 1)	External validation Prospective	Both stable and unstable	30-day All-cause death	1078	0.09	70.1 (67.3-72.9) 29.9 (27.1-32.7)	11.6 (9.4-14.1) 2.2 (0.9-4.4)	
(2008 ESC High Intermediate)						66.4 (63.5-69.2) 33.6 (30.8-36.5)	12.2 (9.8-14.8) 2.2 (0.9-4.3)	NRI (2008 ESC – sPESI)= 0.029



A5.7: sPESI - 2014 ESC

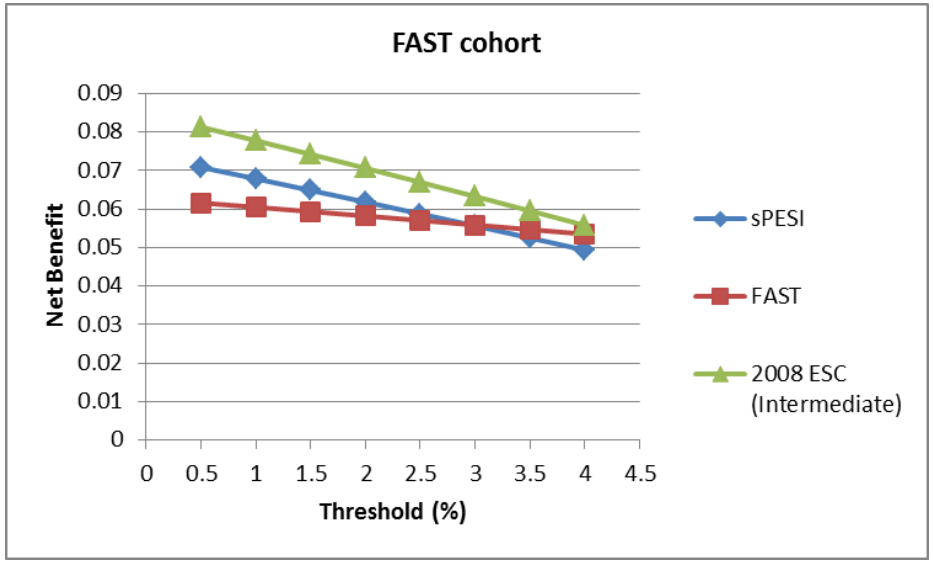
Cordeanu, Gartner et al 2016[10] **(Model - Cut-off)**	**Development phase** **Type of study**	**Patients**	**Time-point** **Outcome**	**Sample size**	**Population event rate**	**Proportion (95% CI)** **High-risk** **Low-risk**	**Event rate (95% CI)** **High-risk** **Low-risk**	**Overall** **Net Reclassification Improvement**
(sPESI)	External validation Retrospective	Both stable and unstable	30-day All-cause death	587	0.02	52.5 (48.3-56.6) 47.5 (43.4-51.7)	2.3 (0.9-4.6) 0.7 (0.1-2.6)	
(2014 ESC High Intermediate)						68.7 (64.7-72.4) 31.3 (27.6-35.3)	2 (0.9-3.9) 0.5 (0-3)	NRI (sPESI - 2014 ESC)= - 0.052



A5.8: sPESI - FAST - ESC (FAST cohort).

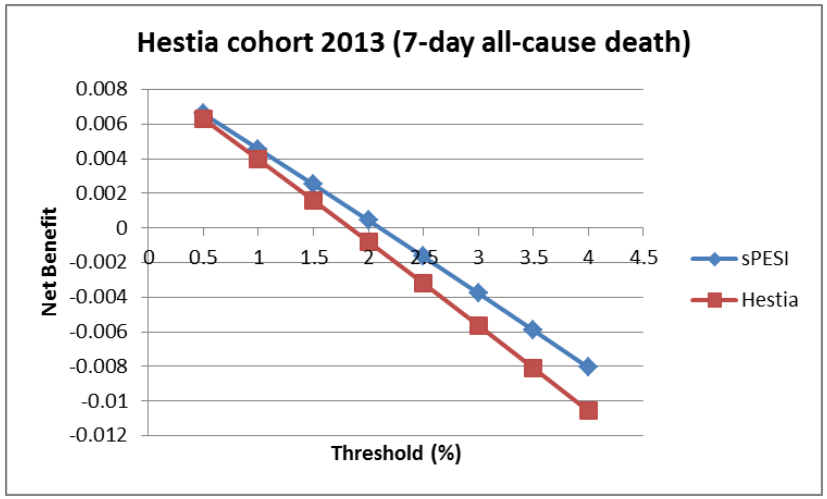
Dellas, Tschepe et al 2014[11] **(Model - Cut-off)**	**Development phase Type of study**	**Patients**	**Time-point Outcome**	**Sample size**	**Population event rate**	**Proportion (95% CI) High-risk Low-risk**	**Event rate (95% CI) High-risk Low-risk**	**Overall Net Reclassification Improvement**
(sPESI ≥ 1)	External validation Prospective	Stable	30-day Adverse outcome	271	0.074	66.1 (60.2-71.4) 33.9 (28.6-39.8)	11.2 (7.3-16.7) 0.5 (0-8)	
(FAST = 3)				271	0.074	28.4 (23.4-34.1) 71.6 (65.9-76.6)	22.1 (14.2-32.7) 1.5 (0.5-4.7)	NRI (FAST - sPESI)= 0.244
(2008 ESC Intermediate)				224	0.085	78.1 (72.2-83.1) 21.9 (16.9-27.8)	10.9 (7-16.4) 1 (0.1-14.1)	NRI (2008 ESC - sPESI)= - 0.128 NRI (2008 ESC - FAST)= - 0.372

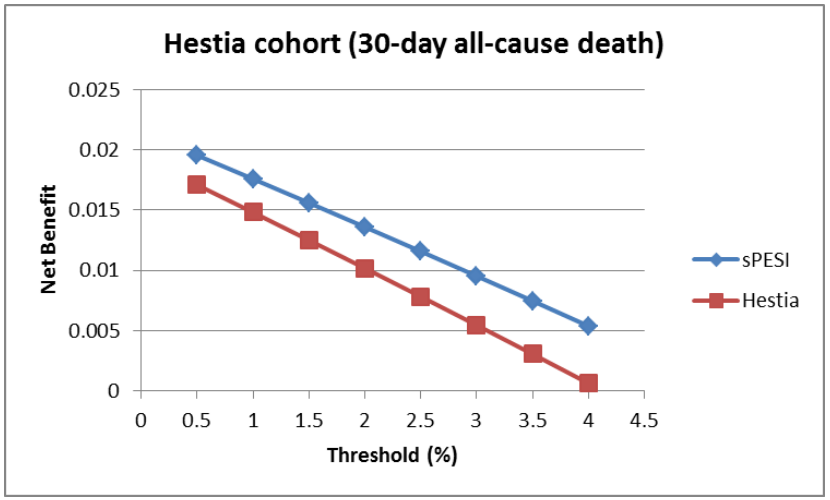
2008 ESC model was feasible for only 224 patients (instead of 271).



A5.9: sPESI - Hestia (Hestia cohort)

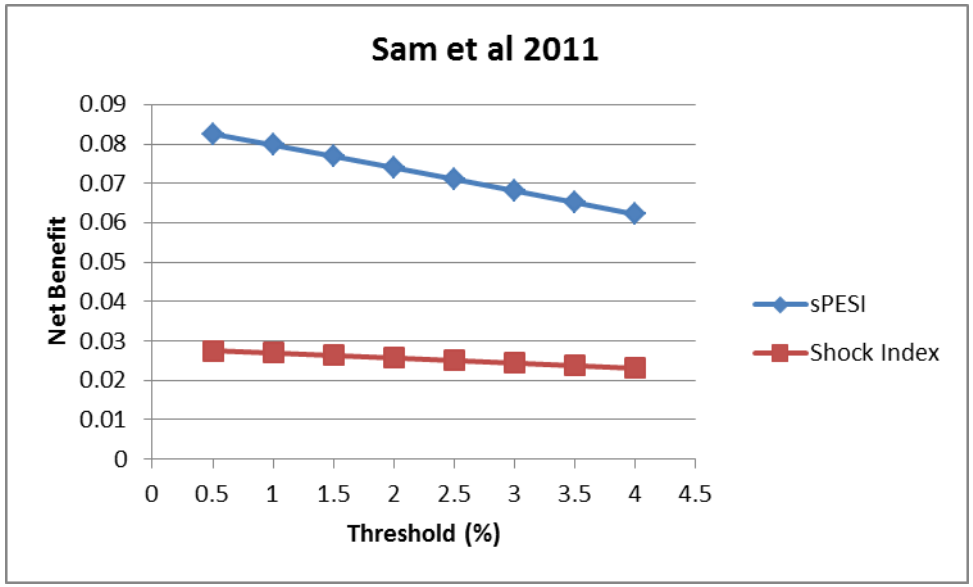
Zondag, den Exter et al 2013[12] **(Model - Cut-off)**	**Development phase** **Type of study**	**Patients**	**Time-point** **Outcome**	**Sample size**	**Population event rate**	**Proportion (95% CI)** **High-risk** **Low-risk**	**Event rate (95% CI)** **High-risk** **Low-risk**	**Overall** **Net Reclassification Improvement**
(sPESI ≥ 1)	External validation Retrospective	Both stable and unstable	7-day All-cause death	465	0.01	40.9 (36.4-45.5) 59.1 (54.5-63.6)	2.1 (0.6-5.3) 0 (0-1.3)	
(Hestia ≥ 1)	External validation Prospective					46.9 (42.3-51.5) 53.1 (48.5-57.7)	1.8 (0.5-4.6) 0 (0-1.5)	NRI (Hestia – sPESI)= - 0.061
(sPESI ≥ 1)	External validation Retrospective		30-day All-cause death	465	0.02	40.9 (36.4-45.5) 59.1 (54.5-63.6)	5.3(2.6-9.5) 0.4 (0-2)	
(Hestia ≥ 1)	External validation Prospective					46.9 (42.3-51.5) 53.1 (48.5-57.7)	4.1 (1.9-7.7) 0.8 (0.1-2.9)	NRI (Hestia – sPESI)= - 0.155





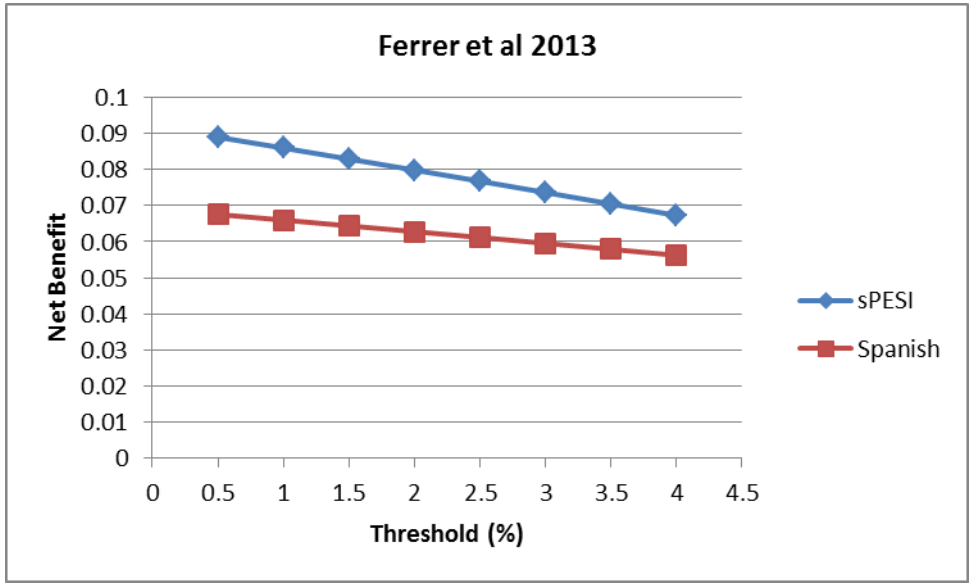
A5.10: sPESI - Shock Index

Sam, Sanchez et al. 2011[13] **(Model - Cut-off)**	**Development phase** **Type of study**	**Patients**	**Time-point** **Outcome**	**Sample size**	**Population event rate**	**Proportion (95% CI)** **High-risk** **Low-risk**	**Event rate (95% CI)** **High-risk** **Low-risk**	**Overall** **Net Reclassification Improvement**
(sPESI ≥ 1)	External validation Retrospective	Not reported	30-day All-cause death	1206	0 .10	64.3 (61.5-67) 33.7 (33-38.5)	13.3 (11-15.9) 3.7 (2.1-6)	
(Shock Index)						15.1 (13.1-17.2) 84.9 (82.8-86.9)	18.7 (13.3-25.1) 8.3 (6.7-10.2)	NRI (Shock Index - sPESI)= - 0.098



A5.11: sPESI - Spanish model

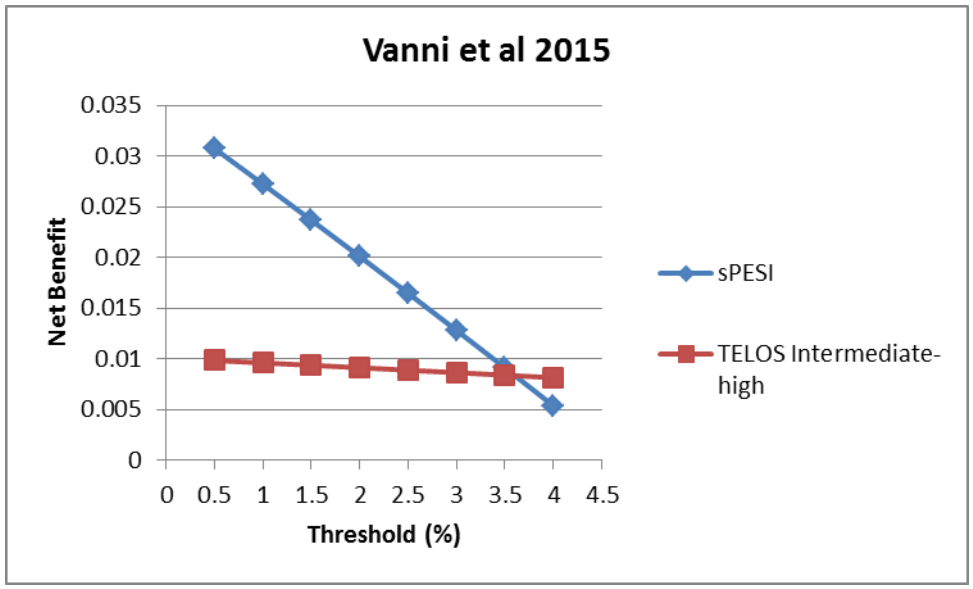
Ferrer, Morillo et al 2013[14] **(Model - Cut-off)**	**Development phase** **Type of study**	**Patients**	**Time-point** **Outcome**	**Sample size**	**Population event rate**	**Proportion (95% CI)** **High-risk** **Low-risk**	**Event rate (95% CI)** **High-risk** **Low-risk**	**Overall** **Net Reclassification Improvement**
(sPESI ≥ 1)	External validation Prospective & Retrospective	Both stable & unstable	30-day All-cause death	1447	0.10	68.3 (65.8-70.7) 31.7 (29.3-34.1)	13.5 (11.4-15.7) 1.1 (0.3-2.5)	
(Spanish model)						37.8 (35.3-40.4) 62.2 (59.6-64.7)	18.3 (15.1-21.8) 4.2 (3-5.7)	NRI (Spanish – sPESI)= 0.073



A5.12: sPESI - TELOS (TELOS cohort)

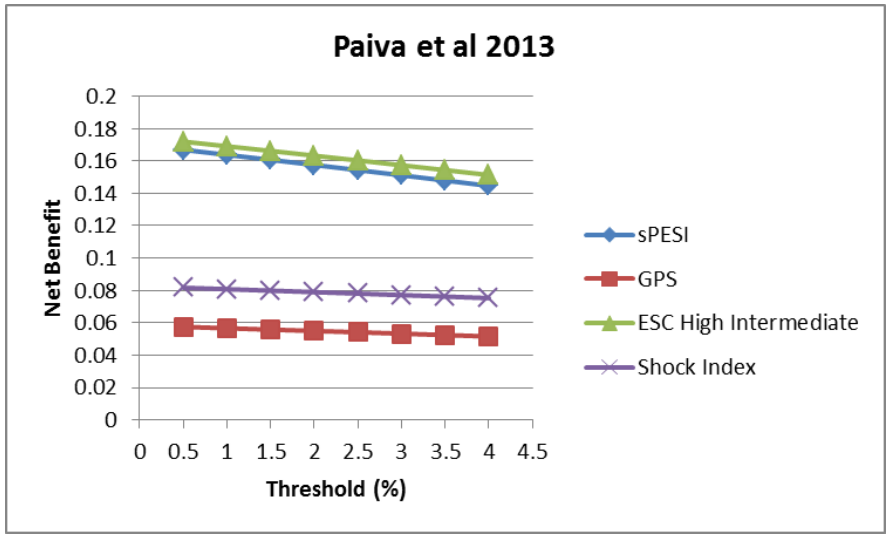
Vanni, Jimenez et al 2015[15] **(Model - Cut-off)**	**Development phase Type of study**	**Patients**	**Time-point Outcome**	**Sample size**	**Population event rate**	**Proportion (95% CI) High-risk Low-risk**	**Event rate (95% CI) High-risk Low-risk**	**Overall Net Reclassification Improvement**
(sPESI ≥ 1)	External validation Prospective	Stable	7-day PE-related complications*	496	0.04	72.8 (68.6-76.7) 27.2 (23.3-31.4)	4.7 (2.8-7.4) 2.2 (0.5-6.4)	
(TELOS Intermediate-high)	Derivation Prospective					5.6 (3.8-8.1) 94.4 (91.9-96.2)	17.9 (6.1-36.9) 3.2 (1.8-5.2)	NRI (TELOS – sPESI)= 0.074

*(PE-related death and non-fatal hemodynamic collapse)



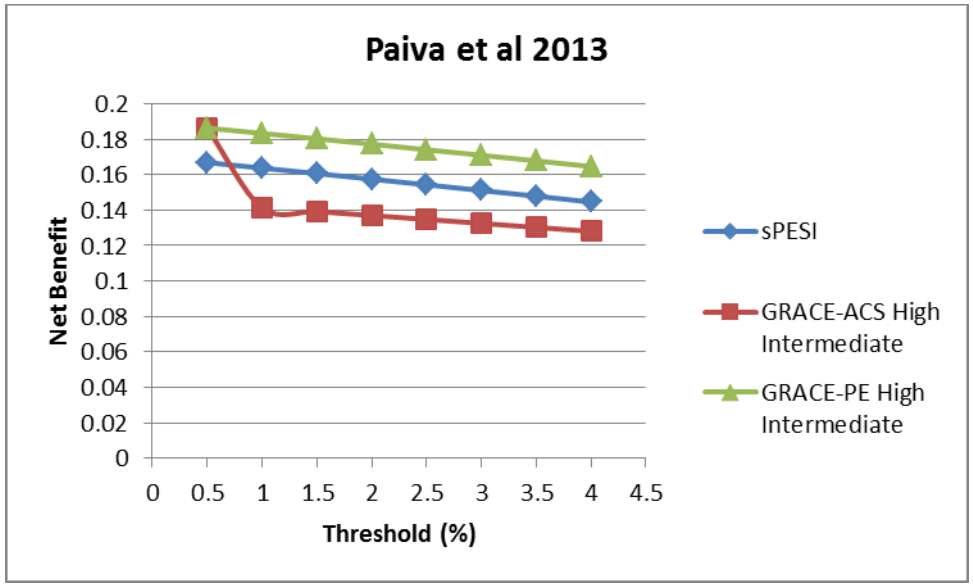
A5.13 (1): sPESI - GPS - ESC - SI

Paiva, Providencia et al 2013[16] **(Model - Cut-off)**	**Development phase** **Type of study**	**Patients**	**Time-point** **Outcome**	**Sample size**	**Population event rate**	**Proportion (95% CI)** **High-risk** **Low-risk**	**Event rate (95% CI)** **High-risk** **Low-risk**	**Overall** **Net Reclassification Improvement**
(sPESI ≥ 1)	External validation Retrospective	Both stable and unstable	30-day All-cause death	206	0.19	77.7 (71.4-83.2) 22.3 (16.8-28.6)	21.9 (15.7-29.1) 8.7 (2.4-20.8)	
(GPS ≥ 3)						21.8 (16.4-28.1) 78.2 (71.9-83.6)	26.7 (14.6-41.9) 16.8 (11.4-23.5)	NRI (GPS – sPESI)= - 0.039
(2008 ESC High Intermediate)						73.8 (67.2-79.7) 26.2 (20.3-32.8)	23.7 (17.2-31.3) 5.6 (1.2-15.4)	NRI (2008 ESC - sPESI)= 0.08
(Shock Index)						25.7 (19.9-32.3) 74.3 (67.7-80.1)	32.1 (19.9-46.3) 14.4 (9.2-21)	NRI (Shock Index – sPESI)= 0.071



A5.13 (2): sPESI - GRACE-ACS - GRACE-PE (GRACE-PE cohort)

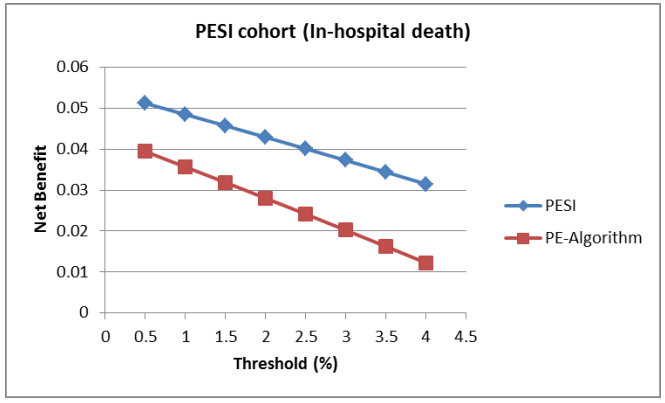
Paiva, Providencia et al 2013[16] **(Model - Cut-off)**	**Development phase** **Type of study**	**Patients**	**Time-point** **Outcome**	**Sample size**	**Population event rate**	**Proportion (95% CI)** **High-risk** **Low-risk**	**Event rate (95% CI)** **High-risk** **Low-risk**	**Overall** **Net Reclassification Improvement**
(sPESI ≥ 1)	External validation Retrospective	Both stable and unstable	30-day All-cause death	206	0.19	77.7 (71.4-83.2) 22.3 (16.8-28.6)	21.9 (15.7-29.1) 8.7 (2.4-20.8)	
(GRACE-ACS High Intermediate)						81.1 (75-86.2) 18.9 (13.8-25)	23.3 (17.2-30.5) 0 (0-9)	NRI (GRACE-ACS – sPESI)= 0.085
(GRACE-PE High Intermediate)						78.2 (71.9-83.6) 21.8 (16.4-28.1)	24.2 (17.8-31.6) 0 (0-7.9)	NRI (GRACE-PE – sPESI)= 0.121

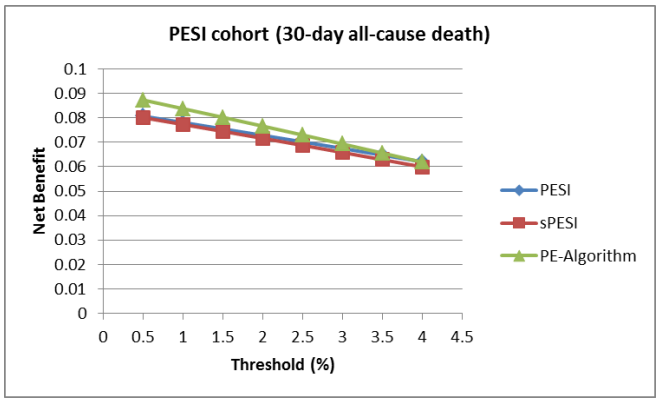


A5.14: PESI - PE Algorithm - sPESI (PESI derivation and internal validation cohort)

Aujesky, Obrosky et al. 2005[17] **(Model - Cut-off)**	**Development phase** **Type of study**	**Patients**	**Time-point** **Outcome**	**Sample size**	**Population event rate**	**Proportion (95% CI)** **High-risk** **Low-risk**	**Event rate (95% CI)** **High-risk** **Low-risk**	**Overall** **Net Reclassification Improvement**
(PESI ≥ III)[17]	Derivation (Int. val.) Retrospective	Both stable and unstable	In-hospital All-cause death	15531	0.06	59.2 (58.4-59.9) 40.8 (40.1-41.6)	9.1 (8.5-9.7) 1.4 (1.1-1.7)	
(PE Algorithm) [18]	Derivation (Int. val.) Retrospective				0.044	78.4 (77.7-79) 21.6 (21-22.3)	5.5 (5.1-5.9) 0.6 (0.3-0.9)	NRI (Algorithm - PESI)= - 0.136
(PESI ≥ III)[17]	Derivation (Int. val.) Retrospective		30-day. All-cause death	15531	0.093	59.2 (58.4-59.9) 40.8 (40.1-41.6)	14.1 (13.4-14.8) 2.3 (1.9-2.7)	
(sPESI ≥ 1)[19]	External validation Retrospective					63.2 (62.4-64) 36.8 (36-37.6)	13.1 (12.4-13.8) 2.7 (2.3-3.1)	NRI (sPESI - PESI)= - 0.051
(PE Algorithm)[18]	Derivation (Int. val.) Retrospective					78.4 (77.7-79) 21.6 (21-22.3)	11.6 (11-12.2) 0.9 (0.6-1.3)	NRI (Algorithm - PESI)= - 0.124 NRI (Algorithm - sPESI)= - 0.073

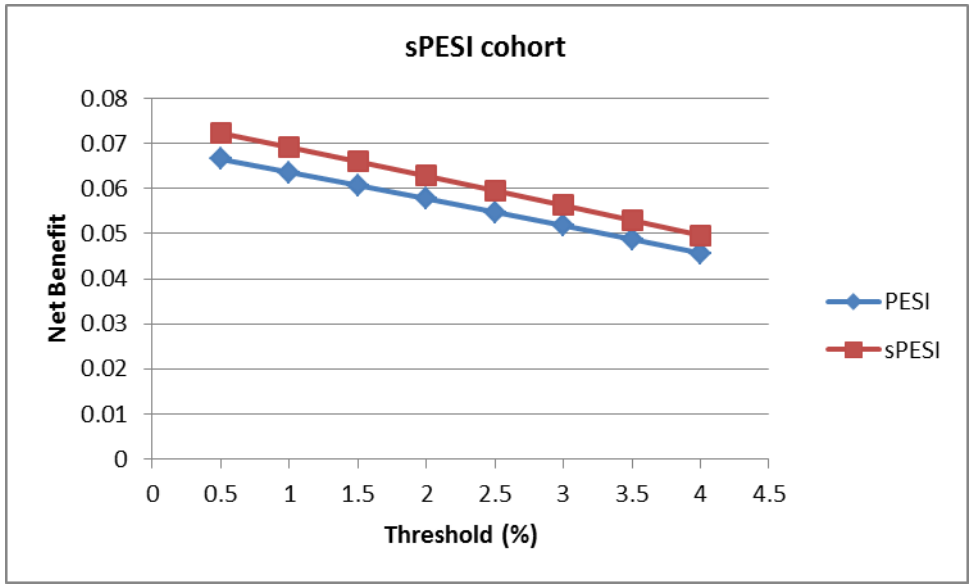
Aujesky, Obrosky et al. 2005[17], Aujesky, Obrosky et al. 2006[18], Venetz, Jimenez et al. 2011[19]. (Int. val. = Internal validation)





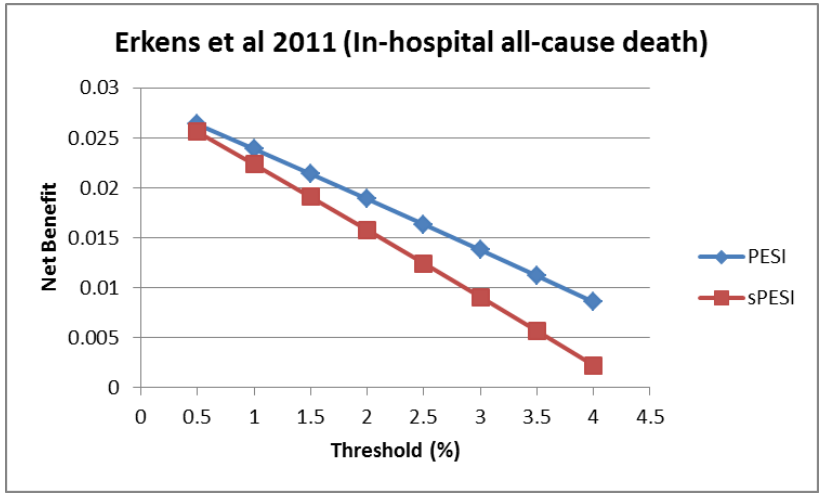
A5.15: PESI - sPESI (sPESI derivation cohort)

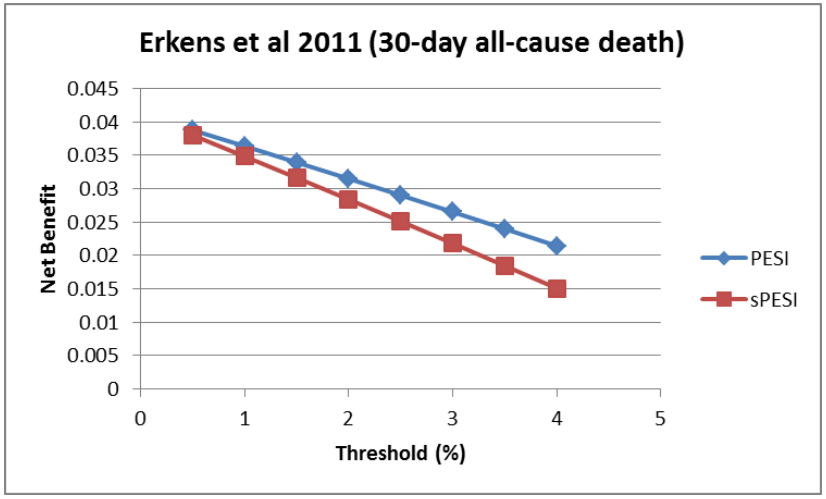
Jimenez, Aujesky et al. 2010[20] **(Model - Cut-off)**	**Development phase Type of study**	**Patients**	**Time-point Outcome**	**Sample size**	**Population event rate**	**Proportion (95% CI) High-risk Low-risk**	**Event rate (95% CI) High-risk Low-risk**	**Overall Net Reclassification Improvement**
(PESI = III)	External validation Retrospective	Not reported	30-day All-cause death	995	0.078	63.7 (60.6-66.7) 36.3 (33.3-39.4)	10.9 (8.6-13.6) 2.5 (1.1-4.7)	
(sPESI ≥ 1)	Derivation Retrospective					69.3 (66.4-72.2) 30.7 (27.8-33.6)	10.9 (8.6-13.4) 1 (0.2-2.8)	NRI (sPESI - PESI)= 0.022



A5.16: PESI - sPESI

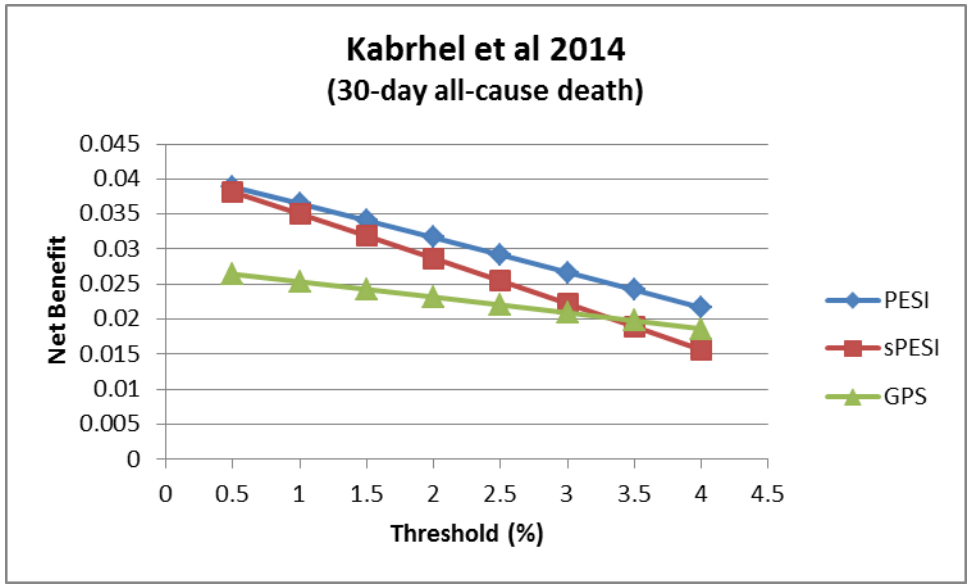
Erkens, Gandara et al. 2011[21] **(Model - Cut-off)**	**Development phase** **Type of study**	**Patients**	**Time-point** **Outcome**	**Sample size**	**Population event rate**	**Proportion (95% CI)** **High-risk** **Low-risk**	**Event rate (95% CI)** **High-risk** **Low-risk**	**Overall** **Net Reclassification** **Improvement**
(PESI ≥ III)	External validation Retrospective	Both stable and unstable	In-hospital All-cause death	243	0.03	51.4 (45-57.9) 48.6 (45-57.9)	5.9 (2.4-11.8) 0 (0-3.1)	
(sPESI ≥ 1)						66.7 (60.4-72.6) 33.3 (27.4-39.6)	4.3 (1.7-8.7) 0 (0- 4.4)	NRI (sPESI - PESI)= - 0.157
(PESI ≥ III)			30-day All-cause death	243	**0.04**	51.4 (45-57.9) 48.6 (45-57.9)	8.7 (4.2-15.4) 0 (0-3.1)	
(sPESI ≥ 1)						66.7 (60.4-72.6) 33.3 (27.4-39.6)	6.1 (3-11.1) 0 (0- 4.4)	NRI (sPESI - PESI)= - 0.159





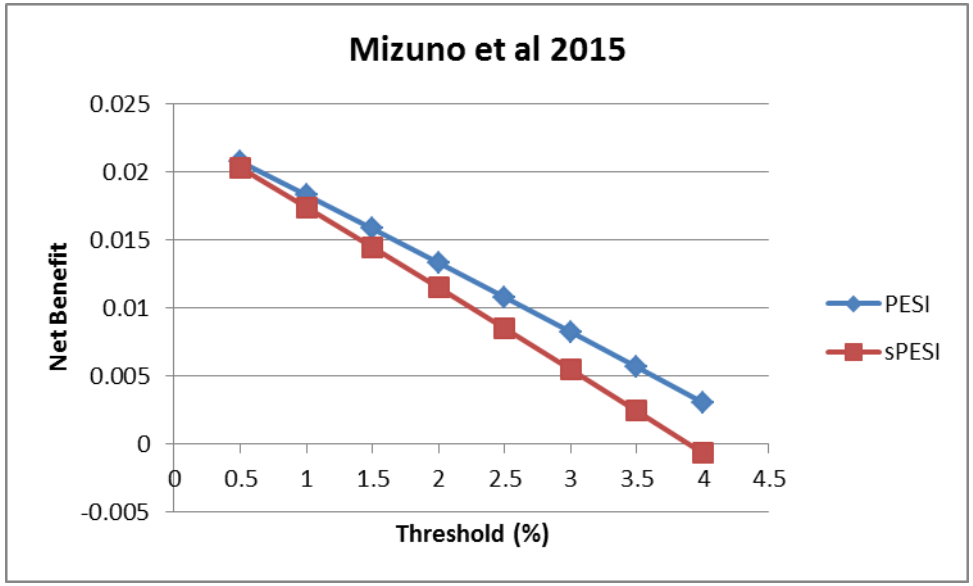
A5.17: PESI - sPESI - GPS

Kabrhel, Okechukwu et al 2014[22] **(Model - Cut-off)**	**Development phase Type of study**	**Patients**	**Time-point Outcome**	**Sample size**	**Population event rate**	**Proportion (95% CI) High-risk Low-risk**	**Event rate (95% CI) High-risk Low-risk**	**Overall Net Reclassification Improvement**
(PESI ≥ III)	External validation Prospective	Stable	30-day All-cause death	291	0.04	51.2 (45.3-57.1) 48.8 (42.9-54.7)	8.1 (4.2-13.6) 0 (0-2.6)	
(sPESI ≥ 1)						65.6 (59.9-71.1) 34.4 (28.9-40.1)	6.3 (3.3-10.7) 0 (0-3.6)	NRI (sPESI - PESI)= - 0.151
(GPS ≥ 3)						24.1 (19.3-29.4) 75.9 (70.6-80.7)	11.4 (5.1-21.3) 1.8 (0.5-4.6)	NRI (GPS - PESI)= = - 0.065



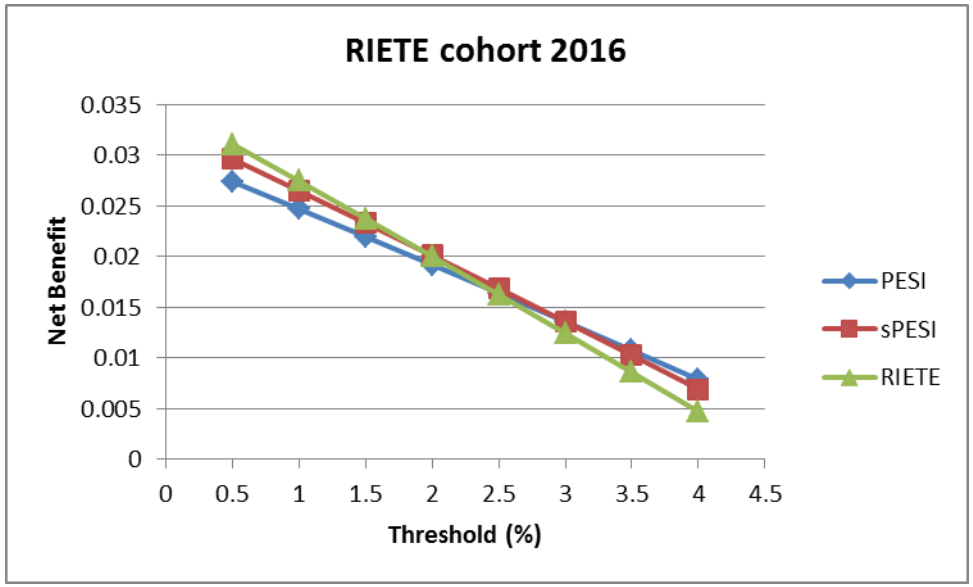
A5.18: PESI - sPESI

Mizuno, Yamamoto et al 2015[23] **(Model - Cut-off)**	**Development phase** **Type of study**	**Patients**	**Time-point** **Outcome**	**Sample size**	**Population event rate**	**Proportion (95% CI)** **High-risk** **Low-risk**	**Event rate (95% CI)** **High-risk** **Low-risk**	**Overall** **Net Reclassification Improvement**
(PESI ≥ III)	External validation Retrospective	Not reported	30-day All-cause death	302	0.02	50.7 (44.9-56.4) 49.3 (43.6-55.1)	4.6 (1.9-9.2) 0 (0-2.4)	
(sPESI ≥ 1)						59.6 (53.8-65.2) 40.4 (34.8-46.2)	3.9 (1.6-7.8) 0 (0-3)	NRI (sPESI - PESI)= - 0.092



A5.19: PESI - sPESI - RIETE (RIETE cohort)

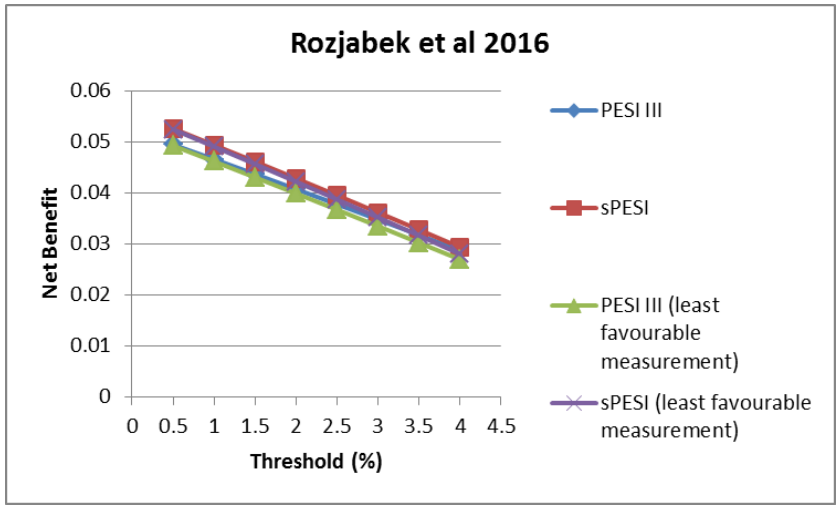
Maestre, Trujillo-Santos et al 2015[24] **(Model - Cut-off)**	**Development phase** **Type of study**	**Patients**	**Time-point** **Outcome**	**Sample size**	**Population event rate**	**Proportion (95% CI)** **High-risk** **Low-risk**	**Event rate (95% CI)** **High-risk** **Low-risk**	**Overall** **Net Reclassification Improvement**
(PESI ≥ III)	External validation Retrospective	Not reported	10-day All-cause death, VTE, major bleeding	18,707	0.04	56.4 (55.7-57.1) 43.6 (42.9-44.3)	5.3 (4.9-5.8) 1.4 (1.2-1.7)	
(sPESI ≥ 1)	External validation Retrospective					65.3 (64.6-66) 34.7 (34-35.4)	5 (4.6-5.4) 1 (0.8-1.3)	NRI (sPESI - PESI)= - 0.016
(RIETE ≥ 1)	Derivation Retrospective					75.6 (75-76.2) 24.4 (23.8-25)	4.6 (4.3-5) 0.6 (0.4-0.9)	NRI (RIETE - PESI)= - 0.066

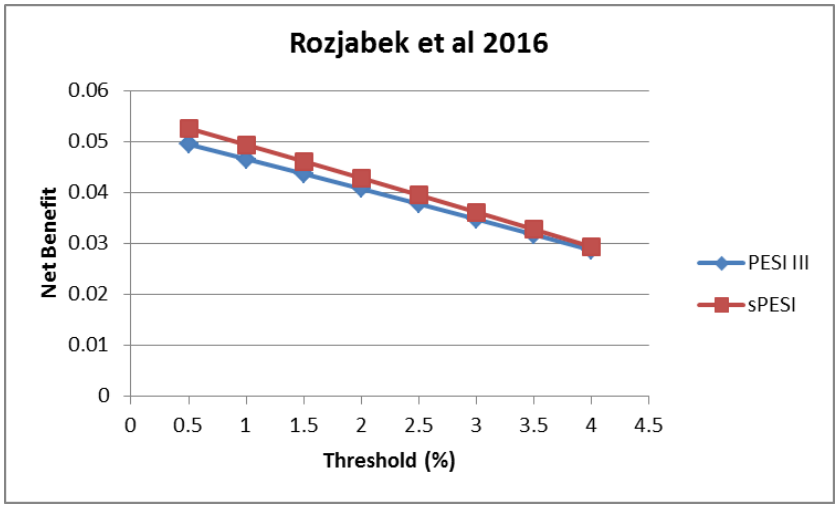


A5.20: PESI - sPESI

Rozjabek, Coleman et al 2016[25] (Model - Cut-off)	Development phase Type of study	Patients	Time-point Outcome	Sample size	Population event rate	Proportion (95% CI) High-risk Low-risk	Event rate (95% CI) High-risk Low-risk	Overall Net Reclassification Improvement
(PESI ≥ III)	External validation Retrospective	Stable	30-day All-cause death	573	0.06	62 (57.8-65.9) 38 (34.1-42.2)	8.5 (5.8-11.8) 1.4 (0.3-4)	
(sPESI ≥ 1)						69.1 (65.1-72.9) 30.9 (27.1-34.9)	8.1 (5.6-11.2) 0.6 (0-3.1)	NRI (sPESI - PESI)= - 0.012
(PESI ≥ III)* (least favourable measurement)						66.1 (62.1-70) 33.9 (30-37.9)	7.9 (5.4-11.1) 1.5 (0.3-4.5)	NRI (PESI* - PESI)= - 0.044
(sPESI ≥ 1)* (least favourable measurement)						72.3 (68.4-75.9) 27.7 (24.1-31.6)	7.7 (5.3-10.7) 0.6 (0-3.5)	NRI (sPESI* - sPESI)= - 0.033

*vital signs measurement timing

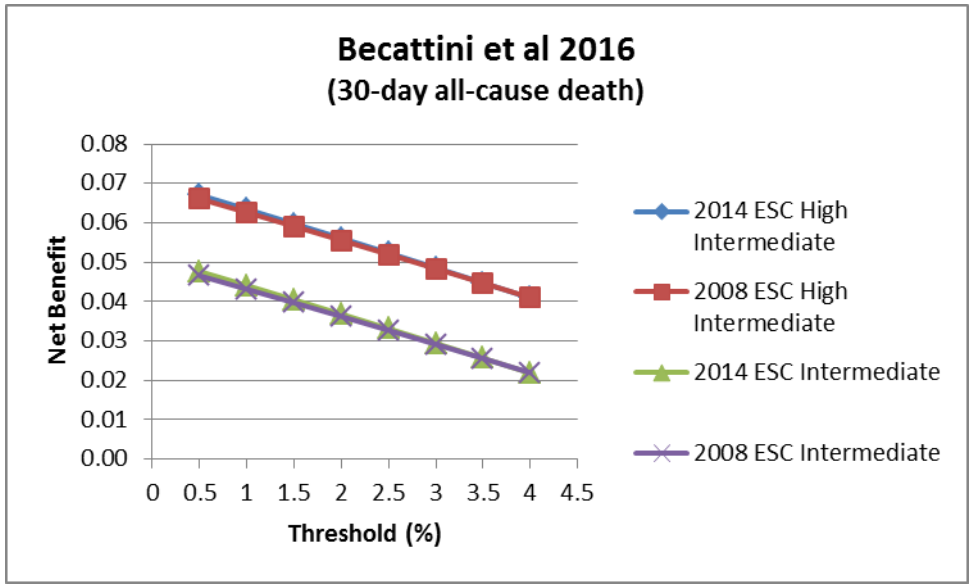




A5.21 (1): 2008 ESC - 2014 ESC

Becattini, Agnelli et al 2016[26] **(Model - Cut-off)**	**Development phase** **Type of study**	**Patients**	**Time-point** **Outcome**	**Sample size**	**Population event rate**	**Proportion (95% CI)** **High-risk** **Low-risk**	**Event rate (95% CI)** **High-risk** **Low-risk**	**Overall** **Net Reclassification** **Improvement**
(2014 ESC High Intermediate)	External validation Retrospective	Both stable and unstable	30-day All-cause death	906	0.07	78.4 (75.5-81) 21.6 (19-24.5)	9 (7-11.4) 0.5 (0-2.8)	
(2008 ESC High Intermediate)						75.4 (72.4-78.2) 24.6 (21.8-27.6)	9.2 (7.2-11.6) 0.9 (0.1-3.2)	NRI* (2008 ESC – 2014 ESC)= 0.016
(2014 ESC Intermediate)		Stable		801	0.05	75.5 (72.4-78.5) 24.5 (21.5-27.6)	6.8 (4.9-9.1) 0.5 (0-2.8)	
2008 ESC Intermediate)						72.2 (68.9-75.2) 27.8 (24.8-31.1)	6.9 (5-9.3) 0.9 (0.1-3.2)	NRI** (2008 ESC – 2014 ESC)= 0.010

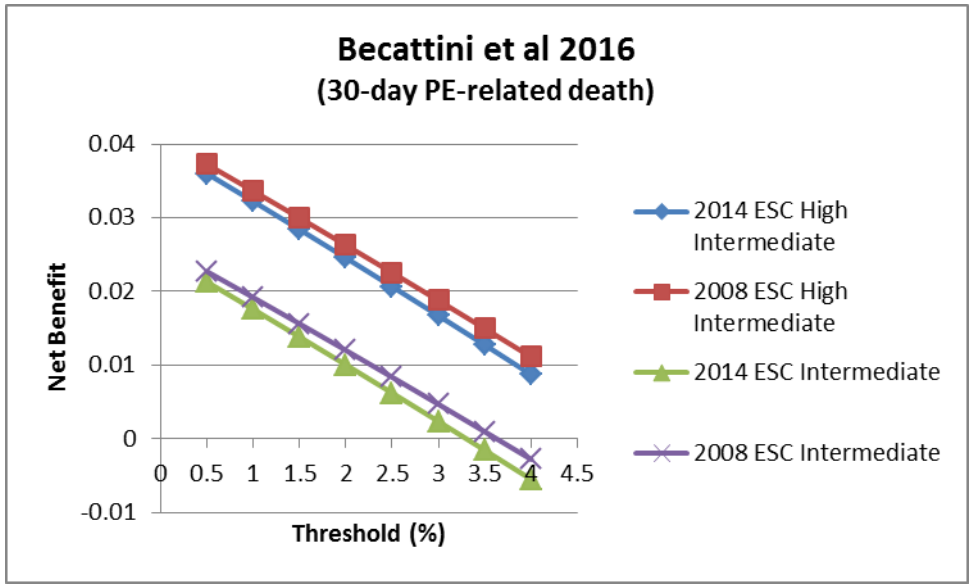
*(High Intermediate), ** (Intermediate)



A5.21 (2): 2008 ESC - 2014 ESC

Becattini, Agnelli et al 2016[26] **(Model - Cut-off)**	**Development phase** **Type of study**	**Patients**	**Time-point** **Outcome**	**Sample size**	**Population event rate**	**Proportion (95% CI)** **High-risk** **Low-risk**	**Event rate (95% CI)** **High-risk** **Low-risk**	**Overall** **Net Reclassification** **Improvement**
(2014 ESC High Intermediate)	External validation Retrospective	Both stable and unstable	30-day PE-related death	906	0.04	78.4 (75.5-81) 21.6 (19-24.5)	5.1 (3.6-7) 0.5 (0-2.8)	
(2008 ESC High Intermediate)						75.4 (72.4-78.2) 24.6 (21.8-27.6)	5.4 (3.8-7.4) 0 (0-1.6)	NRI* (2008 ESC – 2014 ESC)= 0.059
(2014 ESC Intermediate)		Stable		801	0.03	75.5 (72.4-78.5) 24.5 (21.5-27.6)	3.3 (2-5.1) 0.5 (0-2.8)	
(2008 ESC Intermediate)						72.2 (68.9-75.2) 27.8 (24.8-31.1)	3.6 (2.3-5.5) 0 (0-1.6)	NRI** (2008 ESC – 2014 ESC)= 0.084

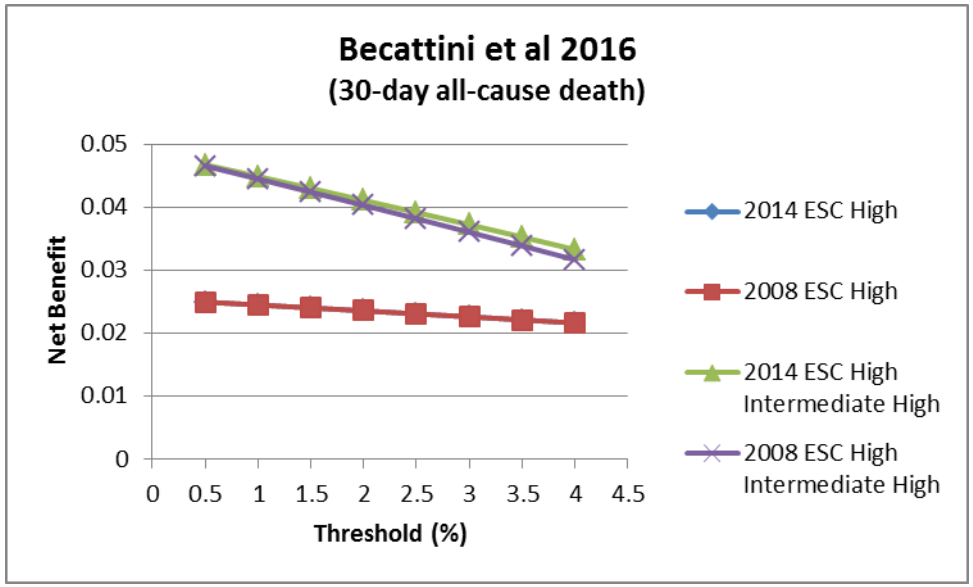
*(High Intermediate), ** (Intermediate)



A5.21 (3): 2008 ESC - 2014 ESC

Becattini, Agnelli et al 2016[26] **(Model - Cut-off)**	**Development phase** **Type of study**	**Patients**	**Time-point** **Outcome**	**Sample size**	**Population event rate**	**Proportion (95% CI)** **High-risk** **Low-risk**	**Event rate (95% CI)** **High-risk** **Low-risk**	**Overall** **Net Reclassification** **Improvement**
(2014 ESC High)	External validation Retrospective	Both stable and unstable	30-day All-cause death	906	0.07	11.6 (9.6-13.9) 88.4 (86.1-90.4)	21.9 (14.4-31) 5.2 (3.8-7)	
(2008 ESC High)						11.6 (9.6-13.9) 88.4 (86.1-90.4)	21.9 (14.4-31) 5.2 (3.8-7)	NRI* (2008 ESC – 2014 ESC)= 0.000
(2014 ESC High Intermediate High)					0.07	41.6 (38.4-44.9) 58.4 (55.1-61.6)	11.7 (8.6-15.3) 4 (2.5-6)	
(2008 ESC High Intermediate High)						45.5 (42.2-48.8) 54.5 (51.2-57.8)	10.7 (7.9-14.1) 4.3 (2.7-6.4)	NRI** (2008 ESC – 2014 ESC)= - 0.042

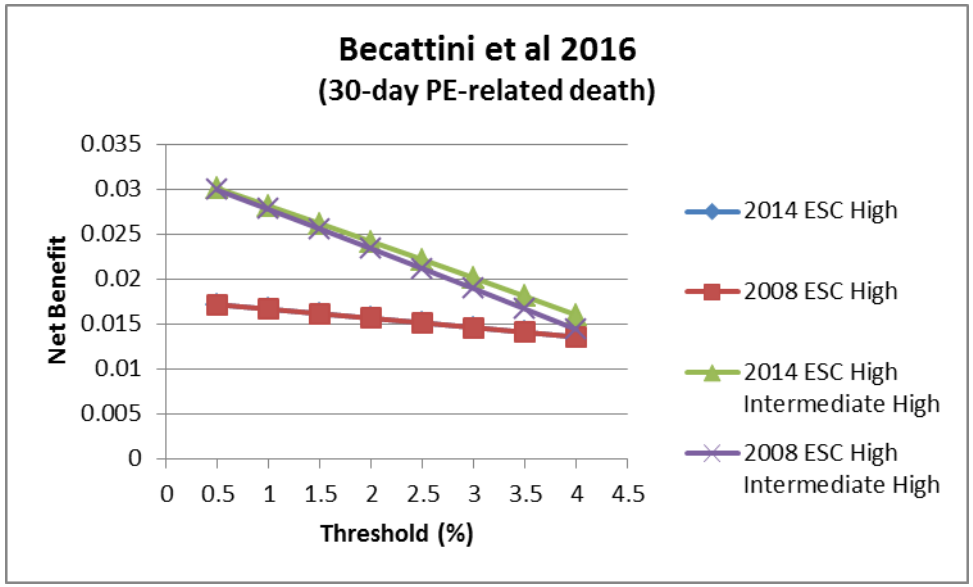
*(High), ** (High Intermediate High)



A5.21 (4): 2008 ESC - 2014 ESC

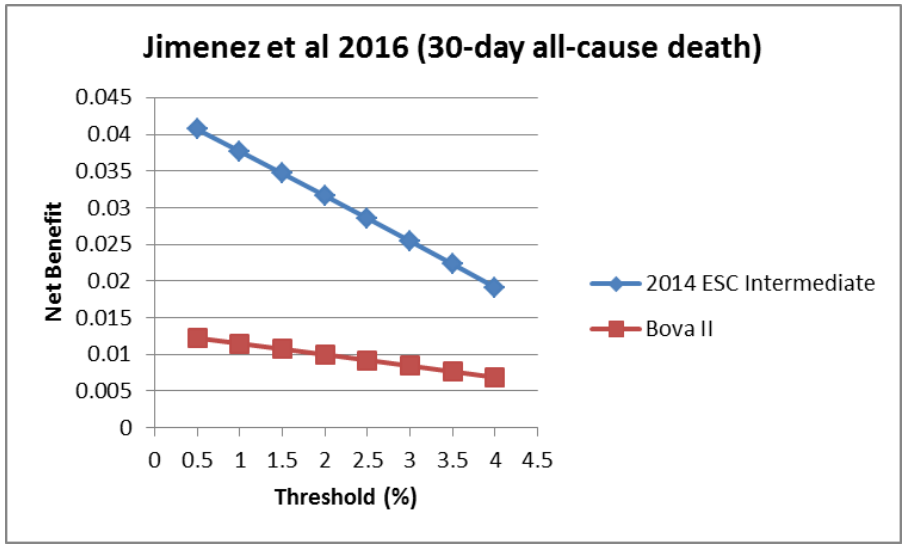
Becattini, Agnelli et al 2016[26] **(Model - Cut-off)**	**Development phase** **Type of study**	**Patients**	**Time-point** **Outcome**	**Sample size**	**Population event rate**	**Proportion (95% CI)** **High-risk** **Low-risk**	**Event rate (95% CI)** **High-risk** **Low-risk**	**Overall** **Net Reclassification Improvement**
(2014 ESC High)	External validation Retrospective	Both stable and unstable	30-day PE-related death	906	0.04	11.6 (9.6-13.9) 88.4 (86.1-90.4)	15.2 (9-23.6) 2.6 (1.6-4)	
(2008 ESC High)						11.6 (9.6-13.9) 88.4 (86.1-90.4)	15.2 (9-23.6) 2.6 (1.6-4)	NRI* (2008 ESC – 2014 ESC)= 0.000
(2014 ESC High Intermediate High)					0.04	41.6 (38.4-44.9) 58.4 (55.1-61.6)	7.7 (5.2-10.9) 1.5 (0.7-3)	
(2008 ESC High Intermediate High)						45.5 (42.2-48.8) 54.5 (51.2-57.8)	7 (4.8-10) 1.6 (0.7-3.2)	NRI** (2008 ESC – 2014 ESC)= - 0.040

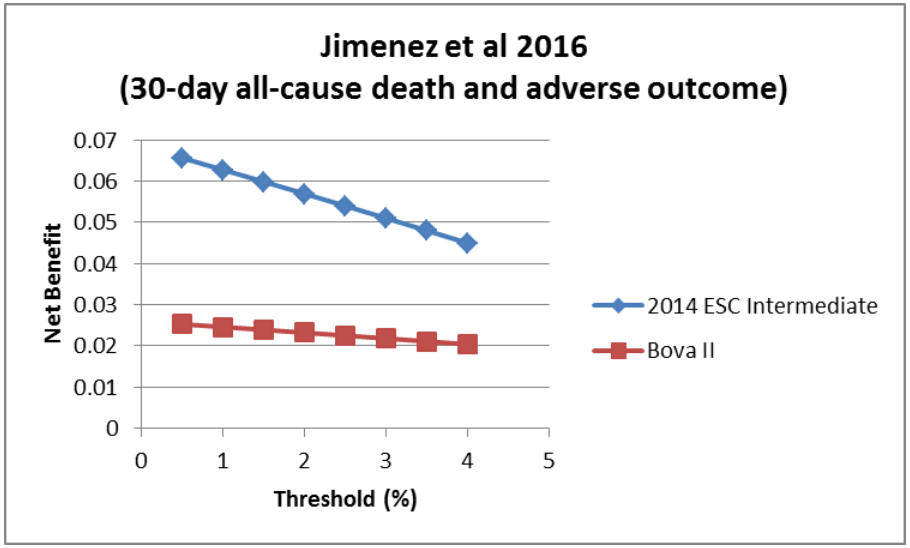
*(High), ** (High Intermediate High)



A5.22: 2014 ESC - Bova

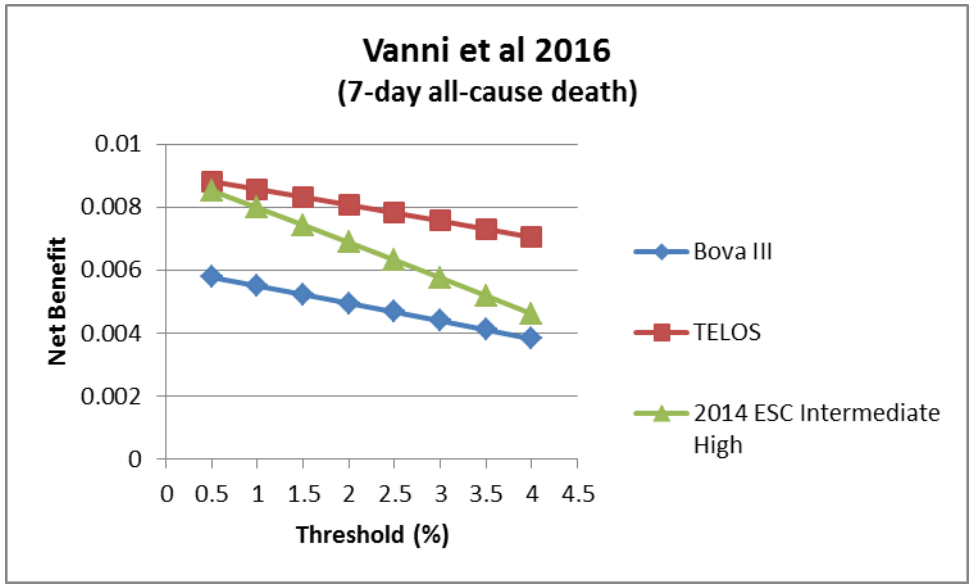
Jimenez, Lobo et al 2016[27] (Model - Cut-off)	Development phase Type of study	Patients	Time-point Outcome	Sample size	Population event rate	Proportion (95% CI) High-risk Low-risk	Event rate (95% CI) High-risk Low-risk	Overall Net Reclassification Improvement
(2014 ESC Intermediate)	External validation Retrospective	Stable	30-day All-cause death	848	0.04	63.1 (59.7-66.3) 36.9 (33.7-40.3)	6.9 (4.9-9.4) 3.2 (0-1.8)	
(Bova ≥ II)						15.9 (13.5-18.6) 84.1 (81.4-86.5)	8.1 (4.1-14.1) 3.8 (2.5-5.5)	NRI (Bova - sPESI)= - 0.222
(2014 ESC Intermediate)			30-day Death Adverse outcome		0.07	63.1 (59.7-66.3) 36.9 (33.7-40.3)	10.8 (8.3-13.8) 1.6 (0.5-3.7)	
(Bova ≥ II)						15.9 (13.5-18.6) 84.1 (81.4-86.5)	16.3 (10.5-23.6) 5.8 (4.2-7.7)	NRI (Bova - sPESI)= - 0.108





A5.23: Bova - TELOS - 2014 ESC

Vanni, Nazerian et al 2016[28] **(Model - Cut-off)**	**Development phase** **Type of study**	**Patients**	**Time-point** **Outcome**	**Sample size**	**Population event rate**	**Proportion (95% CI)** **High-risk** **Low-risk**	**Event rate (95% CI)** **High-risk** **Low-risk**	**Overall** **Net Reclassification Improvement**
(Bova ≥ III)	External validation Retrospective	Stable	7-day All-cause death	994	0.03	5.9 (4.5-7.6) 94.1 (92.4-95.5)	10.2 (3.8-20.8) 2.8 (1.8-4)	
(TELOS)						5.7 (4.4-7.4) 94.3 (92.6-95.6)	15.8 (7.5-27.9) 2.5 (1.6-3.7)	NRI (TELOS - Bova)= 0.099
(2014 ESC Intermediate High)						11.6 (9.6-13.7) 88.4 (86.3-90.4)	7.8 (3.6-14.3) 2.6 (1.7-3.9)	NRI (2014 ESC - Bova)= 0.039



REFERENCES

1. Vanni S, Nazerian P, Pepe G, et al. Comparison of two prognostic models for acute pulmonary embolism: Clinical vs. right ventricular dysfunction-guided approach. Journal of Thrombosis and Haemostasis 2011;**9 (10)**:1916-23.

2. Jimenez D, Yusen RD, Otero R, et al. Prognostic models for selecting patients with acute pulmonary embolism for initial outpatient therapy. Chest 2007;**132**(1):24-30.

3. Sanchez O, Trinquart L, Caille V, et al. Prognostic factors for pulmonary embolism: The PREP study, a prospective multicenter cohort study. American journal of respiratory and critical care medicine 2010;**181 (2)**:168-73.

4. Sanchez O, Trinquart L, Planquette B, et al. Echocardiography and pulmonary embolism severity index have independent prognostic roles in pulmonary embolism. European Respiratory Journal 2013;**42**(3):681-88.

5. Jiménez D, Kopecna D, Tapson V, et al. Derivation and Validation of Multimarker Prognostication for Normotensive Patients with Acute Symptomatic Pulmonary Embolism. American journal of respiratory and critical care medicine 2014;**189**(6):718-26.

6. Chan CM, Woods C, Shorr AF. The validation and reproducibility of the pulmonary embolism severity index. Journal of Thrombosis and Haemostasis 2010;**8 (7)**:1509-14.

7. Chan CM, Woods CJ, Shorr AF. Comparing the pulmonary embolism severity index and the prognosis in pulmonary embolism scores as risk stratification tools. J Hosp Med 2012;**7**(1):22-27.

8. Lankeit M, Gomez V, Wagner C, et al. A strategy combining imaging and laboratory biomarkers in comparison with a simplified clinical score for risk stratification of patients with acute pulmonary embolism. Chest 2012;**141 (4)**:916-22.

9. Ozsu S, Ozlu T, Şentürk A, et al. Combination and comparison of two models in prognosis of pulmonary embolism: Results from TUrkey Pulmonary Embolism Group (TUPEG) study. Thrombosis research 2014;**133**(6):1006-10.

10. Cordeanu M, Gaertner S, Faller A, et al. Prognostic value of the simplified PESI score in comparison with the 2014 ESC risk model in pulmonary embolism. International journal of cardiology 2016;**220**:623-4.

11. Dellas C, Tschepe M, Seeber V, et al. A novel H-FABP assay and a fast prognostic score for risk assessment of normotensive pulmonary embolism. Thrombosis and haemostasis 2014;**111**(5):996-1003.

12. Zondag W, den Exter PL, Crobach MJT, et al. Comparison of two methods for selection of out of hospital treatment in patients with acute pulmonary embolism. Thrombosis and haemostasis 2013;**109**(1):47-52.

13. Sam A, Sanchez D, Gomez V, et al. The shock index and the simplified PESI for identification of low-risk patients with acute pulmonary embolism. European Respiratory Journal 2011;**37 (4)**:762-66.

14. Ferrer M, Morillo R, Elias T, et al. Validation of two clinical prognostic models in patients with acute symptomatic pulmonary embolism. Archivos de bronconeumologia 2013;**49**(10):427-31.

15. Vanni S, Jimenez D, Nazerian P, et al. Short-term clinical outcome of normotensive patients with acute PE and high plasma lactate. Thorax 2015;**70**(4):333-8.

16. Paiva LV, Providencia RC, Barra SN, et al. Cardiovascular risk assessment of pulmonary embolism with the GRACE risk score. The American journal of cardiology 2013;**111**(3):425-31.

17. Aujesky D, Obrosky DS, Stone RA, et al. Derivation and validation of a prognostic model for pulmonary embolism. American journal of respiratory and critical care medicine 2005;**172 (8)**:1041-46.

18. Aujesky D, Obrosky DS, Stone RA, et al. A prediction rule to identify low-risk patients with pulmonary embolism. Archives of internal medicine 2006;**166 (2)**:169-75.

19. Venetz C, Jimenez D, Mean M, et al. A comparison of the original and simplified pulmonary embolism severity index. Thrombosis and haemostasis 2011;**106 (3)**:423-28.

20. Jimenez D, Aujesky D, Moores L, et al. Simplification of the pulmonary embolism severity index for prognostication in patients with acute symptomatic pulmonary embolism. Archives of internal medicine 2010;**170 (15)**:1383-89.

21. Erkens PMG, Gandara E, Wells PS, et al. Does the Pulmonary Embolism Severity Index accurately identify low risk patients eligible for outpatient treatment? Thrombosis research 2012;**129 (6)**:710-14.

22. Kabrhel C, Okechukwu I, Hariharan P, et al. Factors associated with clinical deterioration shortly after PE. Thorax 2014;**69**(9):835-42.

23. Mizuno A, Yamamoto T, Tanabe Y, et al. Pulmonary Embolism Severity Index and Simplified Pulmonary Embolism Severity Index Risk Scores Are Useful to Predict Mortality in Japanese Patients With Pulmonary Embolism. Circulation Journal 2015;**79**(4):889-91.

24. Maestre A, Trujillo-Santos J, Riera-Mestre A, et al. Identification of Low-Risk Patients with Acute Symptomatic Pulmonary Embolism for Outpatient Therapy. Annals of the American Thoracic Society 2015;**12**(8):1122-9.

25. Rozjabek HM, Coleman CI, Weeda ER, et al. Effect of vital sign measurement timing on Pulmonary Embolism Severity Index (PESI) and simplified PESI 30-day mortality risk determination. Thrombosis research 2016;**141**:8-10.

26. Becattini C, Agnelli G, Lankeit M, et al. Acute pulmonary embolism: mortality prediction by the 2014 European Society of Cardiology risk stratification model. European Respiratory Journal 2016;**48**(3):780-6.

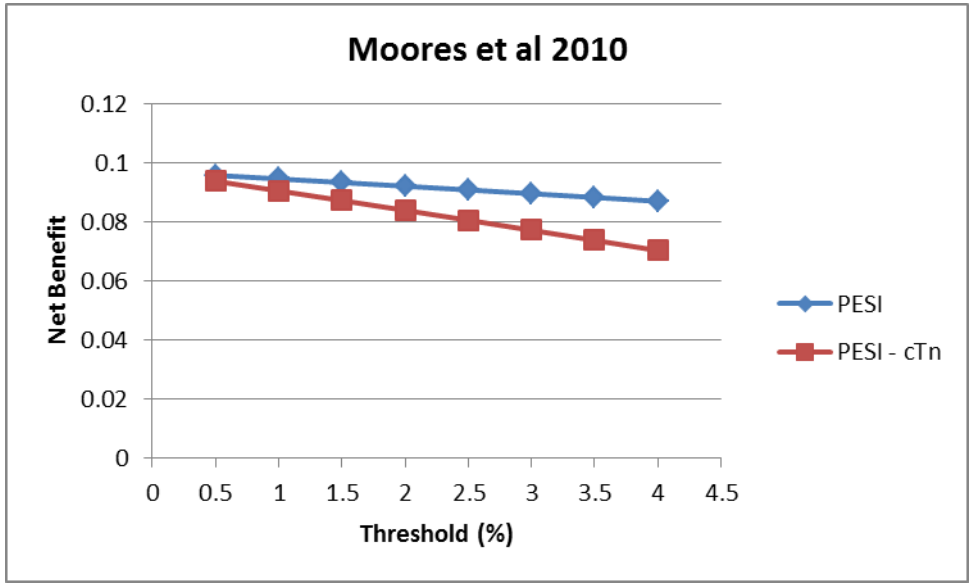
27. Jimenez D, Lobo JL, Fernandez-Golfin C, et al. Effectiveness of prognosticating pulmonary embolism using the ESC algorithm and the Bova score. Thrombosis and haemostasis 2016;**115**(4):827-34.

28. Vanni S, Nazerian P, Bova C, et al. Comparison of clinical scores for identification of patients with pulmonary embolism at intermediate–high risk of adverse clinical outcome: the prognostic role of plasma lactate. Internal and emergency medicine 2016:1-9.

TABLES AND FIGURES A5.24 TO A5.39 (UPDATED MODELS VERSUS ORIGINAL MODELS)

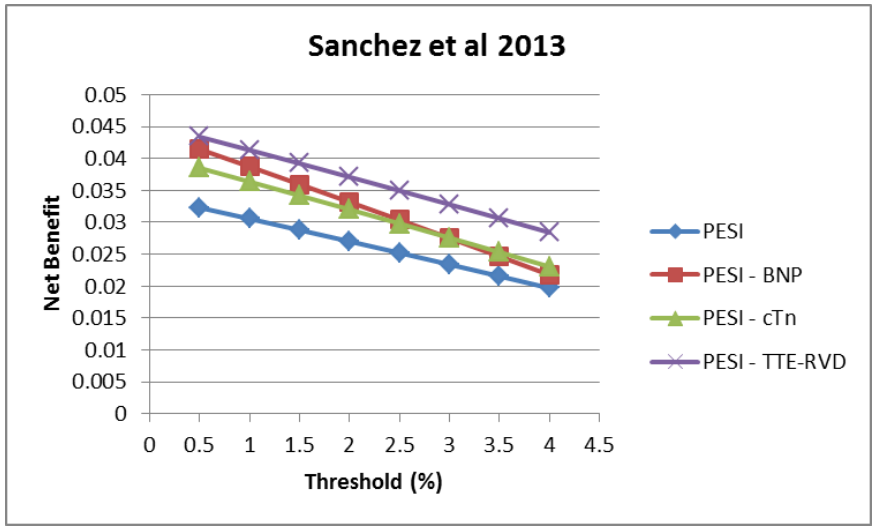
A5.24: PESI - cTn

Moores, Aujesky et al. 2010[1] **(Model - Cut-off)**	**Development phase** **Type of study**	**Patients**	**Time-point** **Outcome**	**Sample size**	**Population event rate**	**Proportion (95% CI)** **High-risk** **Low-risk**	**Event rate (95% CI)** **High-risk** **Low-risk**	**Overall** **Net Reclassification Improvement**
(PESI)	External validation Update Retrospective	Stable	30-day All-cause death	567	0.10	33.7 (29.8-37.7) 66.3 (62.3-70.2)	28.8 (22.5-35.8) 0.5 (0.1-1.96)	
(PESI – cTn)						73.7 (69.9-77.3) 26.3 (22.7-30.1)	13.2 (10.1-16.8) 1.3 (0.2-4.8)	NRI = - 0.445



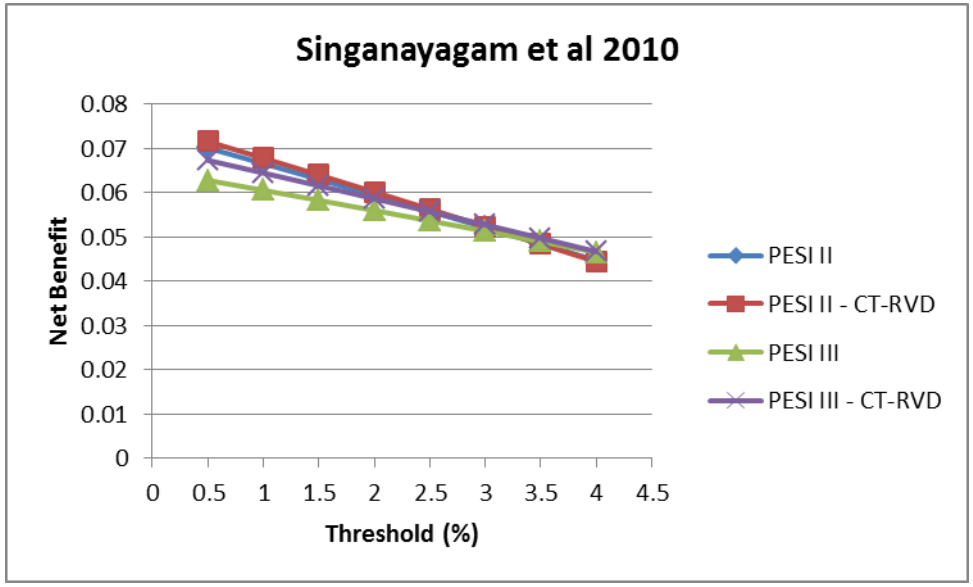
A5.25: PESI - BNP - cTn - TTE-RVD (PREP cohort)

Sanchez, Trinquart et al 2013[2] **(Model - Cut-off)**	**Development phase Type of study**	**Patients**	**Time-point Outcome**	**Sample size**	**Population event rate**	**Proportion (95% CI) High-risk Low-risk**	**Event rate (95% CI) High-risk Low-risk**	**Overall Net Reclassification Improvement**
(PESI ≥ III)	External validation Update Prospective & Retrospective	Stable	30-day Adverse outcome	529	0.05	37.8 (33.7-42.1) 62.2 (57.9-66.3)	9 (5.4-13.9) 2.1 (0.9-4.3)	
(PESI - BNP)				521		58.2 (53.8-62.4) 41.8 (37.6-46.2)	7.6 (4.9-11.2) 0.9 (0.1-3.3)	NRI (PESI BNP - PESI)= - 0.003
(PESI - cTn)				517		46.2 (41.9-50.6) 53.8 (49.4-58.1)	8.9 (5.5-13.1) 1.1 (0.2-3.1)	NRI (PESI cTn - PESI)= 0.074
(PESI - TTE-RVD)				484		45.5 (41-50) 54.5 (50-59)	10 (6.4-14.7) 1.1 (0.2-3.3)	NRI (PESI TTE-RVD - PESI)= 0.09



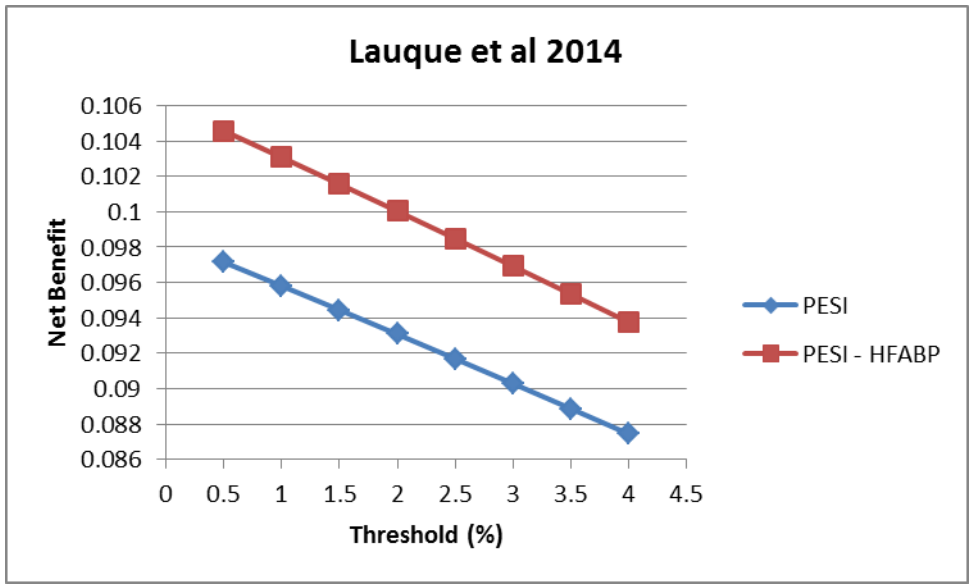
A5.26: PESI - CT-RVD

Singanayagam, Chalmers et al 2010[3] **(Model - Cut-off)**	**Development phase** **Type of study**	**Patients**	**Time-point** **Outcome**	**Sample size**	**Population event rate**	**Proportion (95% CI)** **High-risk** **Low-risk**	**Event rate (95% CI)** **High-risk** **Low-risk**	**Overall** **Net Reclassification** **Improvement**
(PESI ≥ II)	External validation Update Retrospective	Both stable and unstable	30-day All-cause death	585	0.08	76.6 (72.9-80) 23.4 (20-27.1)	9.6 (7-12.7) 0.7 (0-0.4)	
(PESI ≥ II – CT-RVD)						81.5 (78.2-84.6) 18.5 (15.4-21.8)	9.2 (6.8-12.2) 0 (0-3.4)	-0.029
(PESI ≥ III)						50.8 (46.6-54.9) 49.2 (45.1-53.4)	12.8 (9.2-17.1) 2.1 (0.8-4.5)	
(PESI ≥ III – CT-RVD)						63.2 (59.2-67.2) 36.8 (32.8-40.8)	11.1 (8.1-14.7) 1.4 (0.3-4)	-0.061



A5.27: PESI - H-FABP

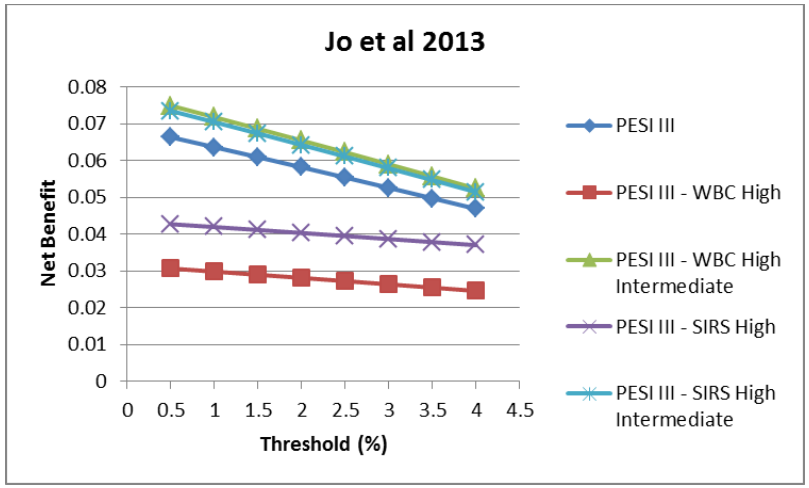
Lauque, Maupas-Schwalm et al 2014[4] **(Model - Cut-off)**	**Development phase** **Type of study**	**Patients**	**Time-point** **Outcome**	**Sample size**	**Population event rate**	**Proportion (95% CI)** **High-risk** **Low-risk**	**Event rate (95% CI)** **High-risk** **Low-risk**	**Overall** **Net Reclassification** **Improvement**
(PESI ≥ III)	External validation Update Prospective	Both stable and unstable	30-day Adverse outcome	132	0.11	36.4 (28.2-45.2) 63.6 (54.8-71.8)	27.1 (15.3-41.8) 1.2 (0-6.5)	
(PESI - H-FABP)						40.2 (31.7-49) 59.8 (51-68.3)	26.4 (15.3-40.3) 0 (0-4.6)	NRI (PESI-H-FABP – PESI)= 0.038



A5.28: PESI - WBC - SIRS

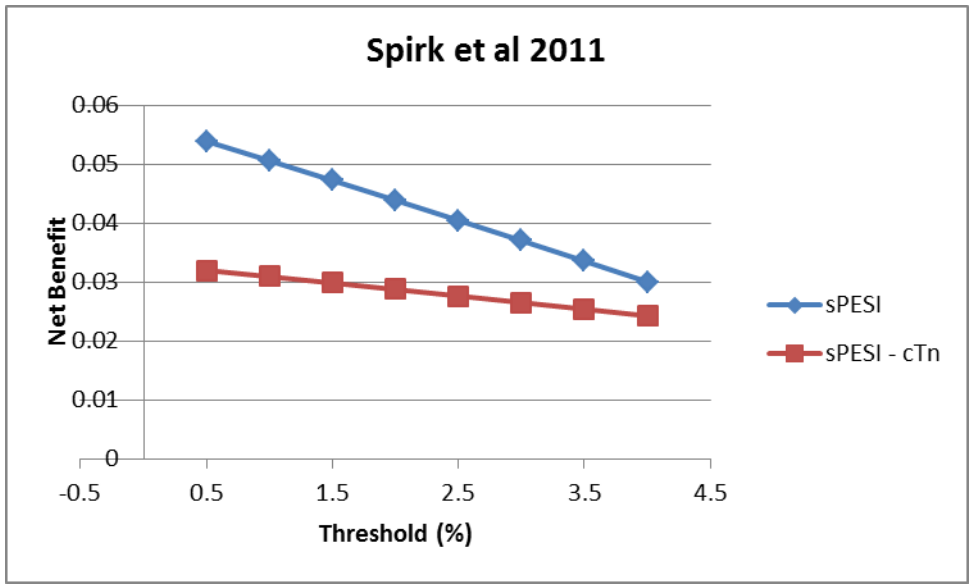
Jo, J., M. Lee, et al. 2013[5] **(Model - Cut-off)**	**Development phase** **Type of study**	**Patients**	**Time-point** **Outcome**	**Sample size**	**Population event rate**	**Proportion (95% CI)** **High-risk** **Low-risk**	**Event rate (95% CI)** **High-risk** **Low-risk**	**Overall** **Net Reclassification Improvement**
(PESI ≥ III)	External validation Update Retrospective	Both stable and unstable	30-day All-cause death	667	0.09	60 (56.1-63.7) 40 (36.3-43.9)	11.5 (8.5-15) 4.1 (2.1-7.3)	
(PESI ≥ III - WBC High)						19.8 (16.8-23) 80.2 (77-83.2)	15.9 (10.1-23.3) 6.7 (4.8-9.2)	*NRI= - 0.040
(PESI ≥ III - WBC High Intermediate)						69.3 (65.6-72.8) 30.7 (27.2-34.4)	11.3 (8.5-14.5) 2.4 (0.8-5.6)	*NRI= 0.013
(PESI ≥ III - SIRS High)						19.9 (17-23.2) 80.1 (76.8-83)	21.8 (15.1-29.8) 5.2 (3.5-7.5)	*NRI= 0.112
(PESI ≥ III - SIRS High Intermediate)						67.8 (64.1-71.3) 32.2 (28.7-35.9)	11.3 (8.5-14.6) 2.8 (1-6)	*NRI= 0.011

*NRI is calculated from Δ sensitivity + Δ specificity of [(PESI + added marker) – (PESI)]



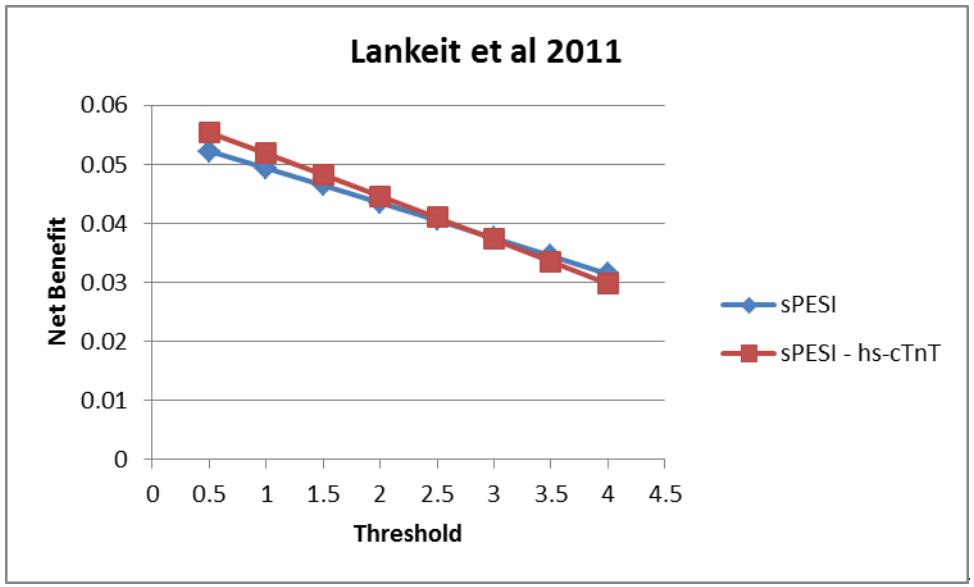
A5.29: sPESI - cTn

Spirk, Aujesky et al. 2011[6] **(Model - Cut-off)**	**Development phase** **Type of study**	**Patients**	**Time-point** **Outcome**	**Sample size**	**Population event rate**	**Proportion (95% CI)** **High-risk** **Low-risk**	**Event rate (95% CI)** **High-risk** **Low-risk**	**Overall** **Net Reclassification Improvement**
(sPESI)	External validation Retrospective	Both stable and unstable	30-day Death VTE	332	0.06	70.8 (65.6-75.6) 29.2 (24.4-34.4)	8.1 (4.9-12.3) 1 (0-5.6)	
(sPESI - cTn)						24.4 (19.9-29.4) 75.6 (70.6-80.1)	13.6 (7-23) 3.6 (1.7-6.7)	NRI (sPESI-cTn – sPESI)= 0.068



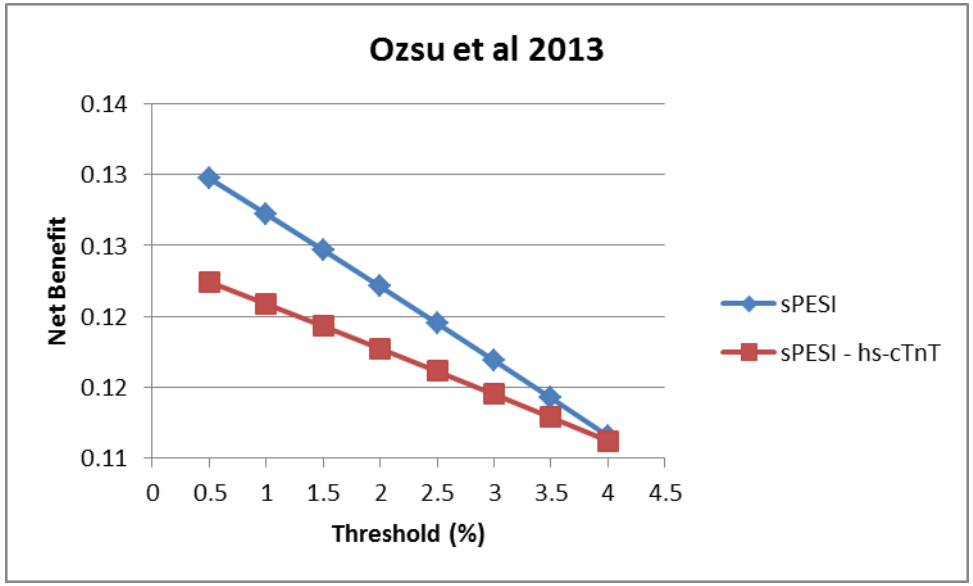
A5.30: sPESI - hs-cTnT

Lankeit, Jimenez et al 2011[7] **(Model - Cut-off)**	**Development phase** **Type of study**	**Patients**	**Time-point** **Outcome**	**Sample size**	**Population event rate**	**Proportion (95% CI)** **High-risk** **Low-risk**	**Event rate (95% CI)** **High-risk** **Low-risk**	**Overall** **Net Reclassification Improvement**
(sPESI)	Update Prospective	Stable	30-day Adverse outcome	526	0.06	62.4 (58.1-66.5) 37.6 (33.5-41.9)	8.8 (6-12.5) 1 (0.1-3.6)	
(sPESI - hs-cTnT)						75.9 (72-79.5) 24.1 (20.5-28)	7.8 (5.3-10.8) 0 (0-2.9)	NRI = - 0.075



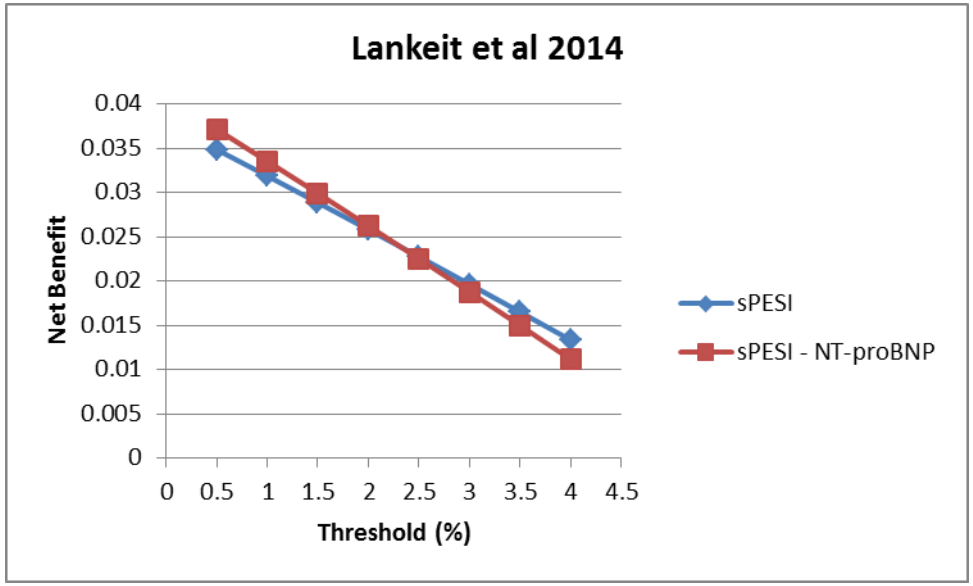
A5.31: sPESI - hs-cTnT

Ozsu, Abul et al 2013[8] **(Model - Cut-off)**	**Development phase** **Type of study**	**Patients**	**Time-point** **Outcome**	**Sample size**	**Population event rate**	**Proportion (95% CI)** **High-risk** **Low-risk**	**Event rate (95% CI)** **High-risk** **Low-risk**	**Overall** **Net Reclassification Improvement**
(sPESI)	External validation Update Prospective	Stable	30-day All-cause death	121	0.13	62.8 (53.6-71.4) 37.2 (28.6-46.4)	21.1 (12.5-31.9) 0 (0-7.8)	
(sPESI - hs-cTnT)						43 (34-52.3) 57 (47.7-66)	28.8 (17.1-43.1) 1.4 (0-7.8)	NRI = 0.157



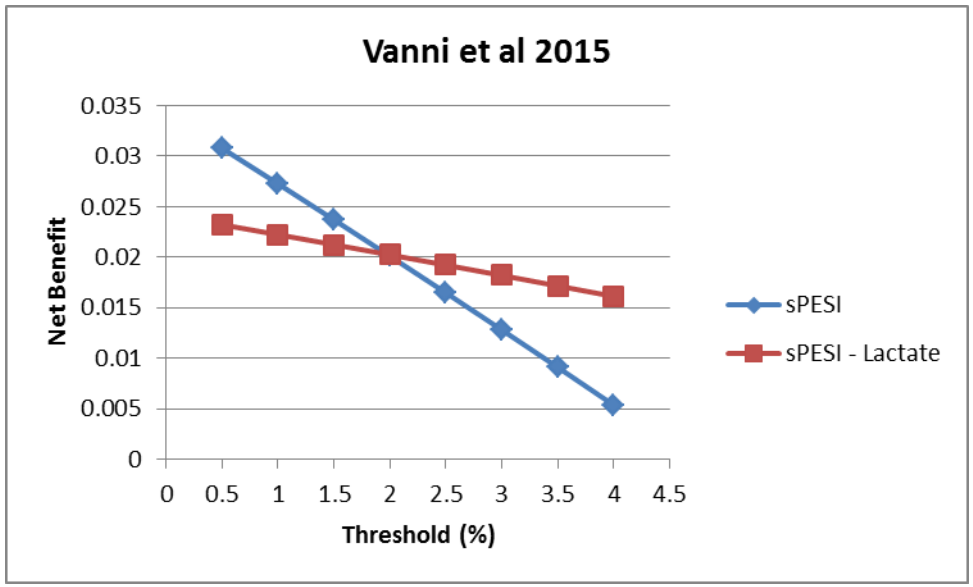
A5.32: sPESI - NT-proBNP

Lankeit, Jiménez et al 2014[9] **(Model - Cut-off)**	**Development phase** **Type of study**	**Patients**	**Time-point** **Outcome**	**Sample size**	**Population event rate**	**Proportion (95% CI)** **High-risk** **Low-risk**	**Event rate (95% CI)** **High-risk** **Low-risk**	**Overall** **Net Reclassification Improvement**
(sPESI)	External validation Update Prospective	Stable	30-day All-cause death	688	0.04	62.5 (58.8-66.1) 37.5 (33.9-41.2)	6 (4-8.7) 0.8 (0-2.8)	
(sPESI - NT-proBNP)						75 (71.6-78.2) 25 (21.8-28.4)	5.4 (3.6-7.7) 0(0-2.1)	NRI = - 0.056



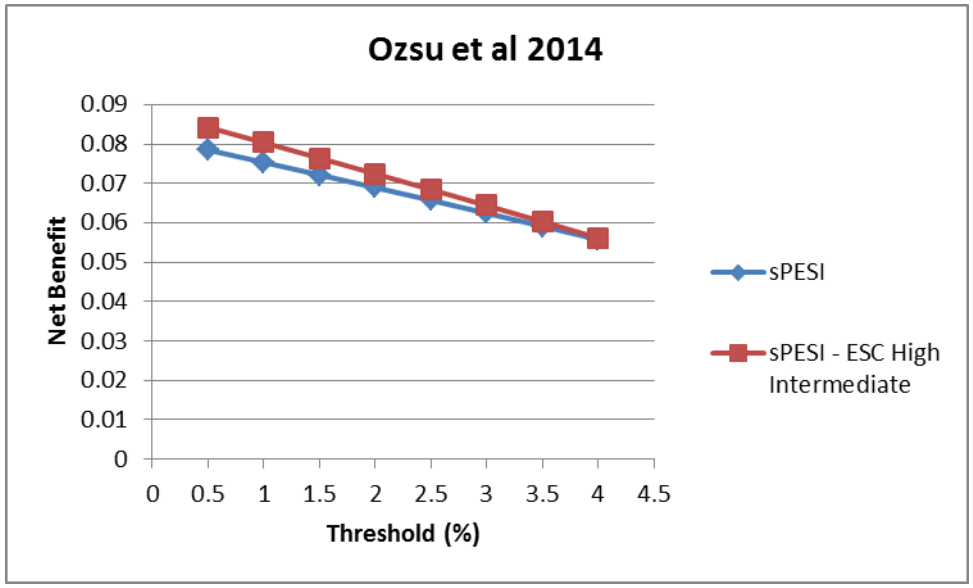
A5.33: sPESI - Lactate (TELOS cohort)

Vanni, Jimenez et al 2015[10] **(Model - Cut-off)**	**Development phase** **Type of study**	**Patients**	**Time-point** **Outcome**	**Sample size**	**Population event rate**	**Proportion (95% CI)** **High-risk** **Low-risk**	**Event rate (95% CI)** **High-risk** **Low-risk**	**Overall** **Net Reclassification Improvement**
(sPESI)	External validation Update Prospective	Stable	7-day PE-related complications	496	0.04	72.8 (68.6-76.7) 27.2 (23.3-31.4)	4.7 (2.8-7.4) 2.2 (0.5-6.4)	
(sPESI – Lactate)						21.8 (18.2-25.7) 78.2 (74.3-81.8)	11.1 (5.9-18.6) 2.1 (0.9-4)	NRI (sPESI-Lactate – sPESI)= 0.271



A5.34: sPESI - ESC

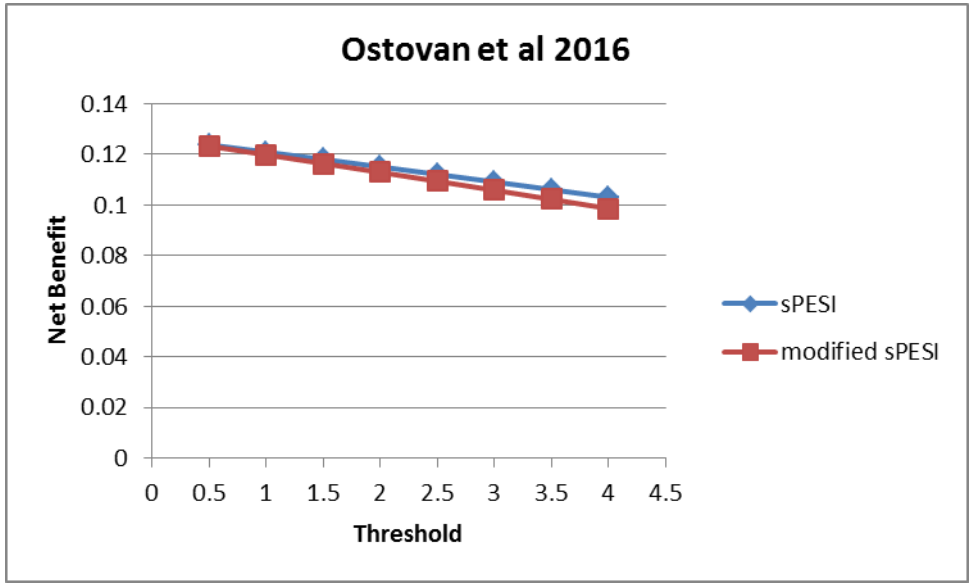
Ozsu, Ozlu et a 2014[11] **(Model - Cut-off)**	**Development phase** **Type of study**	**Patients**	**Time-point** **Outcome**	**Sample size**	**Population event rate**	**Proportion (95% CI)** **High-risk** **Low-risk**	**Event rate (95% CI)** **High-risk** **Low-risk**	**Overall** **Net Reclassification Improvement**
(sPESI)	External validation Prospective	Both stable and unstable	30-day All-cause death	1078	0.09	70.1 (67.3-72.9) 29.9 (27.1-32.7)	11.6 (9.4-14.1) 2.2 (0.9-4.4)	
(sPESI - ESC High Intermediate)	Update Prospective					85.4 (83.2-87.5) 14.6 (12.5-16.8)	10.3 (8.4-12.5) 0 (0-2.3)	NRI (Both – sPESI)=- 0.087



A5.35: sPESI – modified-sPESI

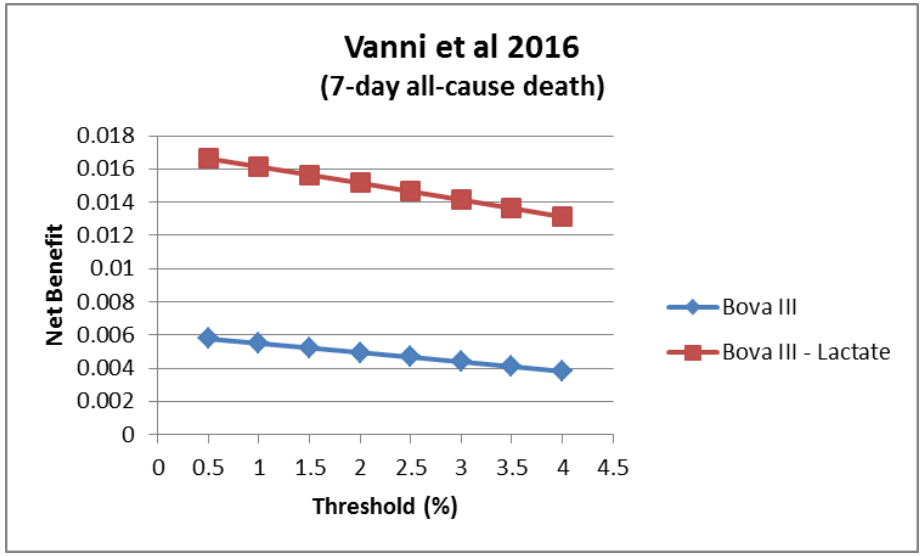
Ostovan, Ghaffari et al 2016[12] **(Model - Cut-off)**	**Development phase** **Type of study**	**Patients**	**Time-point** **Outcome**	**Sample size**	**Population event rate**	**Proportion (95% CI)** **High-risk** **Low-risk**	**Event rate (95% CI)** **High-risk** **Low-risk**	**Overall** **Net Reclassification Improvement**
(sPESI)	External validation Derivation Prospective	Both stable and unstable	In-hospital All-cause death	300	0.13	69.3 (63.8-74.5) 30.7 (25.5-36.2)	18.3 (13.3-24.2) 0 (0-3.9)	
(modified-sPESI)*						80 (75-84.4) 20 (15.6-25)	15.8 (11.5-21.1) 0 (0-6)	NRI (modified-sPESI – sPESI)= - 0.122

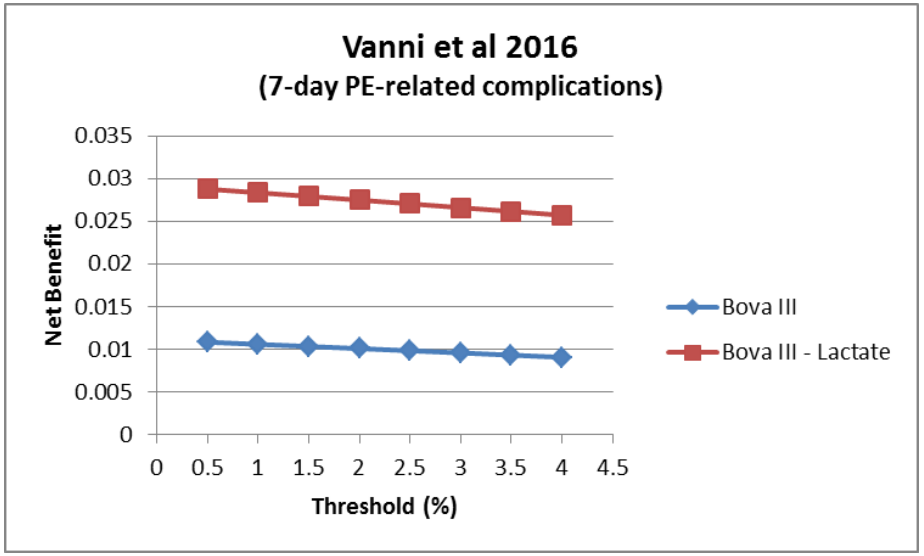
* electrocardiographic evidence of right ventricular strain as a new criteria, and replacement of O2 saturation in sPESI by PaO2 /PaCO2 ratio obtained from the arterial blood gas analysis.



A5.36: Bova - Lactate

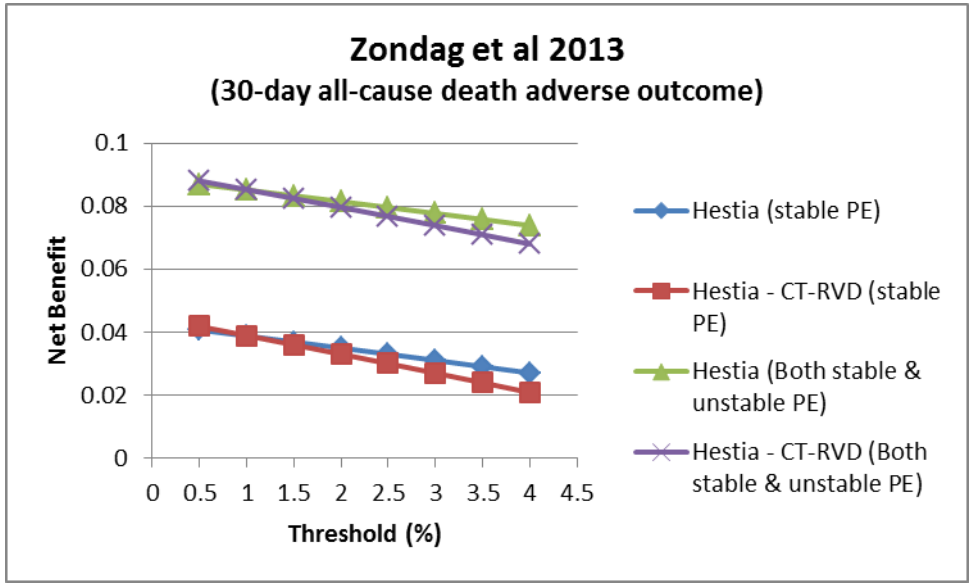
Vanni, Nazerian et al 2016[13] **(Model - Cut-off)**	**Development phase** **Type of study**	**Patients**	**Time-point** **Outcome**	**Sample size**	**Population event rate**	**Proportion (95% CI)** **High-risk** **Low-risk**	**Event rate (95% CI)** **High-risk** **Low-risk**	**Overall** **Net Reclassification Improvement**
(Bova III)	External validation Update Retrospective	Stable	7-day All-cause death	994	0.03	5.9 (4.5-7.6) 94.1 (92.4-95.5)	10.2 (3.8-20.8) 2.8 (1.8-4)	
(Bova III - Lactate)						11.3 (9.4-13.4) 88.7 (86.6-90.6)	15.2 (9.1-23.2) 1.7 (1-2.8)	NRI (Bova-Lactate – Bova)= 0.300
(Bova III)			7-day PE-related complications	994	0.06	5.9 (4.5-7.6) 94.1 (92.4-95.5)	18.6 (9.7-30.9) 5.6 (4.2-7.2)	
(Bova III - Lactate)						11.3 (9.4-13.4) 88.7 (86.6-90.6)	25.9 (18.1-35) 3.9 (2.7-5.3)	NRI (Bova-Lactate – Bova)= 0.248





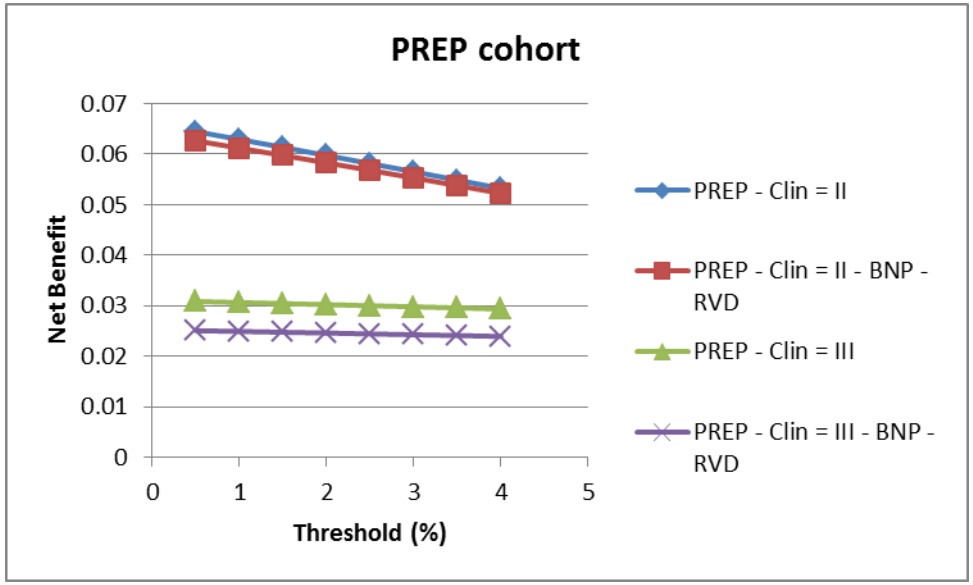
A5.37: Hestia - CT-RVD (Hestia cohort)

Zondag, Vingerhoets et al 2013[14] **(Model - Cut-off)**	**Development phase** **Type of study**	**Patients**	**Time-point** **Outcome**	**Sample size**	**Population event rate**	**Proportion (95% CI)** **High-risk** **Low-risk**	**Event rate (95% CI)** **High-risk** **Low-risk**	**Overall** **Net Reclassification Improvement**
(Hestia)	External validation Prospective	Stable	30-day Death Adverse outcome	470	0.05	41.5 (37-46.1) 58.5 (53.9-63)	10.3 (6.4-15.4) 0.7 (0-2.6)	
(Hestia - CT-RVD)	Update Retrospective					61.7 (57.1-66.1) 38.3 (33.9-42.9)	7.2 (4.5-10.9) 0.6 (0-3.1)	Hestia - CT-RVD – Hestia=- 0.164
(Hestia)	External validation Prospective	Both stable and unstable		496	0.09	44.6 (40.1-49.1) 55.4 (50.9-59.9)	19.9 (14.9-25.8) 0.7 (0.1-2.6)	
((Hestia - CT-RVD)	Update Retrospective					63.7 (59.3-67.9) 36.3 (32.1-40.7)	14.2 (10.6-18.6) 0.6 (1.4-3.1)	Hestia - CT-RVD – Hestia= - 0.187



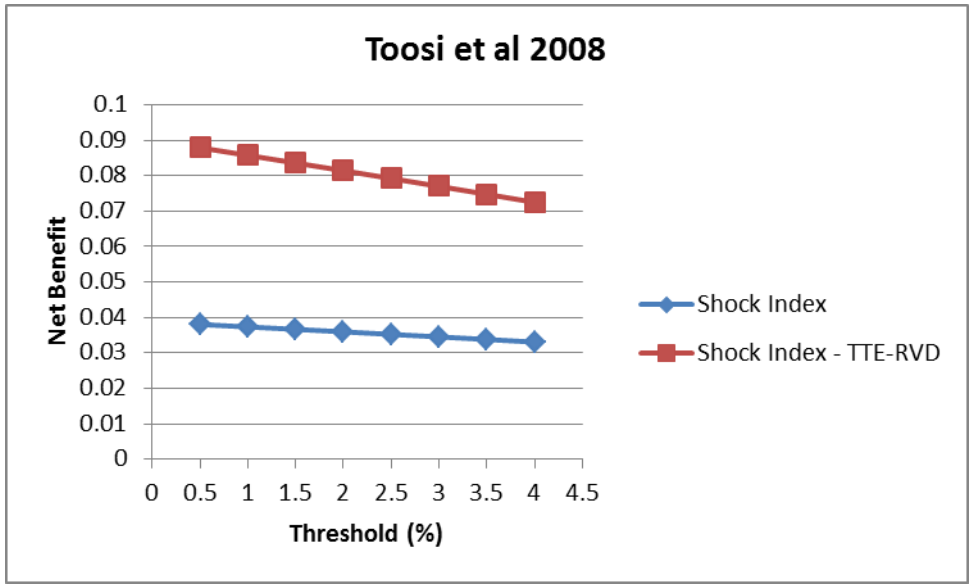
A5.38: PREP - BNP - TTE-RVD (PREP cohort)

Sanchez, Trinquart et al. 2010[15] (Model - Cut-off)	Development phase Type of study	Patients	Time-point Outcome	Sample size	Population event rate	Proportion (95% CI) High-risk Low-risk	Event rate (95% CI) High-risk Low-risk	Overall Net Reclassification Improvement
(PREP - Clin II)	Derivation Update Prospective	Both stable and unstable	30-day Death VTE	515	0.05	37.3 (33.1-41.6) 62.7 (58.4-66.9)	17.7 (12.6-23.9) 2.5 (1.1-4.8)	
(PREP - Clin II - BNP – RVD)						34.8 (30.6-39) 65.2 (61-69.4)	18.4 (13-24.9) 2.1 (0.8-4.2)	NRI (PREP-BNP-RVD – PREP)= 0.042
(PREP - Clin III)						7.2 (5.1-9.8) 92.8 (90.2-94.9)	43.2 (27.1-60.5) 5.4 (3.6-7.9)	
(PREP - Clin III - BNP - RVD)						5.6 (3.8-8) 94.4 (92-96.2)	44.8 (26.4-64.3) 5.6 (3.7-8)	NRI (PREP-BNP-RVD – PREP)= - 0.045



A5.39: Shock Index - TTE-RVD

Toosi, Merlino et al. 2008[16] **(Model - Cut-off)**	**Development phase** **Type of study**	**Patients**	**Time-point** **Outcome**	**Sample size**	**Population event rate**	**Proportion (95% CI)** **High-risk** **Low-risk**	**Event rate (95% CI)** **High-risk** **Low-risk**	**Overall** **Net Reclassification Improvement**
(Shock Index)	External validation Retrospective	Not reported	In-hospital All-cause death	155	0.07	17.4 (11.8-24.3) 82.6 (75.7-88.2)	22.2 (8.6-42.3) 3.9 (1.3-8.9)	
(Shock Index - TTE-RVD)	Update Retrospective			100	0.09	51 (40.8-61.1) 49 (38.9-59.2)	17.6 (8.4-30.9) 0 (0-7.3)	NRI (Both – Shock Index)= 0.139



REFERENCES

1. Moores L, Aujesky D, Jimenez D, et al. Pulmonary Embolism Severity Index and troponin testing for the selection of low-risk patients with acute symptomatic pulmonary embolism. Journal of Thrombosis and Haemostasis 2010;**8 (3)**:517-22.

2. Sanchez O, Trinquart L, Planquette B, et al. Echocardiography and pulmonary embolism severity index have independent prognostic roles in pulmonary embolism. European Respiratory Journal 2013;**42**(3):681-88.

3. Singanayagam A, Chalmers JD, Scally C, et al. Right ventricular dilation on CT pulmonary angiogram independently predicts mortality in pulmonary embolism. Respiratory Medicine 2010;**104**(7):1057-62.

4. Lauque D, Maupas-Schwalm F, Bounes V, et al. Predictive value of the heart-type fatty acid-binding protein and the Pulmonary Embolism Severity Index in patients with acute pulmonary embolism in the emergency department. Academic Emergency Medicine 2014;**21**(10):1143-50.

5. Jo J, Lee M, Lee J, et al. Leukocytes and systemic inflammatory response syndrome as prognostic factors in pulmonary embolism patients. BMC Pulmonary Medicine 2013;**13**(1):74.

6. Spirk D, Aujesky D, Husmann M, et al. Cardiac troponin testing and the simplified pulmonary embolism severity index the swiss venous thromboembolism registry (SWIVTER). Thrombosis and haemostasis 2011;**106 (5)**:978-84.

7. Lankeit M, Jimenez D, Kostrubiec M, et al. Predictive value of the high-sensitivity troponin T assay and the simplified pulmonary embolism severity index in hemodynamically stable patients with acute pulmonary embolism: A prospective validation study. Circulation 2011;**124 (24)**:2716-24.

8. Ozsu S, Abul Y, Orem A, et al. Predictive value of troponins and simplified pulmonary embolism severity index in patients with normotensive pulmonary embolism. Multidiscip 2013;**8**(1):34.

9. Lankeit M, Jiménez D, Kostrubiec M, et al. Validation of N-terminal pro-brain natriuretic peptide cut-off values for risk stratification of pulmonary embolism. European Respiratory Journal 2014;**43**(6):1669-77.

10. Vanni S, Jimenez D, Nazerian P, et al. Short-term clinical outcome of normotensive patients with acute PE and high plasma lactate. Thorax 2015;**70**(4):333-8.

11. Ozsu S, Ozlu T, Şentürk A, et al. Combination and comparison of two models in prognosis of pulmonary embolism: Results from TUrkey Pulmonary Embolism Group (TUPEG) study. Thrombosis research 2014;**133**(6):1006-10.

12. Ostovan MA, Ghaffari S, Pourafkari L, et al. Modification of Simplified Pulmonary Embolism Severity Index and its Prognostic Value in Patients with Acute Pulmonary Embolism. Heart, Lung and Circulation 2016;**25**(2):184-90.

13. Vanni S, Nazerian P, Bova C, et al. Comparison of clinical scores for identification of patients with pulmonary embolism at intermediate–high risk of adverse clinical outcome: the prognostic role of plasma lactate. Internal and emergency medicine 2016:1-9.

14. Zondag W, Vingerhoets LMA, Durian MF, et al. Hestia criteria can safely select patients with pulmonary embolism for outpatient treatment irrespective of right ventricular function. Journal of Thrombosis and Haemostasis 2013;**11**(4):686-92.

15. Sanchez O, Trinquart L, Caille V, et al. Prognostic factors for pulmonary embolism: The PREP study, a prospective multicenter cohort study. American journal of respiratory and critical care medicine 2010;**181 (2)**:168-73.

16. Toosi MS, Merlino JD, Leeper KV. Prognostic Value of the Shock Index Along With Transthoracic Echocardiography in Risk Stratification of Patients With Acute Pulmonary Embolism. American Journal of Cardiology 2008;**101 (5)**:700-05.

Appendices A6 - Opinion and Practice Survey about the Use of Prognostic Models in Acute Pulmonary Embolism (OPSUM-PE)

TABLE A6.1: PRACTICE SURVEY QUESTIONNAIRE

Personal information

1. ID (not mandatory unless you need feedback about the results of the survey). Whatever you decide, your answers will be collected and recorded anonymously and stay undisclosed.

First name: ……..

Family name: ……

E-mail address: ……..

* 2. Age: ……

* 3. Gender

- ☐ Male
- ☐ Female

* 4. Level of training (please select one answer only):

- ☐ Medical student
- ☐ Resident
- ☐ Fellow
- ☐ Attending
- ☐ Other

* 5. Duration of professional activity as attending physician in emergency department
(in years, please note 0 if it does not apply): ……

Information about your centre

* 6. Location of your workplace

Country: ……..

City: ……

* 7. Type of hospital (please select one answer only):

- ☐ University hospital
- ☐ Non-university but teaching hospital
- ☐ Non-university and non-teaching hospital
- ☐ Other type (please specify)

* 8. Type of department/care unit (please select more than one if necessary):

- ☐ Emergency Department
- ☐ Intensive care unit
- ☐ Other type of department/care unit (please specify)

* 9. Estimated number of patients with acute pulmonary embolism (P.E.) who attend your service in a year: Please provide a number …….

* 10. Estimated average proportion of patients with PE being completely managed as out-patients **(%):**
……

* 11. Estimated average proportion of patients with P.E. being discharged within 72 hours **(%):**
……

Your personal use of prognostic models in acute PE

* 12. What type of prognostic tools do you personally use in patients with acute PE? (please identify all that apply for each answer and select "N/A" or “1”, “2”, “3”, “4” or "5" to rank, "1" being the most used tool and "5" the least used one)

Prognostic model(s) (a model includes at least 2 combined variables)	"N/A" or “1”, “2”, “3”, “4” or "5"
Prognostic indicator(s) (a single variable)	"N/A" or “1”, “2”, “3”, “4” or "5"
Personal clinical judgment	"N/A" or “1”, “2”, “3”, “4” or "5"
Pre-established checklist of criteria for P.E. management (like “Ottawa PE criteria”, “Hestia criteria”, "Davies criteria" or other checklist …)	"N/A" or “1”, “2”, “3”, “4” or "5"
None	"N/A" or “1”, “2”, “3”, “4” or "5"

* 13. Which prognostic model(s) do you personally use (please select more than one if necessary)?

- ☐ PESI
- ☐ Simplified PESI
- ☐ PESI-derived algorithm
- ☐ PREP
- ☐ Shock index
- ☐ ESC guidelines
- ☐ None
- ☐ Others (please specify any other prognostic model you use):……

* 14. If you do use a prognostic model when evaluating a patient with acute PE, how often do you personally use it? (please select one answer only)

- ☐ In more than 75% of PE patients
- ☐ 51-75% of PE patients
- ☐ 26-50% of PE patients

- ☐ 5-25% of PE patients
- ☐ Less than 5% PE patients

* 15. Which of these prognostic factors/indicators do you personally use (please select more than one if necessary)?

- ☐ Demographic factors (age, gender)
- ☐ Comorbidities and clinical context
- ☐ Vital signs
- ☐ Troponin (cTnT, cTnl, high-sensitive cTnT)
- ☐ Natriuretic peptides (BNP, NT-proBNP)
- ☐ H-FABP
- ☐ D-dimer
- ☐ Lower limb venous ultrasound
- ☐ Echocardiography
- ☐ CT scan
- ☐ None
- ☐ Others

* 16. Do you use at least one of these factors/indicators: in addition to a prognostic model, on its own without a prognostic model or not at all? (please select one answer only)

- ☐ In additon to a prognostic model
- ☐ Without a prognostic model
- ☐ Not at all

* 17. What characteristics of a prognostic model would influence your decision to use it? (Please answer each question with "Yes", "No" or "Don't know").

The model was "well" constructed (using a derivation set, internal validation not mandatory)	Yes No Don't know
It was externally validated	Yes No Don't know
It has a good predictive performance	Yes No Don't know
It has been subjected to a study of impact	Yes No Don't know
It helps to inform medical decisions	Yes No Don't know
It is easy to use	Yes No Don't know
Variables included in the model are readily available in clinical practice	Yes No Don't know
It is reproducible (reliable)	Yes No Don't know
It is not costly	Yes No Don't know

Other reasons (please provide more information): Yes No Don't know

* 18. What are the potential barriers for the use of prognostic models in acute P.E. in your practice (please select more than one if necessary)?

- ☐ Lack of awareness or familiarity with the models
- ☐ Lack of acces to information
- ☐ Lack of training (or workshop attendance)
- ☐ Lack of revelance (not convinced that prognosis needs to be assessed in acute PE patients)
- ☐ Lack of confidence (no conviction on model's predictive performance)
- ☐ Lack of perceived usefulness (no conviction that models are useful, lack of implication for practice)
- ☐ Beliefs that clinical judgment is sufficient
- ☐ Lack of practicality
- ☐ Lack of time in general or in rush hours
- ☐ Individual barriers to change
- ☐ Lack of resources (personnel, equipment)
- ☐ No guidelines in center or hospital
- ☐ Management not interested
- ☐ No implementation strategies

Your personal management of patients with acute PE in the emergency department

* 19. If you have to compare clinical judgment against prognostic models for early discharge and outpatient management in acute PE would you say clinical judgment is “better”, “as good” or “worse” than prognostic models:

- ☐ Better
- ☐ As good
- ☐ Worse
- ☐ Don't know

* 20. If you have to compare a pre-established checklist of hospital criteria (checklist includes not only prognostic factors but also medical and social criteria) against prognostic models for early discharge and outpatient management in acute PE would you say checklist is “better”, “as good” or “worse” than prognostic models:

- ☐ Better
- ☐ As good
- ☐ Worse
- ☐ Don't know

* 21. In acute PE patients considered at low-risk, what 30-day mortality rate limit would be too high for you to manage these patients as out-patients? (please select one answer only)

- ☐ Less than 0.5%
- ☐ 0.5%
- ☐ 1%
- ☐ 2%
- ☐ 3%
- ☐ Other (please specify): ……

*22. In stable acute PE patients (stable defined by a systolic blood pressure SBP >= 90 mmHG) but considered at high-risk, what would be the 30-day mortality rate at which you would almost always administer a thrombolytic therapy? (please select one answer only)

- ☐ Less than or equal to 5%
- ☐ Between 6% and 10%
- ☐ Between 11% and 15%
- ☐ Between 16% and 20%
- ☐ Between 21% and 30%
- ☐ More than 30%
- ☐ Other value (please specify what level): ……

TABLE A6.2: SAMPLE SIZE CALCULATION

alpha	power	N	N1	N2	nratio	delta	p1	p2
0.05	0.8	239	199	40	0.2	-0.25	0.5	0.25
0.05	**0.8**	**218**	**177**	**41**	**0.23**	**-0.25**	**0.5**	**0.25**
0.05	0.8	208	166	42	0.25	-0.25	0.5	0.25

alpha	power	N	N1	N2	nratio	delta	p1	p2
0.05	0.8	374	311	63	0.2	-0.2	0.5	0.3
0.05	**0.8**	**341**	**277**	**64**	**0.23**	**-0.2**	**0.5**	**0.3**
0.05	0.8	324	259	65	0.25	-0.2	0.5	0.3

nratio ("allocation ratio): ratio of the number of respondents in the French sample (SFMU) relative to the number of respondents in the European sample (EuSEM), the proportion of response rate assumed to be similar.
delta is the difference between the frequency in the use of prognostic models between the French (SFMU) and the European (EuSEM) samples
N1: number of respondents in the European sample
N2: number of respondents in the French sample

Sample size calculation was based on the detection of an absolute difference of 25% in the frequency of the use of a prognostic model (Q14) between the French sample and the European sample (assumed: 50%), and a ratio of 0.23 (0.20 to 0.25) for the number of respondents in the French sample relative to the number of respondents in the European sample, assuming that the response rate is similar for both groups and the number of physicians in the European group is 4 to 5 times larger than the number of those in the French group (alpha = 0.05 and power = 0.80).

Appendices A7 - Development and Assessment of Ascertainment Strategy in Acute Pulmonary Embolism

A7.1: RESEARCH ETHICS

Mr Antoine Elias
ICS Block B
Royal Hospital
Belfast
Northern Ireland

18th March 2015

Dear Mr Elias

CUREC application: Development and assessment of ascertainment strategy in acute pulmonary embolism

I am pleased to confirm that this application has been reviewed by the Officer of the relevant Oxford University Ethics Committee, with reference to formally approved process and has determined that it does not raise any issues of research ethics with human participants.

Yours sincerely

Gill Halstead

Research Ethics Co-ordinator, Medical Sciences
Research Services
University of Oxford
University Offices, Wellington Square. OX1 2JD
T: +44 01865 616575 **E:** ethics@medsci.ox.ac.uk

Please note I work Monday, Wednesday and Thursday

www.admin.ox.ac.uk/researchsupport

A7.2: INSTITUTIONAL REVIEW BOARD

CENTRE HOSPITALIER INTERCOMMUNAL
TOULON - LA SEYNE SUR MER

Institutional Review Board
A. Lafeuillade, M.D, Vice-Chair Clinical Research
P. Collignon, M.D, Ethics Board Coordinator

Toulon - January 28, 2011

Antoine Elias, MD
Vascular Medicine
Centre Hospitalier Intercommunal
Toulon - La Seyne Sur Mer
BP 1412, 83056 Toulon Cedex
FRANCE

Subject: Institutional Review Board Approval

Dear Dr. Elias,

After deliberation the Clinical Research and Innovation Review Board, together with the Hospital Ethics Board have approved, on the 27th of January 2011, the following protocol:

Development and assessment of ascertainment strategy in acute pulmonary embolism

Reference CH-2010.2
Provided documents: Protocol version 3.0 - 04/01/2011
Information letter version 2.0 - 11/01/2011

Sponsor: Centre Hospitalier Intercommunal
Toulon-La Seyne Sur Mer,
BP 1412, 83056 Toulon Cedex

Principal Investigator: Antoine ELIAS M.D.
Department of Vascular Medicine

TOUT COURRIER DOIT ETRE ADRESSE IMPERSONNELLEMENT
A M. LE DIRECTEUR DU CENTRE HOSPITALIER INTERCOMMUNAL TOULON – LA SEYNE-SUR-MER

B.P.1412 - 83056 TOULON CEDEX - TEL : 04 94 61 61 61 - FAX : 04 94 61 61 12 - NET : www.ch-toulon.fr

HOPITAUX SAINTE-MUSSE - FONT-PRE - CHALUCET (TOULON)
GROUPE HOSPITALIER DE LA SEYNE-SUR-MER Centre de Gérontologie Georges CLEMENCEAU (LA GARDE)

CENTRE HOSPITALIER INTERCOMMUNAL
TOULON - LA SEYNE SUR MER

Individuals who reviewed the project:

Biomedical Researcher:
Mr Alain LAFEUILLADE M.D.
Mr Jean Michel ARNAL M.D.
Hospital Chemist:
Mrs Annie DUPONCHEL
Ethics Board Coordinator:
Mr Patrick COLLIGNON M.D.
Clinical Research Unit Representative:
Mr Jean-Philippe SUPPINI Ph.D.

With best regards,

Clinical Research & Innovation Review Board
Representative

Alain LAFEUILLADE,

Ethics Committee
Representative

Patrick COLLIGNON,

TOUT COURRIER DOIT ETRE ADRESSE IMPERSONNELLEMENT
A M. LE DIRECTEUR DU CENTRE HOSPITALIER INTERCOMMUNAL TOULON – LA SEYNE-SUR-MER

B.P.1412 - 83056 TOULON CEDEX - TEL : 04 94 61 61 61 - FAX : 04 94 61 61 12 - NET : www.ch-toulon.fr

HOPITAUX SAINTE-MUSSE - FONT-PRE - CHALUCET (TOULON)
GROUPE HOSPITALIER DE LA SEYNE-SUR-MER Centre de Gérontologie Georges CLEMENCEAU (LA GARDE)

A7.3: PROTOCOL AND PRACTICAL ISSUES

Patients

Acute symptomatic PE: Patients with a clinically suspected acute PE in whom the diagnosis is confirmed by objective methods and who will have anticoagulant treatment (usual care). Patients are recruited in the Toulon city hospital whether they are out-patients (patients admitted for this condition) or in-patients (patients develop PE during hospitalisation).

Patients are included as soon as diagnosis is confirmed, in case of re-admission for adverse outcomes or other condition or for investigation if patients were not identified at previous hospitalisation.

Sources of patients

Outpatients are referred to the hospital from different private or public hospitals around Toulon (Brignoles city, Hyères city), from hospitals in Toulon city, from GPs or specialists in cardiology, vascular medicine, pneumology, rehabilitation and other specialties.

Inpatients from different services are notified directly to the vascular medicine department.

Services where in-patients and out-patients can be found are either: medical services (emergency transportation services, ED, critical care, cardiology ICU, departments of cardiology, vascular medicine, pneumology, neurology, geriatrics, gastroenterology, oncology, psychiatry, infection, rehabilitation – surgery - gynecology/ obstetrics - day-hospital and week-hospital – outpatient clinics. Clinical units within the hospital are listed in details in the data extraction form in the Appendices

Patients' pathways

Potential pathways for outpatients

Patients can be admitted to the ED or directly to the vascular medicine or other services.

Patients may be discharged from the first unit where they have been admitted with a confirmed diagnosis of PE, without a confirmed diagnosis of PE (diagnostic work up was not done or was not completed) or with no clinical suspicion of PE. They can be sent to the vascular medicine department or to other medical departments.

Potential pathways for inpatients

Patients develop symptoms and signs suggestive of PE while they are hospitalised in medical units (departments of medicine, gynaecology and surgery, intensive care units, oncology, geriatrics, psychiatry, infection, rehabilitation). They may remain in their same unit, or referred to the vascular medicine department or to other departments. Whatever, they are usually notified to the vascular medicine.

More complex pathways could be related to patient transfer from one department to a second and a third … ones. Day and time of admission in each of these departments and day and time of discharge are noticed

Role of research team

Aim of research staff: case-identification (with diagnostic confirmation), inclusion in the study and data collection of prognostic and outcome variables

Objectives of research staff:

- identifying patients who have a clinical suspicion or a confirmed PE everyday week-ends included - by performing a database search and by access to different source documents on paper (manual search) or in computer (electronic search) - by calling services twice daily– and if needed by visiting services. Access to source documents by daily review of admission and discharge documents/ reports – by daily review of diagnostic tests documents/ reports either from biology laboratories (only D-dimer tests, troponins and NT-pro-BNP being not specific for PE) or of imaging-based diagnostic tests documents/ reports (venous ultrasound in the department of vascular medicine, CT angio scan from the department of radiology, ventilation perfusion scan from the nuclear medicine department). Daily review enhances rapid case ascertainment. Relying on multiple sources help to identify more effectively and enables better description. Using electronic searching software (IMPAX viewer for CT-PA, VENUS for V/Q scan), laboratory and ultrasound registers, and emergency department terminal. Source documents related to surgery schedules for pulmonary embolectomy or placement of caval filter, and to pharmacy provision of thrombolytics or filter devices seem less efficient for case-identification because of the low number of patients who need such treatment.

- ensuring the diagnosis has been confirmed (by checking diagnostic procedures) and the patient has got his treatment (list of treatments with dose regimen available)
- verifying inclusion and non-inclusion criteria, informing the patient, and listing non-inclusion
- recording administrative data (coding system including family name and first name, date of birth, code number will be used for patient identification and follow up, contact details of the patient, family, trustworthy person, family physician/ specialist, in- hospital reference physician)
- planning outcome visits and phone calls
- calling the patient (or relatives or physiscian),
- collecting data on admission,
- collecting data on follow-up,
- checking completeness of case-identification, completeness of follow-up (all cases have been reviewed) and completeness of data collection,
- reporting data on CRF and checking all cases reported and reporting performed regularly.

Diagnosis of PE

<u>Diagnosis referral</u>

Patients are referred to the ED or directly to "medical" services/departments with a clinically suspected PE and the diagnosis is confirmed in the hospital (ED/"medical" services). PE may be unsuspected before admission and only suspected in the ED and the diagnosis is established in the hospital (ED/"medical" services).

Diagnostic work-up

Diagnostic work-up may be incomplete or uncertain for different reasons: an imaging-based diagnostic test cannot be performed because of contra-indications (to contrast medium injection) or because of some limitations in the interpretation of the test (image inadequate). Follow-up will not be performed but would have been of interest to check for missing diagnostic work-up.

Diagnostic work-up may be complete and PE ruled out. Follow-up will not be performed but would have been of interest to check for missing diagnostic outcome.

Diagnostic work-up may be complete and PE ruled-in. A 3-month follow-up will be performed to avoid missing prognostic outcome.

Standard diagnostic criteria to rule in and rule out PE

Diagnostic criteria for ruling-in PE:

- Filling defect on CT pulmonary angiography
- High probability ventilation perfusion scan (V/Q scan) with 75% segmental perfusion defect and normal ventilation
- Ultrasound-detected proximal vein thrombosis with high clinical probability of PE and inadequate CT scan or non-diagnostic V/Q scan results
- Filling defect on pulmonary angiography

Diagnostic criteria for ruling-out PE:

- Non-high clinical probability and negative D-dimer test
- Good quality negative CT angiogram, non-high clinical probability and no proximal vein thrombosis on ultrasound (ultrasound showing either no thrombosis or a distal vein thrombosis)
- V/Q scan normal

Diagnosis of PE uncertain in two situations:

- Inadequate multidetector CT result mainly at subsegmental level and absence of proximal vein thrombosis with the ultrasound test. The patient may have a distal vein thrombosis or no vein thrombosis. Management at the discretion of the physician in charge of the patient.
- Non-diagnostic V/Q scan and absence of proximal vein thrombosis with the ultrasound test. The patient may have a distal vein thrombosis or no vein thrombosis. Management at the discretion of the physician in charge of the patient.

Practical reasons for choosing CT and V/Q diagnostic methods:

- Multidetector CT angio is the most commonly used test
- V/Q scan could be useful in case of a contra indication to contrast injection (history of allergic reaction, renal failure with an MDRD glomerular filtration rate < 60 ml/ mn/ 1.72 m²)
- Pulmonary angiography and venography are not any more used.
- CT venography is not performed in local hospital and is replaced by venous ultrasound

PE management

When to start treatment for PE?

As soon as the diagnosis is suspected even before diagnosis is confirmed when there is a high clinical suspicion and if there is no contraindication because of bleeding risk

Anticoagulant treatment in the acute phase

Treatment will be standardised or randomised

Heparin, low molecular weight heparin (LMWH) Enoxaparin and Tinzaparin, antiXa Fondaparinux are the anticoagulant drugs authorised in France for the treatment of acute PE patients at the time the study was performed

Heparin is administered either intravenously or by subcutaneous injections

IV heparin: bolus injection 50 - 100 IU/ kg followed by initial dose of 20 IU/ kg/ h. Maintenance dose adjusted to APTT ratio (1.5 to 3) or to antiXa activity (0.2 – 0.6 IU/ml).

SC heparin: bolus injection 50 - 100 IU/ kg followed by 500 IU/kg/24h split into 2 sc injections or 3 sc injections (if volume injection > 0.6 ml).

Maintenance dose adjusted to APTT ratio (1.5 to 3) or to antiXa activity (0.2 – 0.6 IU/ml).

Enoxaparin: bid sc injections 100 IU/ kg x 2 / 24h

Tinzaparin: od sc injections 175 IU anti-Xa/ kg/ 24h

Fondaparinux: od sc injections

Body weight < 50 kg: 5 mg

Body weight 50-100 kg: 7.5 mg

Body weight > 100 kg: 10 mg

Standard indications for type of treatment

Heparin intravenously preferable at the initial phase in patients with bleeding risk or with renal failure as attested by GFR

Heparin subcutaneously preferable on the long term in patients with renal failure as attested by GFR

LMWH (Enoxaparin, Tinzaparin) or AntiXa drugs (Fondaparinux) are commonly used

Oral anticoagulant treatment: Warfarin (Coumadine) used as soon as possible, starting dosage depending on age and weight of patients, and bleeding risk. Maintenance dose adjusted according to INR (2<INR<3). Other medications such as Fluindione (Préviscan) or Acenocoumarol (Sintrom) are accepted for use in France. Dosage adjustment according to INR will preferably be done under the control of the anticoagulant clinics.

New non vitamin K oral anticoagulants (direct oral anticoagulant) used: Rivaroxaban 15 mg bid for 21 days, and then 20 mg od (use in patients with no impaired renal function as attested by Cockroft GFR estimate).

Indications for thrombolytics and partial interruption of inferior vena cava are done according to guidelines [1,2].

Patient mobilisation

As soon as they are under anticoagulant treatment and does not have any bad conditions that forced them to stay in bed. The duration and the reason why the patient stays in bed need to be recorded.

Elastic compression stockings?

French class 3 elastic compression [1] is recommended for patients who present with proximal vein thrombosis or with “massive” calf vein thrombosis (involving main distal veins like the posterior tibial veins and the peroneal veins). French class 2 elastic compression [1] is recommended for patients with small and limited vein thrombosis either in the main vein segments or in the soleal or muscular veins)

Length of hospital stay

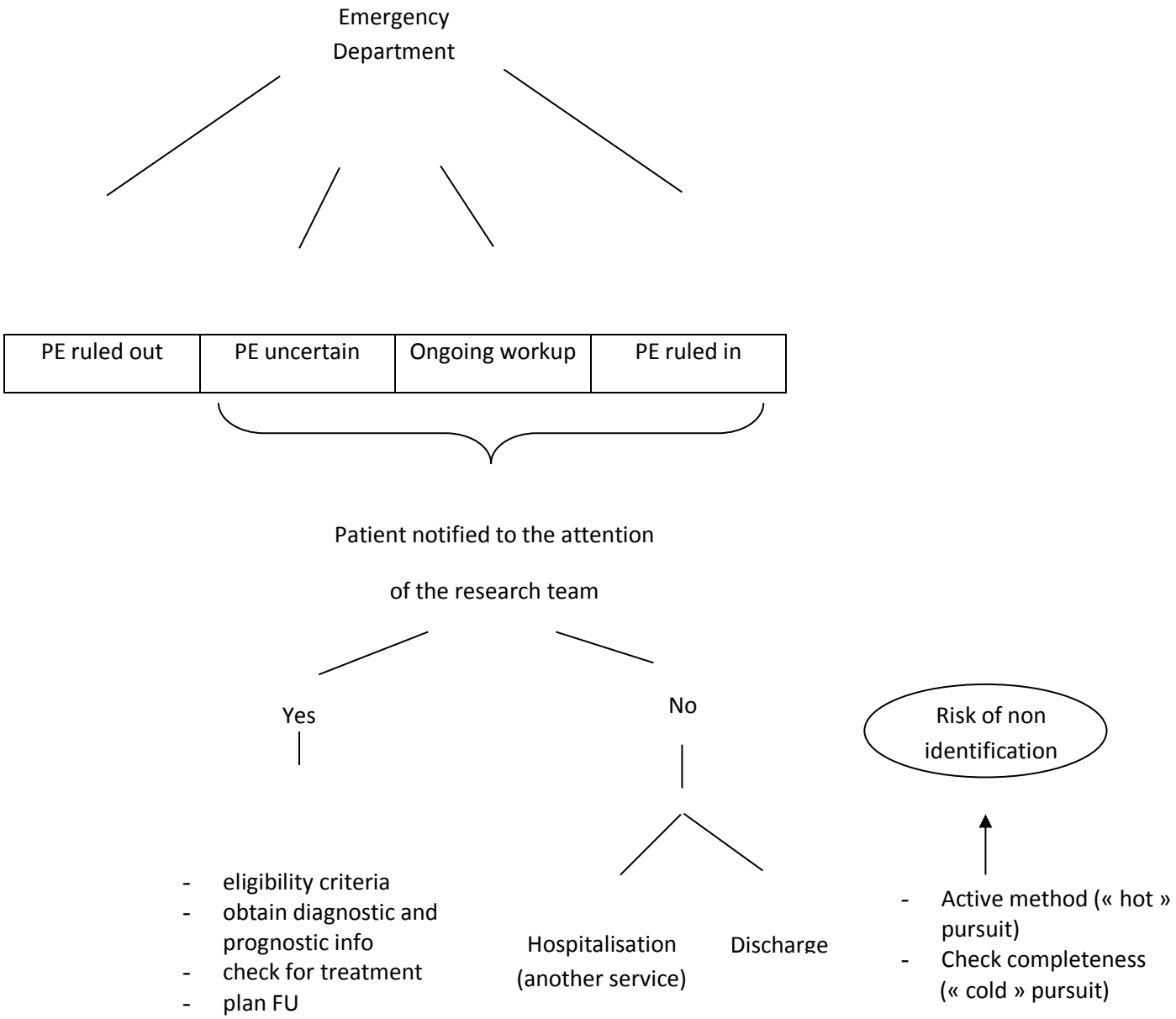
Mean hospital stay is 8±2 days for PE patients in France. The duration may vary according to various factors: patient general conditions, disease severity needing to manage patients in hospital, and other different social logistic and administrative conditions. Complete bridging to oral anticoagulants (INR range 2-3) is preferable in hospital but not mandatory before discharge.

Procedure codes and primary and secondary discharge diagnosis codesInternational Statistical Classification of Diseases and Related Health Problems - 10th Revision (http://www.who.int/classifications/icd/en/): **Diagnostic list**

Pulmonary embolism ICD codes: I26.0 - I26.9

Vein thrombosis ICD codes: I80.0 - I82.9

Identification of patients admitted to the emergency department with clinical suspicion or confirmed diagnosis of pulmonary embolism



Identification of patients in medical units/ services/ departments other than the emergency ward

- Reasons for hospitalisation and diagnosis

1
- PE ruled out (other diagnosis)
- PE uncertain
- Ongoing workup
- PE ruled in

2
- PE not suspected on admission but later (rectification of diagnosis)

3
- PE as a complication in a patient hospitalised for another reason (acute medical condition, oncology, surgery)

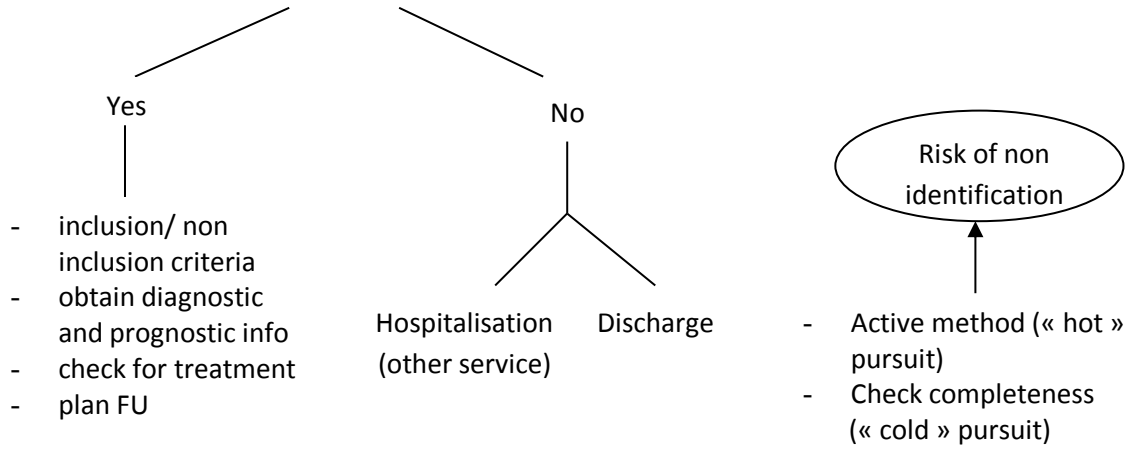
- Sources of admissions in the «medical» units

Med / Surg / Gyne/ Oncology

Med care / ICU / card ICU

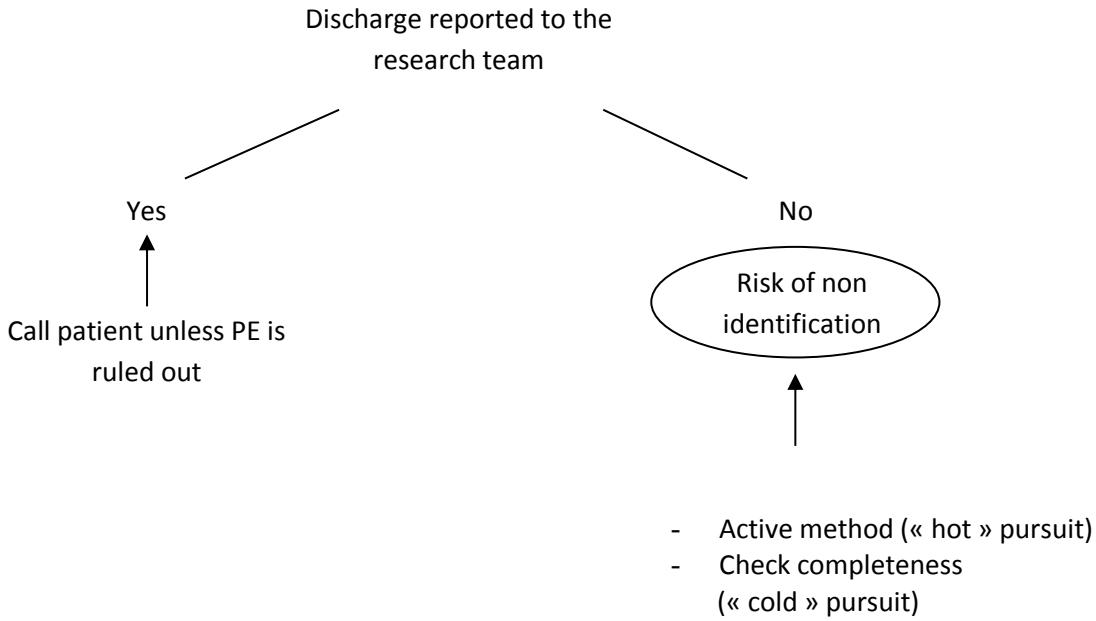
- Direct admission
- From ED
- From other Emergency Unit SAMU
- From other « medical » unit

- Patient notified to attention of the research team



Patient after discharge

From ED	From « medical » unit



Appendices A7 - Development and Assessment of Ascertainment Strategy in Acute Pulmonary Embolism

A7.4: RESULTS

Table A7.4.1. Patient characteristics - Source of patients and in-hospital healthcare pathways.

Source of patients and in-hospital healthcare pathway	**All patients**		**Patients found by passive detection**		**Patients found by hot pursuit only**	
	N		**N**		**N**	
Main sources of patients	501		462		39	
- Outpatients		459 (91.6)		424 (91.8)		35 (89.7)
o General practitioner		135 (26.9)		124 (26.8)		11 (28.2)
o Other hospitals*		105 (21)		104 (22.5)		1 (2.6)
o Other sources**		219 (43.7)		196 (42.4)		23 (59)
- In-patients		42 (8.4)		38 (8.2)		4 (10.3)
First place	501		462		39	
- Emergency		300		274		26
- Vascular medicine		112		112		0
- ICU		4		3		1
- ICU – cardiology		26		25		1
- Cardiology		23		21		2
- Medicine		0		0		0
- Other services		36		27		9
- Discharged		0		0		0
- Death		0		0		0
Second place	501		462		39	
- Emergency		2		2		0
- Vascular medicine		162		162		0
- ICU		13		11		2
- ICU – cardiology		27		26		1
- Cardiology		40		39		1
- Medicine		16		7		9
- Other services		104		89		15
- Discharged		133		124		9
- Death		4		2		2

* Patients are referred from ED of other hospitals - ** other sources of referral: various medical specialties. Only the first and the second places of hospital stay are displayed **–** First place is the place where patients are first referred to. Second place is the place where patients are then admitted to - N (%).

Table A7.4.2: Risk classification according to PESI/s-PESI models and to detection methods, and all-cause death at different time-points in the whole study cohort including "both stable and unstable PE" patients.

	Stable & unstable PE				Total
PESI ≥ III vs PESI ≤ II	Low-risk 191		High-risk 310		501
sPESI ≥ 1 vs sPESI = 0	Low-risk 131	High-risk 60	Low-risk 22	High-risk 288	501
Passive detection	127	57	18	260	462
3-month death	2	2	2	57	63
1-month death	2	1	0	36	39
8-day death	2	0	0	7	9
Hot pursuit only	4	3	4	28	39
3-month death	1	0	1	15	17
1-month death	0	0	1	12	13
8-day death	0	0	0	9	9
Total 3-month death	3	2	3	72	80
	3/131 (2.3%)	2/60 (3.3%)	3/22 (13.6%)	72/288 (25%)	80/501 (16.0%)
Total 1-month death	2	1	1	48	
	2/131 (1.5%)	1/60 (1.7%)	1/22 (4.5%)	48/288 (16.7%)	52/501 (10.4%)
Total 8-day death	2	0	0	16	18
	2/131 (1.5%)	0/60 (0.0%)	0/22 (0.0%)	16/288 (5.6%)	18/501 (3.6%)

Table A7.4.3: Risk classification according to PESI and s-PESI models in "both stable and unstable PE" patients - Proportion of patients in risk groups and all-cause death within risk groups.

Risk groups	PESI	sPESI
Low-risk		
- Proportion	191/501 38.1 (33.8, 42.5)	153/501 30.5 (26.5, 34.8)
- 8-day all-cause death	2/191 1.0 (0.1, 3.7)	2/153 1.3 (0.2, 4.6)
- 1-month all-cause death	3/191 1.6 (0.3, 4.5)	3/153 1.9 (0.4, 5.6)
- 3-month all-cause death	5/191 2.6 (0.9, 6.0)	6/153 3.9 (1.4, 8.3)
High-risk		
- Proportion	310/501 61.9 (57.5, 66.1)	348/501 69.5 (65.2, 73.5)
- 8-day all-cause death	16/310 5.2 (3.0, 8.2)	16/348 4.6 (2.7, 7.3)
- 1-month all-cause death	49/310 15.8 (11.9, 20.4)	49/348 14.1 (10.6, 18.2)
- 3-month all-cause death	75/310 24.2 (19.5, 29.4)	74/348 21.3 (17.1, 25.9)

Two patients having missing variables died at 1-month time-point and were classified at low-risk: one by s-PESI (missing room air O2, SpO2 93% under O2 2l/mn, respiratory rate 38) and another one by both PESI and s-PESI (missing O2 room air, SpO2 98% under O2 2l/mn). Worst-case scenario: missing variables accounted for as normal in the low-risk group; results are shown in table (between parentheses: 95% confidence interval). Best-case scenario: missing variables accounted for as abnormal; 1-month all-cause death in the low-risk group 1.05 (0.1, 3.8) for PESI and 0.7 (0.02, 3.6) for s-PESI, 3-month all-cause death in the low-risk group 2.1 (0.6, 5.3) for PESI and 2.6 (0.7, 6.6) for s-PESI.

Table A7.4.4: Risk classification according to PESI/s-PESI models and to detection methods, and all-cause death at different time-points in "stable PE" patients.

	Stable PE				Total
PESI ≥ III vs PESI ≤ II	Low-risk 190		High-risk 282		472
sPESI ≥ 1 vs sPESI = 0	Low-risk 131	High-risk 59	Low-risk 22	High-risk 260	472
Passive detection	127	56	18	239	440
3-month death	2	2	2	50	56
1-month death	2	1	0	29	32
8-day death	2	0	0	2	4
Hot pursuit only	4	3	4	21	32
3-month death	1	0	1	10	12
1-month death	0	0	1	7	8
8-day death	0	0	0	4	4
Total 3-month death	3	2	3	60	68
	3/131 (2.3%)	2/59 (3.4%)	3/22 (13.6%)	60/260 (23.1%)	68/472 (14.4%)
Total 1-month death	2	1	1	36	40
	2/131 (1.5%)	1/59 (1.7%)	1/22 (4.5%)	36/260 (13.8%)	40/472 (8 .5%)
Total 8-day death	2	0	0	6	8
	2/131 (1.5%)	0/59 (0%)	0/22 (0%)	6/260 (2.3%)	8/472 (1.7%)

Table A7.4.5: Risk classification according to PESI and s-PESI models in "stable PE" patients - Proportion of patients in risk groups and all-cause death within risk groups.

Risk groups	PESI	sPESI
Low-risk		
- Proportion	190/472 40.2 (35.8, 44.8)	153/472 32.4 (28.2, 36.8)
- 8-day all-cause death	2/190 1.1 (0.1, 3.8)	2/153 1.3 (0.2, 4.6)
- 1-month all-cause death	3/190 1.6 (0.3, 4.5)	3/153 1.96 (0.4, 5.6)
- 3-month all-cause death	5/190 2.6 (0.9, 6.0)	6/153 3.9 (1.4, 8.3)
High-risk		
- Proportion	282/472 59.8 (55.2, 64.2)	319/472 67.6 (63.2, 71.8)
- 8-day all-cause death	6/282 2.1 (0.8, 4.6)	6/319 1.9 (0.7, 4.0)
- 1-month all-cause death	37/282 13.1 (9.4, 17.6)	37/319 11.6 (8.3, 15.6)
- 3-month all-cause death	63/282 22.3 (17.6, 27.7)	62/319 19.4 (15.2, 24.2)

Missing variables were accounted for as normal. Two patients having missing variables were classified at low-risk: one by s-PESI (missing room air O2, SpO2 93% under O2 2l/mn, respiratory rate 38) and another one by both PESI and s-PESI (missing O2 room air, SpO2 98% under O2 2l/mn). Worst-case scenario: missing variables accounted for as normal in the low-risk group; results are shown in table (between parentheses: 95% confidence interval). Best-case scenario: missing variables accounted for as abnormal; 1-month all-cause death in the low-risk group 1.06 (0.1, 3.8) for PESI and 0.7 (0.02, 3.6) for s-PESI, 3-month all-cause death in the low-risk group 2.1 (0.6, 5.3) for PESI and 2.6 (0.7, 6.6) for s-PESI.

APPENDICES A8 - Physician's Clinical Judgment in Addition to Simplified PESI for Selecting Patients with Acute Pulmonary Embolism for Out-Of-Hospital Management.

Table A8.1: Strategies for selecting patients for early discharge or home treatment.

Patient selection for early discharge or home treatment, may be based on 3 types of management tools

- Risk assessment using prognostic models (Low-risk PESI, low-risk s-PESI models).
- Hospitalisation criteria (Ottawa criteria, Davies criteria, Hestia criteria) based on assessing excess risk, social reasons or medical need for hospitalisation for PE or for comorbidities, presence of contra-indication to treatment.
- Clinical judgment

Table A8.2: Pulmonary Embolism Severity Index (PESI): original and simplified versions[1].

Predictors	Original score*	Simplified score[¶]
Demographic characteristics		
Age > 80 years	Age, in years	1
Male sex	+ 10	
Comorbid illnesses		
Cancer[†]	+ 30	1
Heart failure	+ 10	1**
Chronic lung disease	+ 10	
Clinical findings		
Pulse ≥ 110/min	+ 20	1
Systolic blood pressure < 100 mm Hg	+ 30	1
Respiratory rate ≥ 30/min	+ 20	
Temperature < 36 °C	+ 20	
Altered mental status[‡]	+ 60	
Arterial oxygen saturation < 90%[§]	+ 20	1

* A total point score for a given patient is obtained by summing the patient's age in years and the points for each predictor when present. The score corresponds with the following risk classes: < 65, class I; 66 – 85, class II; 86 – 105, class III; 106 – 125, class IV; and ≥ 125, class V. Patients in risk class I and II are defined as being at low risk.

[†] Cancer defined as a history of cancer or active cancer;[‡] Defined as disorientation, lethargy, stupor or coma;[§] With and without the administration of supplemental oxygen.

[¶] A total point score for a given patient is obtained by summing the points. The score corresponds with the following risk classes: 0, low risk; ≥ 1, high risk. Empty cells indicate that the variable was not included.

** The variables were combined into a single category of chronic cardiopulmonary disease.

Table A8.3: Davies criteria[2]- Hospital criteria

Reasons given for non-suitability for early discharge
Patient required admission for additional monitoring, administration of any form of oxygen therapy for hypoxaemia or for another medical reason (e.g. significant respiratory and/or cardiovascular disease and/or treatment for active malignancy)
Likelihood of poor compliance or difficulty ensuring appropriate follow-up, including complex elderly patients, the infirm, and those with significant immobility, geographical inaccessibility or a history of noncompliance, and intravenous drug abusers
History of previous PE or further PE while currently on treatment
Co-existing major DVT (high-segment femoral and above)
Other (*e.g.* bleeding disorders or active bleeding and pregnancy)

Table A8.4: Ottawa criteria [3 4]- Home criteria

Patients who do not have a systolic blood pressure of 100 mmHg or less,
Patients who have an oxygen saturation of 92% or more and do not require supplemental oxygen,
Patients who do not have contraindications for the use of LMWH (such as a high bleeding risk or renal failure)
Patients who do not need hospitalization for other comorbidities (such as severe cancer, heart failure, chronic obstructive pulmonary disease, coronary artery disease, cerebrovascular events, etc.).

Table A8.5: Hestia criteria[5-8] - Hospital criteria

1. Hemodynamically unstable?*
2. Thrombolysis or embolectomy necessary?
3. Active bleeding or high risk of bleeding?†
4. Oxygen supply to maintain oxygen saturation > 90% > 24 h?
5. Pulmonary embolism diagnosed during anticoagulant treatment?
6. Intravenous pain medication > 24 h?
7. Medical or social reason for treatment in the hospital > 24 h?
8. Creatinine clearance of less than 30 mL/min?‡
9. Severe liver impairment?§
10. Pregnant?
11. Documented history of heparin-induced thrombocytopenia?

If one of the questions is answered with YES, **The patient can NOT be treated at home**

*Include the following criteria, but are left to the discretion of the investigator: systolic blood pressure <100 mmHg with heart rate > 100 beats per minute; condition requiring admission to an intensive care unit.
†Gastrointestinal bleeding in the preceding 14 days, recent stroke (less than 4 weeks ago), recent operation (less than 2 weeks ago), bleeding disorder or thrombocytopenia (platelet count < 75 9 109/L), uncontrolled hypertension (systolic blood pressure > 180 mm Hg or diastolic blood pressure > 110 mm Hg).
‡Calculated creatinine clearance according to the Cockroft-Gault formula.
§Left to the discretion of the physician.

TABLE A8.6: ANTICOAGULANT TREATMENT

Anticoagulant treatment: The anticoagulants will be prescribed at the recommended dosage as in the Summary of Product Characteristics and taking account of contraindication for their use, in accordance with the local practice and the following standardized local policy:

Unfractionated heparin (UFH) (in France Calciparine®, héparine Choay®, héparine sodique panpharma®): optional bolus of 50 - 80 IU/kg, then either intravenous administration with continuous infusion or sub-cutaneous injections (2 to 3 injections/day) at a starting dose of 18 UI/ kg/ hour, then at dose adjusted to the anti-Xa activity to be maintained between 0.3 – 0.6 IU / ml or to the aPTT ratio to be maintained between 1.5 - 3.

Low Molecular Weight Heparin (LMWH) products are administered subcutaneously with various regimens:
- Enoxaparin (Lovenox®) at fixed dose of 100 UI/kg BID
- Tinzaparin (Innohep®) at fixed dose of 175 UI/kg QD (can be used in case of associated cancer)
- Dalteparin (Fragmine®) at fixed dose of 200 UI/kg QD for the first month then 150 UI/kg QD during 2 to 5 months in case of associated cancer

Anti Xa agents are given subcutaneously: Fondaparinux (Arixtra®) 7.5 mg QD if body weight is between 50 and 100 Kg (5 mg QD if body weight is less than 50 kg, and 10 mg QD if body weight is over 100 kg)

Vitamin K Antagonists (VKA): warfarin (Coumadine®), fluindione (Préviscan®) or acenocoumarol (Sintrom®) are prescribed in replacement of the intravenous or subcutaneous injections (UFH, LMWH or fondaparinux) with at least a 5-day overlap of the injections and the oral VKA, and a dose-adjustment of the VKA to obtain an international normalized ratio (INR) between 2 and 3.

New Direct Oral Anticoagulants (DOAs): use of new DOAs will depend upon the absence of contraindications, their individual approval by local authorities (Marketing Authorisation) and the acceptance of reimbursement for PE treatment indication:
- Rivaroxaban (Xarelto®) at fixed dose of 15 mg BID during 21 days, then 20 mg QD orally
- Apixaban (Eliquis®) at fixed dose of 10 mg BID during 7 days, then 5 mg BID orally
- Dabigatran (Pradaxa®) and Edoxaban (Lixiana®) do not have a Marketing Authorisation and will not be used[1].

1 - Dabigatran (Pradaxa®) at fixed dose of 150 mg BID orally following a 5-day parenteral treatment (by UFH, LMWH or fondaparinux). - Edoxaban (Lixiana®) following a 5-day parenteral treatment (by UFH, LMWH or fondaparinux), at a fixed dose of 60 mg QD orally, or 30 mg QD orally in patients with a creatinine clearance of 30 to50 ml per minute or a body weight of 60 kg or less or in patients receiving concomitant treatment with potent P-glycoprotein inhibitors (Verapamil, Quinidine).

Sample Size (Supplementary Material)

Sample size for assessing event rates according to the combined strategy (sPESI + physician's clinical judgment) in low-risk sPESI patients (Table A8.7).

Sample size calculation is based on a 7-day adverse event rate defined as any outcome that requires or would have required hospital care or intervention, or induces unscheduled hospitalisation/ visits within the first 7 days following enrolment. This is best represented by a composite outcome that includes death, VTE recurrence, major bleeding and clinically relevant non major bleeding (CRNMB), and unscheduled hospitalisation/ visits for the outpatient suitable subgroup, to which clinical deterioration is added-on for the outpatient unsuitable subgroup. The components of the outcomes are as defined and referenced in the text document. The two subgroups are identified according to the combined strategy in low-risk sPESI patients (Table A8.7). The sample size needed is calculated to test 1 proportion (1-sample, 1-sided) in each subgroup. The sample size needed is 900 patients in the outpatient suitable subgroup and 510 patients in the outpatient unsuitable subgroup. The sample size in the whole cohort is 3900 patients (Table A8.7).

Table A8.7: Sample size for adverse event rates in low-risk PE (sPESI= 0) subgroups according to physician's clinical judgment in addition to sPESI (i.e. the combined strategy)

	Outpatient suitable (sPESI=0, no factor against home management)	**Outpatient unsuitable** (sPESI=0, ≥1 factor against home management)
Research hypothesis	Supplementing sPESI with relative contraindications could further **identify patients with PE with an even lower risk suitable for complete outpatient management**	Supplementing sPESI with relative contraindications could further **identify patients with PE with an even higher risk against home management**
Design	Single arm prospective cohort observational study (1)	Single arm prospective cohort observational study (1)
Outcome	Adverse event Death, VTE recurrence, Major bleeding and CRNMB (2) Unscheduled hospitalisation/ visits *Without clinical deterioration (patient treated at home)*(3)	Adverse event Death, VTE recurrence, Major bleeding and CRNMB Unscheduled hospitalisation/ visits Clinical deterioration (i.e. needs for cardiopulmonary resuscitation, respiratory support, intravenous vasopressors or inotropic, thrombolysis or clot extraction)
Time-point	7±2 days	7±2 days
Test for sample size[2] based on event rate	1 proportion: 1-sample, 1-sided Sample size needed to test whether a proportion p is equal to a reference value p0 Power 0.8 Type 1 error rate, α 5%	1 proportion: 1-sample, 1-sided Sample size needed to test whether a proportion p is equal to a reference value p0 Power 0.8 Type 1 error rate, α 5%
Null hypothesis (H0) Alternative hypothesis (H1)	p= p0 p< p0	p= p0 p> p0
Values and references	p0=0.01[Maestre et al[9] reporting on composite outcome of "Death, VTE, Major bleeding" in low-risk sPESI] p= 0.003 [no event (Vinson et al)[10] and 0.003 (Weeda et al[11] for all-cause death with Hestia)]	p0=0.01 [Maestre et al[9] reporting on composite outcome of "Death, VTE, Major bleeding" in low-risk sPESI] p= 0.023 [between 0.013 (Vinson et al)[10] and 0.032 (summary estimate for in-hospital all-cause death in my systematic review)]
Sample size	**Outpatient suitable:** **897 patients (4)** (Outpatient unsuitable: 507 patients)	**Outpatient unsuitable:** **497 patients (5)** (Outpatient suitable: 879 patients)
N of events	≤ 3 (instead of 9 events)	≥ 11 (instead of 5 events)

(1): A randomised trial would be the most robust design to compare patient outcomes if the "clinical judgment + sPESI" combined strategy is used versus the outcomes if a "sPESI" alone strategy was used, but this is not feasible because it is unlikely that patients in the second group would be discharged if sPESI=0 but the clinician did not feel it was safe to discharge the patient. This may result in lack of signal for comparison because a number of patients will not receive the allocated intervention with sPESI alone strategy. (2): CRNMB: clinically relevant non major bleeding. (3): The outcome in patients in an "outpatient suitable" subgroup is different from that in the "outpatient unsuitable" subgroup. This is related to the differences in the type of observation of patients treated at home and in the hospital. This differential observation may lead to surveillance or

2 http://powerandsamplesize.com/Calculators/Test-1-Proportion/1-Sample-1-Sided

detection bias, and it confounds direct comparison of outcomes between these two subgroups. (4) and (5): This sample size will also help to assess adverse events (clinical deterioration not included) at 30 days.

Sample size for assessing consistency between "sPESI + clinical judgment" combined strategy and "sPESI" alone strategy

Sample size calculation is based on a formula[12] derived from the kappa test statistic formula, using a simple proportion of agreement instead of the expected kappa, between two independent raters for a binary outcome under a given marginal prevalence in the (same) population sample. The formula is the following:

$$\mathrm{N} = \frac{\lambda}{((p1 - p0)^2) * \left(\left(\frac{p0}{(p0 + 2\pi - 1)(p0 - 2\pi + 1)}\right) + \left(\frac{1}{1 - p0}\right)\right)}$$

where N is the sample size, λ the non-centrality parameter that has a chi-squared distribution with one degree of freedom under the null hypothesis and equals to 7.849 under the significance level of 5% and power of 80%, p0 the proportion of agreement under the null hypothesis (i.e. the minimum acceptable proportion agreement between the two strategies), p1 the proportion of agreement under the alternative hypothesis, and π the marginal prevalence (i.e. the proportion of patients at low-risk sPESI).

The combined strategy and the sPESI strategy are assessed independently for the binary outcome i.e. the suitability for management at home or in the hospital (Table A8.4). The proportion of agreement is 0.8 under the null hypothesis and expected to be 0.86 under the alternative hypothesis (expected difference 0.06). This is calculated from the marginal prevalence and the proportion of patients suitable for outpatient management among patients at low-risk (no contraindications to home management and no need for hospital care). The marginal prevalence is 0.36-0.37 (or at high-risk 0.63-0.64) and comes from the summary estimate of the proportion of patients at low-risk sPESI in the systematic review (Chapter 4). The proportion of patients suitable for outpatient management among patients at low-risk is 0.641 according to Vinson et al[10]. The sample size to achieve 80% power with alpha level at 0.05 is 341 patients.

Table 8.8: Sample size based on agreement between "clinical judgment + sPESI" combined strategy versus "sPESI" alone strategy

Null hypothesis	Combined strategy against home management	Combined strategy for home management
sPESI ≥ 1	64	0
sPESI =0	20	16

Alternative hypothesis	Combined strategy against home management	Combined strategy for home management
sPESI ≥ 1	64	0
sPESI =0	13	23

Agreement (H0): 0.80, agreement (H1): 086 – 0.87. References: Summary estimate of proportion of patients at low-risk based on sPESI (sPESI=0) in my systematic review: 0.36 - 0.37. Proportion of patients belonging to the outpatient eligible subgroup among patients identified as low-risk PESI: 64.1% (35.9% for the outpatient ineligible subgroup)[10]. Assumption: similar distribution with sPESI.

REFERENCES

1. Jimenez D, Aujesky D, Moores L, et al. Simplification of the pulmonary embolism severity index for prognostication in patients with acute symptomatic pulmonary embolism. Archives of internal medicine 2010;**170 (15)**:1383-89.
2. Davies CWH, Wimperis J, Green ES, et al. Early discharge of patients with pulmonary embolism: a two-phase observational study. European Respiratory Journal 2007;**30**(4):708-14.
3. Erkens PM, Gandara E, Wells P, et al. Safety of outpatient treatment in acute pulmonary embolism. Journal of Thrombosis and Haemostasis 2010;**8**(11):2412-7.
4. Erkens PMG, Gandara E, Wells PS, et al. Does the Pulmonary Embolism Severity Index accurately identify low risk patients eligible for outpatient treatment? Thrombosis research 2012;**129 (6)**:710-14.
5. Zondag W, Mos IC, Creemers-Schild D, et al. Outpatient treatment in patients with acute pulmonary embolism: the Hestia Study. Journal of Thrombosis and Haemostasis 2011;**9**(8):1500-7.
6. Zondag W, Hiddinga BI, Crobach MJT, et al. Hestia criteria can discriminate high- from low-risk patients with pulmonary embolism. European Respiratory Journal 2013;**41**(3):588-92.
7. Zondag W, den Exter PL, Crobach MJT, et al. Comparison of two methods for selection of out of hospital treatment in patients with acute pulmonary embolism. Thrombosis and haemostasis 2013;**109**(1):47-52.
8. Zondag W, Vingerhoets LMA, Durian MF, et al. Hestia criteria can safely select patients with pulmonary embolism for outpatient treatment irrespective of right ventricular function. Journal of Thrombosis and Haemostasis 2013;**11**(4):686-92.
9. Maestre A, Trujillo-Santos J, Riera-Mestre A, et al. Identification of Low-Risk Patients with Acute Symptomatic Pulmonary Embolism for Outpatient Therapy. Annals of the American Thoracic Society 2015;**12**(8):1122-9.
10. Vinson DR, Drenten CE, Huang J, et al. Impact of Relative Contraindications to Home Management in Emergency Department Patients with Low-Risk Pulmonary Embolism. Annals of the American Thoracic Society 2015;**12**(5):666-73.
11. Weeda ER, Kohn CG, Peacock WF, et al. External Validation of the Hestia Criteria for Identifying Acute Pulmonary Embolism Patients at Low Risk of Early Mortality. Clinical and Applied Thrombosis/Hemostasis 2016.
12. Hong H, Choi Y, Hahn S, et al. Nomogram for sample size calculation on a straightforward basis for the kappa statistic. Ann Epidemiol 2014;**24**(9):673-80.