Thrombosis Research 178 (2019) 173–181

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Full Length Article

Sex-specific differences in pulmonary embolism

Karsten Keller[a], Lisa Rappold[b,c], Aslihan Gerhold-Ay[a,d], Lukas Hobohm[a,e], Gerd Hasenfuß[c], Stavros V Konstantinides[a,f], Claudia Dellas[g], Mareike Lankeit[a,c,h,*]

[a] Center for Thrombosis and Hemostasis (CTH), University Medical Center of the Johannes Gutenberg-University Mainz, Mainz, Germany
[b] Clinic for Internal Medicine, Siloah St. Trudpert Clinic, Pforzheim, Germany
[c] Clinic for Cardiology and Pulmonology, Heart Center, University Medical Center Göttingen, Göttingen, Germany
[d] Institute of Medical Biostatistics, Epidemiology and Informatics (IMBEI), Mainz, Germany
[e] Department of Cardiology, Cardiology I, University Medical Center of the Johannes Gutenberg-University Mainz, Mainz, Germany
[f] Department of Cardiology, Democritus University Thrace, Alexandroupolis, Greece
[g] Department of Paediatric Cardiology and Intensive Care, GUCH Center, University Medical Center Göttingen, Göttingen, Germany
[h] Department of Internal Medicine and Cardiology, Campus Virchow Klinikum (CVK), Charité – University Medicine Berlin, Berlin, Germany

ARTICLE INFO

Keywords:
Gender
Pulmonary embolism
Prognosis
Mortality
Risk stratification

ABSTRACT

Introduction: Sex-specific differences regarding risk factors, symptoms and prognosis have been reported for several cardiovascular diseases. For patients with pulmonary embolism (PE), sex-specific data are limited and inconsistent. We aimed to investigate sex-specific differences in PE.

Materials and methods: Over a 10-year period (01/2003–09/2013), patients with confirmed PE were enrolled in a prospective single-centre cohort study.

Results: We prospectively examined 569 PE patients (55.9% women). Men more often had cancer (20.7% vs. 13.5%, p = 0.024) and unprovoked PE (61.0% vs. 47.5%, p = 0.001) while women more frequently presented with risk factors for venous thromboembolism such as older age (median, 71 [IQR, 55–79] vs. 67 [53–75] years, p = 0.008), surgery/trauma/immobilisation (38.4% vs. 29.5%, p = 0.026) and sex-hormone therapy (14.8% vs. 0.8%, p < 0.001).

Overall, 84 patients (14.8%) had an adverse 30-day outcome and 43 (7.6%) died within 30 days; outcomes did not differ between males and females and were not influenced by the patients' sex. Risk stratification markers and models such as right ventricular dysfunction on TTE/CT, cardiac troponin, sPESI, Bova score and 2014 ESC guidelines algorithm predicted adverse outcome in normotensive female patients only, while tachycardia, hypoxia, NT-proBNP and modified FAST score were able to predict an adverse outcome in both sexes. Using sex-specific biomarker cut-off values, the 2014 ESC guidelines algorithm was able to predict adverse outcome in both sexes.

Conclusions: The 30-day adverse outcomes did not differ between male and female PE patients and were not influenced by the patients' sex despite sex-specific differences in the prognostic performance of risk stratification markers/models.

1. Introduction

Sex-specific differences in cardiovascular diseases (CVD) are well known [1–6]. Male sex increases both, the risk for CVD (particularly coronary artery disease [CAD]) [1,7] and stroke [3]) and the risk for fatal outcomes in CVD [4,7]. Although women and men share most cardiovascular risk factors, the relative importance of these factors in both sexes is different [5]. Meanwhile it is increasingly acknowledged

Abbreviations: AHA, American Heart Association; AUC, area under the curve; BNP, brain natriuretic peptide; CAD, coronary artery disease; CI, confidence interval; CT, computed tomography; cTn, cardiac troponin; cTnT, cardiac troponin T; CVD, cardiovascular disease; DAGs, directed acyclic graphs; ESC, European Society of Cardiology; hsTnT, high-sensitive troponin T; hsTnI, high-sensitive troponin I; IQR, interquartile range; LV, left ventricle/ventricular; NPV, negative predictive value; NT-proBNP, N-terminal pro-brain natriuretic peptide; OR, odds ratio; PE, pulmonary embolism; PEITHO, Pulmonary Embolism Thrombolysis study; PERGO, Pulmonary Embolism Registry Göttingen; PPV, positive predictive value; ROC, receiver operating characteristics; RV, right ventricle/ventricular; (s)PESI, (simplified) Pulmonary Embolism Severity Index; TTE, transthoracic echocardiogram/echocardiography; VTE, venous thromboembolism

* Corresponding author at: Department of Internal Medicine and Cardiology, Campus Virchow Klinikum (CVK), Charité – University Medicine Berlin, Augustenburger Platz 1, 13353 Berlin, Germany.
E-mail address: mareike.lankeit@charite.de (M. Lankeit).

https://doi.org/10.1016/j.thromres.2019.04.020
Received 17 January 2019; Received in revised form 12 April 2019; Accepted 19 April 2019
Available online 23 April 2019

that women with acute coronary syndrome (ACS) frequently present with atypical symptoms such as epigastric pain, indigestion-like symptoms or isolated dyspnoea [1,5,8,9] and the evaluation of women with symptoms suggestive of CAD is hampered by the definition of "typical" angina, derived from largely male dominated studies [5,8]. Lack of awareness for CAD in women resulted in an underuse of invasive procedures for CAD and ACS [1,4,7,8] associated with poorer outcome [4,8]. Similarly, thrombolytic treatment for ischemic stroke was less common in female patients resulting in less favourable outcome [10]. Therefore, the American Heart Association (AHA) and the World Heart Federation have started an international awareness campaign dedicated to sex-specific differences in CVD [6].

Despite this increasing body of evidence regarding sex-related differences in CVD, current available data on sex-related disparities in pulmonary embolism (PE) are limited and controversial. The nationwide inpatient sample of the United States of America (with > 276,000 patient discharge files) showed a higher incidence of PE in females compared to males [11]. In accordance, in most large registries females represented the majority of patients enrolled [12–15]. Most studies congruently reported that women were older at the PE event [11–14] and presented more frequently with dyspnoea while haemoptysis was more often observed in men [12,16]. Some studies demonstrated that cancer was more prevalent in male PE patients [13,16], while others did not [12]. As in CVD [4,8,10,17], women appeared to be at higher risk for short-term mortality after acute PE compared to men [11,18]. However, data on the prevalence and prognostic relevance of indicators of PE severity such as signs of right ventricular (RV) injury or dysfunction never were considered for comparison in male and female PE patients.

Therefore, in the present study we aimed i) to investigate whether females present with "atypical" symptoms and the impact of symptoms and initial presentation on treatment and outcome and ii) to compare the prognostic performance of risk stratification markers and models in males and females in a real-world cohort of PE patients.

2. Methods

2.1. Study design and definitions

Consecutive patients aged 18 years or older diagnosed with acute PE at the University Medical Center Göttingen, Germany between January 2003 and September 2013 were enrolled in an ongoing, observational, prospective cohort study (Pulmonary Embolism Registry of Göttingen [PERGO]). The study protocol has been described in detail previously [19]. Diagnostic and therapeutic management was in accordance with (at this time) current guidelines. Although all related decisions were left to the discretion of the treating physicians and were not influenced by the study protocol, performance of a transthoracic echocardiography (TTE) was strongly recommended within 48 h. Complete baseline data on clinical, electrocardiographic, echocardiographic, radiologic and laboratory parameters were obtained on admission/time of PE diagnosis using a standardised questionnaire case report form.

As shown in Fig. S1 in the Supplementary material, patients were excluded from analysis if they fulfilled at least one of the following criteria: 1) withdrawal of prior given consent for participation in the study, 2) PE event was an asymptomatic or incidental finding in the diagnostic process for other suspected diseases, 3) acute left heart or respiratory failure responsible for symptoms and initial presentation, and 4) missing data.

All patients were stratified into risk classes according to the simplified Pulmonary Embolism Severity Index (sPESI) (high- and low-risk) and the algorithm proposed by the European Society of Cardiology (ESC) 2014 guidelines [20] (high-, intermediate-high-, intermediate-low- and low-risk). Additionally, normotensive patients were further stratified using the Bova score [21] (high-, intermediate- and low-risk) and the modified FAST score [22] (high- and low-risk). For calculation of the scores, missing values were considered to be normal.

Biomarker elevation was defined as elevated cardiac troponin (cTn) (high sensitive troponin T [hsTnT] ≥14 pg/ml, high sensitive troponin I [hsTnI] ≥13 pg/ml in females and ≥33 pg/ml in males or cardiac troponin T [cTnT] ≥0.03 ng/ml) or elevated N-terminal pro-brain natriuretic peptide (NT-proBNP) levels ≥600 pg/ml; RV dysfunction was defined as i) RV dilatation (end-diastolic RV diameter ≥ left ventricular [LV] diameter) or end-diastolic RV diameter > 30 mm combined with absence of the inspiratory collapse of the inferior vena cava on TTE or ii) RV/LV ratio ≥1.0 on computed tomography (CT). Tachycardia was defined as heart rate ≥100 beats per minute, hypoxia as oxygen saturation < 90% or partial oxygen pressure < 60 mm Hg (8 kPa) in arterial blood gas analysis and renal insufficiency as glomerular filtration rate < 60 ml/min/1.73 m^2 body surface area.

All patients provided written informed consent for participating in the study. The local ethics board (ethics committee of the University Medical Center Göttingen, Göttingen, Germany; application numbers 11/5/02 and 14/6/10) approved the study protocol and the study conforms to Good Clinical Practice and Good Epidemiological Practice and the principles outlined in the Declaration of Helsinki.

2.2. Study outcome and follow-up

All patients were followed for 30 days. An adverse outcome (primary study outcome) was defined as PE-related death, need for mechanical ventilation, cardiopulmonary resuscitation or administration of catecholamines (except for dopamine at an infusion rate of ≤5 μg/kg body weight/min). The secondary study outcome was all-cause death. Death was determined to be PE-related if either confirmed by autopsy or following a clinically severe episode of acute PE in absence of an alternative diagnosis. All events and causes of death were independently adjudicated by two of the authors (K.K. and L.R.) and disagreement was resolved by a third author (M.L.). Recurrent PE was confirmed according (at this time) current guidelines. Major bleeding was defined as fatal and/or symptomatic bleeding in a critical area or organ and/or bleeding causing a fall in haemoglobin level of ≥2 g/dl or transfusion of ≥2 units of erythrocyte concentrates [23].

2.3. Statistical analysis

Descriptive statistics for baseline comparisons of both sexes were provided as median and interquartile range (IQR) for continuous variables or absolute numbers and corresponding percentages for categorical variables. All continuous variables were found not to follow a normal distribution tested with the modified Kolmogorov-Smirnov test (Lilliefors test) and therefore were compared using the Mann-Whitney *U* test. Categorical variables were compared using the Fisher's exact or chi^2-test, as appropriate.

We analysed associations between several predefined parameters (such as symptoms, VTE risk factors, comorbidities and risk stratification markers and models) and both, an adverse outcome and all-cause death with univariate logistic regression analyses in all normotensive patients, as well as in normotensive female and male patients separately. Odds ratios (OR) are given with the corresponding 95% confidence intervals (CIs).

We used directed acyclic graphs (DAGs) for i) graphic display of associations between risk stratification markers and an adverse outcome (separately for normotensive women and men) and for ii) identification of variables to be included in multivariate regression models and bias assessment. DAGs are frequently used to calibrate and choose the degree of adjustment and to avoid over-adjustment [24,25]. Based on pathophysiological considerations [20,26] we supposed that acute RV dysfunction on TTE/CT would have the strongest impact on outcome and therefore defined it as reference "exposure" variable; further risk stratification markers were added to the model and identified as "ancestors of outcome" and/or "ancestor of exposure", respectively. To

test the independence of the prognostic value of parameters univariably associated with an adverse outcome, head-to-head comparisons including two variables each in multivariable logistic models were performed. Receiver operating characteristics (ROC) curves were calculated for risk stratification markers and models with regard to an adverse outcome in women and men, respectively, and the area under the curve (AUC) is presented with the corresponding 95% CI. Sensitivity, specificity, negative (NPV) and positive predictive values (PPV) were computed for dichotomised risk stratification markers and models. Additionally, patient cohort-optimised sex-specific cut-off values of continuous and categorical risk stratification markers and models with regard to an adverse outcome were calculated based on ROC analyses using Youden index quantification. The global significance level was set to $\alpha_{global} = 5\%$. Additionally, Bonferroni-Holm method was used for baseline comparison between male and female patients resulting in local significance levels of $\alpha_{local} = 0.18\%$ for all patients and $\alpha_{local} = 0.17$ for normotensive PE patients. The softwares SPSS® (version 22.0; SPSS Inc., Chicago, Illinois, USA) and DAGitty version 2.3 software [27] were used.

3. Results

During the 10-year study period, 600 patients with acute PE were enrolled in PERGO and 569 patients (94.8%) included in the present analysis (Fig. S1 of the Supplementary material). Diagnosis of PE was confirmed in 504 patients (88.3%) by CT pulmonary angiography, in 52 (9.1%) by ventilation-/perfusion- lung scintigraphy (showing perfusion defects in ≥2 segments in 93.5% of the female and 95.0% of the male patients), in 5 (0.9%) by pulmonary angiography and in 29 (5.1%) by TTE showing mobile thrombi in the right atrium or ventricle or in the proximal portions of the pulmonary artery, or acute RV dysfunction in haemodynamic unstable patients. Overall, 21 patients (3.7%) had more than one diagnostic imaging procedures. A TTE was performed in 384 patients (67.3%) within 48 h after admission.

Patients' characteristics at baseline are presented in Table 1. The majority of patients was of female sex (318 [55.9%] vs. 251 [44.1%], p = 0.098). Although almost 60% of patients < 50 years were female, in total, females were older compared to males (median, 71 [IQR, 55–79] vs. 67 [53–75] years; p = 0.008) (Fig. S2 of the Supplementary material).

3.1. Men and women present with similar symptoms

Unprovoked PE was more frequently present in males, explained by a higher frequency of transient VTE risk factors such as trauma, surgery or immobilisation and sex hormone (replacement) therapy in females. Comorbidities of the present cohort showed real-world distribution with a higher prevalence of cancer and CAD in men and rheumatoid arthritis and renal insufficiency in women (Table 1, left columns). Of note, after using the Bonferroni-Holm correction, only the variables contraceptives or sex hormone (replacement) therapy, unprovoked PE and CAD remained significantly different between both sexes. Overall, 95 patients (16.7%) had active cancer. The most prevalent cancer types in females and males are shown in Fig. S3 of the Supplementary material.

In contrast to the study hypothesis expecting more “atypical” symptoms in women, we observed only small sex-related differences: Women presented slightly more frequently with dyspnoea, whereas men had more often haemoptysis. Interestingly, no sex-specific differences were observed in the number of patients presenting with chest pain, although men more often had CAD (Table 1, left columns). Risk stratification markers such as tachycardia, RV dysfunction on TTE and NT-proBNP plasma concentrations ≥600 pg/ml were more frequently present in women than in men (Table 1, left columns). However, if patients were stratified to risk classes using the 2014 ESC guidelines algorithm, no significant sex-related differences were observed (Fig. S4 of the Supplementary material).

3.2. Sex-specific differences in the prognostic performance of risk stratification markers and models

In total, 84 patients (14.8%) had an adverse outcome and 43 patients (7.6%) died; of those, 36 deaths (83.7%) were related to PE. Additionally, 9 patients (1.6%) had recurrent PE during the in-hospital stay. Thirty-day outcomes did not differ between males and females (Table S1 of the Supplementary material, left columns) and were consequently not influenced by sex (adverse outcome: OR, 1.12 [95% CI, 0.70–1.80]; p = 0.625; all-cause death: OR, 1.10 [0.59–2.07]; p = 0.757). Unsurprisingly, the 30-day all-cause mortality rate was highest in high-risk patients (44.7% in females and 40.0% in males, p = 0.695).

To investigate and compare the prognostic performance of markers and models for risk stratification in male and female patients, further analyses were based on 501 normotensive patients (88.0% of the overall cohort). Female patients showed a higher frequency of tachycardia, hypoxia, RV dysfunction on TTE and elevated NT-proBNP levels and were thus more often classified to the intermediate-high-risk class according the 2014 ESC guidelines algorithm (39.6% vs. 30.8%, p = 0.042) (Table 1, right columns). As shown in Table S1 of the Supplementary material (right columns), 31 normotensive patients (6.2%) had an adverse outcome and 14 (2.8%) died during the first 30 days. Again, no differences were observed between male and female patients regarding 30-day outcomes and patients' sex had neither an impact on adverse outcome (OR, 1.10 [0.53–2.30]; p = 0.801) nor on all-cause mortality (OR, 1.05 [0.36–3.08]; p = 0.924). Predictors of an adverse outcome in normotensive patients are shown in Table 2. Interestingly, tachycardia, hypoxia, NT-proBNP and the modified FAST score were the only variables able to predict an adverse outcome in both sexes. DAGs illustrate sex-specific differences in the prognostic importance of risk stratification markers regarding an adverse outcome in female (Fig. 1A) and male (Fig. 1B) patients. The initial assumption that acute RV dysfunction on TTE/CT is the most powerful risk stratification marker for the prediction of an adverse outcome in both sexes had to be rejected. Instead, RV dysfunction on TTE/CT, elevated cTn levels and syncope were predictors of an adverse outcome in females only. Since age influenced cTn in both sexes, NT-proBNP and RV dysfunction on TTE/CT in females and cardiopulmonary disease in males, age was added to the subsequent multivariate regression models. The results of the multivariable logistic regression analyses using head-to-head comparisons of variables identified by DAGs and adjusted for age are shown in Table S2 of the Supplementary material. Summarising these findings, only tachycardia was identified as an independent predictor of an adverse outcome in both sexes.

As shown in Table 3, risk stratification markers and models using established cut-off values were associated with a better prognostic performance in women than in men. While all risk stratification markers and models were characterised by high NPVs, PPVs and specificity remained low, respectively. To optimise the prognostic performance of risk stratification markers, we calculated sex-specific optimal cut-off values for hsTnT (men: ≥17 pg/ml; women: ≥32 pg/ml), NT-proBNP (men: ≥770 pg/ml; women: ≥1712 pg/ml) and RV/LV ratio on CT (men: ≥1.2; women: ≥1.3) (Table S3 in the Supplementary material). While sex-specific thresholds were associated with slightly higher specificity but did not improve the overall prognostic performance in men, a sex-specific RV/LV ratio cut-off value was able to predict an adverse outcome in women (OR, 6.00 [95% CI, 1.52–23.70]; p = 0.011). Use of sex-specific biomarker cut-off values for stratification of male patients into risk classes according the 2014 ESC guidelines algorithm helped to improve its prognostic performance (OR, 5.81 [95% CI, 1.49–22.73]; p = 0.011 for intermediate-high-risk patients compared to intermediate-low- and low-risk patients; Table S3 of the Supplementary material).

Table 1
Baseline characteristics, medical history and baseline findings of study patients (stratified according sex).

Parameters		All study patients				Normotensive patients			
		All study patients (n = 569)	Females (n = 318; 55.9%)	Males (n = 251; 44.1%)	p-Value	Normotensive patients (n = 501)	Females (n = 280; 55.9%)	Males (n = 221; 44.1%)	p-Value
Age (years)		69 (54–77)	71 (55–79)	67 (53–75)	**0.008**	69 (54–77)	71 (55–79)	68 (53–75)	**0.017**
BMI (kg/m^2)		27.4 (24.2–31.1), n = 553	27.3 (23.3–31.6), n = 308	27.6 (24.9–30.5), n = 245	0.562	27.4 (24.2–30.9), n = 497	27.3 (23.5–31.6), n = 275	27.5 (25.0–30.1), n = 216	0.468
Hospital stay (days)		10 (7–15)	10 (7–15)	10 (6–15)	0.702	10 (7–15)	11 (7–15)	10 (7–14)	0.118
VTE risk factors									
History of VTE		158 (27.9%), n = 567	89 (28.1%), n = 317	69 (27.6%), n = 250	0.925	148 (29.5%)	84 (30.0%)	64 (29.0%)	0.844
Surgery, trauma or immobilisation[a]		195 (34.5%), n = 566	121 (38.4%), n = 315	74 (29.5%)	**0.026**	165 (32.9%)	103 (36.8%)	62 (28.1%)	**0.039**
Cancer[b]		95 (16.7%)	43 (13.5%)	52 (20.7%)	**0.024**	88 (17.6%)	40 (14.3%)	48 (21.7%)	**0.033**
Contraceptives or sex hormone (replacement) therapy		49 (8.6%), n = 568	47 (14.8%), n = 317	2 (0.8%)	**< 0.001**	46 (9.2%)	45 (16.1%)	1 (0.5%)	**< 0.001**
Unprovoked PE[c]		304 (53.4%)	151 (47.5%)	153 (61.0%)	**0.001**	270(53.9%)	133 (47.5%)	137 (62.0%)	**0.001**
Comorbidities									
Chronic (left) heart failure		101 (17.8%)	57 (17.9%)	44 (17.5%)	0.913	82 (16.4%)	47 (16.8%)	35 (15.8%)	0.809
Coronary artery disease		106 (18.6%)	43 (13.5%)	63 (25.1%)	**0.001**	87 (17.4%)	33 (11.8%)	54 (24.4%)	**< 0.001**
Chronic lung disease[d]		81 (14.2%)	43 (13.5%)	38 (15.1%)	0.692	69 (13.8%)	37 (13.2%)	32 (14.5%)	0.697
Renal insufficiency		200 (35.7%), n = 560	123 (39.4%), n = 312	77 (31.0%), n = 248	**0.042**	157 (31.8%), n = 494	99 (36.0%), n = 275	58 (26.5%), n = 219	**0.024**
Diabetes mellitus		97 (17.0%)	58 (18.2%)	39 (15.5%)	0.433	83 (16.6%)	51 (18.2%)	32 (14.5%)	0.278
Rheumatoid disease[e]		41 (7.2%), n = 567	30 (9.5%), n = 317	11 (4.4%)	**0.022**	35 (7.0%), n = 500	24 (8.6%)	11 (5.0%), n = 220	0.157
Symptoms									
Chest pain		294 (52.0%), n = 565	161 (51.1%), n = 315	133 (53.2%), n = 250	0.672	275 (55.0%), n = 500	149 (53.2%), n = 279	126 (57.0%)	0.469
Dyspnoea		487 (86.0%), n = 566	280 (88.9%), n = 315	207 (82.5%)	**0.037**	438 (87.6%), n = 500	250 (89.6%), n = 279	188 (85.1%)	0.135
Haemoptysis		19 (3.4%), n = 567	6 (1.9%), n = 316	13 (5.2%)	**0.036**	19 (3.8%)	6 (2.1%)	13 (5.9%)	**0.035**
Syncope		120 (21.1%)	65 (20.4%)	55 (21.9%)	0.608	74 (14.8%)	41 (14.6%)	33 (14.9%)	1.000
Onset of symptoms < 24 h		323 (56.8%)	184 (57.9%)	139 (55.4%)	0.609	255 (50.9%)	146 (52.1%)	109 (49.3%)	0.589
Risk stratification									
Tachycardia		208 (37.5%), n = 554	131 (42.3%), n = 310	77 (31.6%), n = 244	**0.010**	179 (36.1%), n = 496	114 (41.3%), n = 276	65 (29.5%), n = 220	**0.008**
Hypoxia		158 (31.7%), n = 499	100 (35.2%), n = 284	58 (27.0%), n = 215	0.053	121 (27.8%), n = 435	79 (31.7%), n = 249	42 (22.6%), n = 186	**0.040**
RV dysfunction on TTE/CT		332(65.0%), n = 511	194 (68.6%), n = 283	138(60.5%), n = 228	0.059	278 (61.9%), n = 449	161 (65.2%), n = 247	117 (57.9%), n = 202	0.115
RV dysfunction on TTE		198 (51.4%), n = 385	124 (56.6%), n = 219	74 (44.6%), n = 166	**0.019**	153 (46.5%), n = 329	95 (51.4%), n = 185	58 (40.3%), n = 144	**0.046**
RV/LV ratio ≥ 1.0 on CT		232 (67.8%), n = 342	122 (71.3%), n = 171	110 (64.3%), n = 171	0.165	204 (66.0%), n = 309	109 (70.8%), n = 154	95 (61.3%), n = 155	0.078
Elevated cTn[f]		351 (63.9%), n = 549	197 (63.5%), n = 310	154 (64.4%), n = 239	0.858	304 (62.3%), n = 488	169 (61.5%), n = 275	135 (63.4%), n = 213	0.663
NT-proBNP ≥600 pg/ml		292 (55.8%), n = 523	181 (61.6%), n = 294	111 (48.5%), n = 229	**0.003**	254 (54.5%), n = 466	157 (60.4%), n = 260	97 (47.1%), n = 206	**0.004**
sPESI ≥1 point(s)		410 (72.1%)	236 (74.2%)	174 (69.3%)	0.197	342 (68.3%)	198 (70.7%)	144 (65.2%)	0.185
2014 ESC guidelines algorithm	High-risk	68 (12.0%)	38 (11.9%)	30 (12.0%)	0.248	–	–	–	–
	Intermediate-high-risk	178 (31.3%)	110 (34.6%)	68 (27.1%)		178 (35.5%)	110 (39.3%)	68 (30.8%)	0.127
	Intermediate-low-risk	261 (45.9%)	139 (43.7%)	122 (48.6%)		261 (52.1%)	139 (49.6%)	122 (55.2%)	
	Low-risk	62 (10.9%)	31 (9.7%)	31 (12.4%)		62 (12.4%)	31 (11.1%)	31 (14.0%)	
Bova score > 4 points		–	–	–	–	85 (17.0%)	57 (20.4%)	28 (12.7%)	**0.023**
Modified FAST score ≥3 points		–	–	–	–	172 (34.3%)	103 (36.8%)	69 (31.2%)	0.193

Abbreviations: BMI indicates body mass index; VTE, venous thromboembolism; PE, pulmonary embolism; RV, right ventricular/ventricle; TTE, transthoracic echocardiography; CT, computed tomography; LV, left ventricular/ventricle; cTn, cardiac troponin; NT-proBNP, N-terminal pro-brain natriuretic peptide; sPESI, simplified Pulmonary Embolism Severity Index; ESC, European Society of Cardiology.
P-values < 0.05 are marked in bold.

[a] Within the past 4 weeks.

[b] Active or anti-tumour therapy within the last 6 months, or metastatic state.

[c] In the absence of a temporary or reversible risk factor such as surgery, trauma, immobilisation, pregnancy/postpartal period, contraceptives or sex hormone replacement therapy.

[d] Bronchial asthma, chronic obstructive lung disease, or interstitial lung diseases.

[e] Rheumatoid arthritis, granulomatosis with polyangiitis, systemic sclerosis or systemic lupus erythematosus.

[f] 308 of 462 patients had a high sensitive troponin T [hsTnT] ≥14 pg/ml, 52 of 82 patients had a high sensitive troponin I [hsTnI] ≥13 pg/ml in females and ≥ 33 pg/ml in males and 112 of 299 patients had a cardiac troponin T [cTnT] ≥0.03 ng/ml; of note, in 274 patients (48.2%) cTn levels were determined with more than one cTn assay.

As shown in Table S4 of the Supplementary material, only hypoxia predicted all-cause mortality regardless of sex. RV dysfunction on TTE/CT, elevated cTn, elevated NT-proBNP, the modified FAST score and the 2014 ESC guidelines algorithm were of predictive value in female PE patients only.

3.3. Impact of treatment on outcomes

The anticoagulation treatment at discharge is shown in Fig. S5 of the Supplementary material). The majority of patients was treated with vitamin K antagonists.

Overall, 123 patients (21.6%) received reperfusion therapy (systemic thrombolysis or inclusion in the Pulmonary Embolism Thrombolysis [PEITHO] study [28] and/or surgical embolectomy). Of those, 16 patients received out-of-hospital systemic thrombolysis, 57 patients early systemic thrombolysis (within 24 h), two patients secondary systemic thrombolysis (> 24 h), 34 patients were included in the PEITHO study and randomised to either single-bolus tenecteplase or placebo and 14 patients underwent surgical embolectomy. No patient received an inferior vena cava filter.

Although the proportion of high-risk patients was comparable in both sexes (Table 1, left column), females were more often treated with systemic thrombolysis compared to males (16.4% vs. 9.2%, p = 0.013) while no sex-related differences were observed regarding inclusion in the PEITHO study or surgical embolectomy. The relative risk for an adverse outcome of patients classified as high- and intermediate-high-risk by the 2014 ESC guidelines algorithm was reduced by the use of reperfusion therapy from 11.97 (95% CI, 6.18–23.17; p < 0.001) to 6.49 (95% CI, 3.23–13.06; p < 0.001); the effect was more pronounced in females (reduction from 39.09 [95% CI, 9.29–164.40]; p < 0.001 to 23.43 [95% CI, 5.44–101.00]; p < 0.001) than in males (reduction from 5.78 [95% CI, 2.57–12.98]; p < 0.001 to 2.69 [95% CI, 1.07–6.78]; p = 0.036).

Major bleeding occurred in 41 patients (7.2%) and was more prevalent in females compared to males (10.1% vs. 3.6%, p = 0.003); no patient died due to bleeding. Interestingly, major bleeding was a predictor of all-cause death in females (OR, 4.17 [95% CI, 1.59–10.94]; p = 0.004) but failed to reach statistical significance in males (OR, 4.04 [95% CI, 0.77–21.04]; p = 0.098).

4. Discussion

In this large prospective observational cohort study, we observed sex-related differences regarding risk stratification and treatment, but not regarding initial presentation and outcomes in acute PE. The key study findings can be summarised as follows: i) in contrast to patients with ACS, male and female PE patients present with similar symptoms, ii) most risk stratification markers and models were not able to predict an adverse outcome in men, iii) the prognostic performance of the 2014 ESC guidelines algorithm was improved by the use of sex-specific biomarker cut-off values in male patients, and iv) 30-day outcomes did not differ between males and females and were not influenced by sex.

4.1. Sex-specific differences in comorbidities and initial presentation

As consistently reported by other registries and cohort studies [11–15], in the present single-centre study, the proportion of females was higher (55.9%) and females were older compared to males although almost 60% of patients < 50 years were women. Risk factors and comorbidities showed real-world distribution with expected differences in males and females. In accordance with the literature, we observed that females slightly more often presented with dyspnoea,

Table 2
Predictors of an adverse outcome in female and male normotensive patients.

Parameters	All normotensive patients (n = 501)			Females (n = 280)			Males (n = 221)		
	OR (95% CI)	p-Value	n/N	OR (95% CI)	p-Value	n/N	OR (95% CI)	p-Value	n/N
Symptoms									
Chest pain	0.50 (0.24–1.04)	0.064	12/500	0.31 (0.11–0.90)	**0.031**	5/279	0.87 (0.28–2.69)	0.812	7/221
Syncope	2.55 (1.12–5.78)	**0.025**	9/501	4.27 (1.55–11.76)	**0.005**	7/280	1.04 (0.22–4.91)	0.962	2/221
Comorbidities									
Chronic (left) heart failure	3.09 (1.42–6.73)	**0.004**	11/501	2.70 (0.96–7.59)	0.060	6/280	3.71 (1.14–12.10)	**0.030**	5/221
Renal insufficiency	1.84 (0.88–3.84)	0.103	14/501	3.02 (1.13–8.06)	**0.027**	11/275	0.82 (0.22–3.10)	0.774	3/219
Risk stratification markers and models									
Tachycardia	7.06 (3.18–15.68)	< **0.001**	19/496	6.88 (2.34–20.25)	< **0.001**	12/276	7.70 (2.30–25.77)	< **0.001**	7/220
Hypoxia	4.20 (1.89–9.33)	< **0.001**	16/435	3.38 (1.23–9.23)	**0.018**	10/249	5.83 (1.56–21.77)	**0.009**	6/186
RV dysfunction on TTE/CT	2.36 (0.94–5.95)	0.068	22/449	9.38 (1.22–71.99)	**0.031**	16/247	0.87 (0.26–2.93)	0.816	6/202
RV dysfunction on TTE	6.84 (2.29–20.41)	0.001	21/329	Non-calculable, therefore chi^2-test was used	< **0.001**	16/185	1.93 (0.50–7.53)	0.342	5/144
RV/LV ratio ≥ 1.0 on CT	1.40 (0.53–3.70)	0.492	16//309	4.44 (0.55–35.79)	0.161	10/154	0.74 (0.22–2.55)	0.635	6/154
Elevated cTn[a]	8.87 (2.08–37.76)	**0.003**	27/488	Non-calculable, therefore chi^2-test was used	< **0.001**	17/275	3.04 (0.65–14.25)	0.158	10/213
NT-proBNP ≥ 600 pg/ml	5.68 (1.94–16.58)	**0.002**	25/466	5.34 (1.19–23.84)	**0.028**	15/260	6.15 (1.31–28.81)	**0.021**	10/206
sPESI ≥ 1 point(s)	15.19 (2.05–112.43)	**0.008**	30/501	Non-calculable, therefore chi^2-test was used	**0.002**	18/280	6.91 (0.88–54.18)	0.066	12/221
2014 ESC guidelines algorithm[b]	3.59 (1.68–7.68)	**0.001**	20/501	14.30 (3.22–63.54)	< **0.001**	16/280	1.00 (0.30–3.37)	1.000	4/221
Bova score > 4 points	4.63 (2.18–9.81)	< **0.001**	14/501	7.38 (2.72–20.05)	< **0.001**	11/280	2.20 (0.57–8.52)	0.256	3/221
Modified FAST score ≥ 3 points	7.46 (3.14–17.70)	< **0.001**	24/501	16.09 (3.62–71.57)	< **0.001**	16/280	3.86 (1.21–12.26)	**0.022**	8/221

n = number of patients with event in this category/N = number of patients with information available. Abbreviations: OR indicates Odds ratio; CI, confidence interval, RV, right ventricular; TTE, transthoracic echocardiography; CT, computed tomography; LV, left ventricular/ventricle; cTn, cardiac troponin; NT-proBNP, N-terminal pro-brain natriuretic peptide; sPESI, simplified Pulmonary Embolism Severity Index; ESC, European Society of Cardiology.
P-values < 0.05 are marked in bold.

[a] 276 of 425 patients had a high sensitive troponin T [hsTnT] ≥ 14 pg/ml, 45 of 73 patients had a high sensitive troponin I [hsTnI] ≥ 13 pg/ml in females and ≥ 33 pg/ml in males and 86 of 261 patients had a cardiac troponin T [cTnT] ≥ 0.03 ng/ml; of note, in 258 patients (51.5%) cTn levels were determined with more than one cTn assay.

[b] Intermediate-high-risk vs. intermediate-low-risk and low-risk.

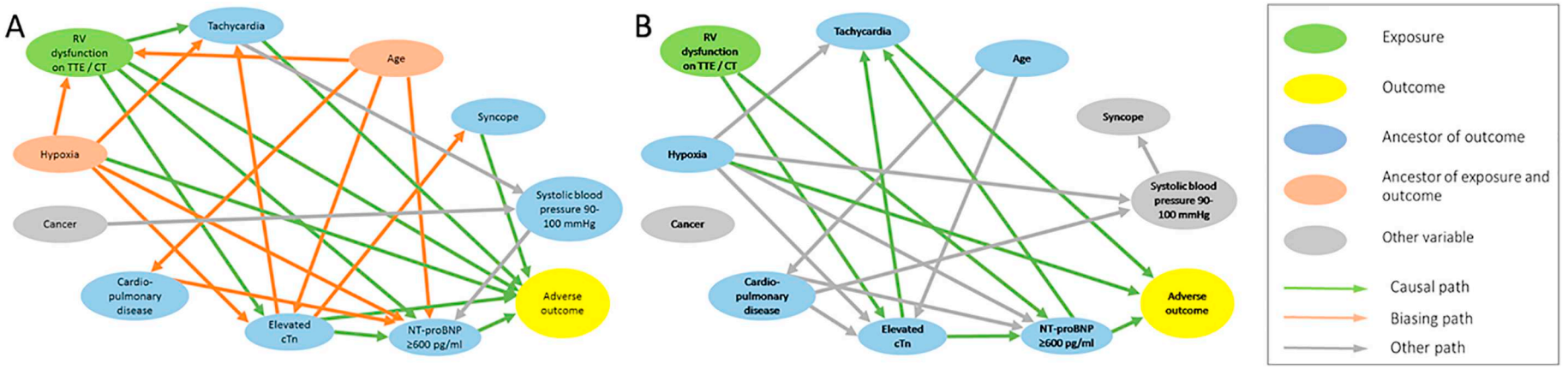

Fig. 1. Directed acyclic graphs (DAGs) showing associations between risk stratification markers and an adverse outcome in women (A) and men (B).
RV dysfunction on TTE/CT (green node) was assumed to be the most powerful prognostic marker in both sexes and therefore defined as reference "exposure" variable. An adverse outcome (yellow node) was defined as "outcome" variable. Risk stratification markers were defined as "ancestors" if a direct or indirect (over a second risk stratification marker) influence on "exposure" or "outcome" was observed.
Every arrow represents a significant association identified by univariable logistic regression analysis or chi^2 test. Arrows starting from the predefined "exposure" (green node) and/or ending directly or indirectly (over a second risk stratification marker) at the predefined "outcome" (yellow node) represent "causal paths" (green arrows). Arrows not fulfilling this criterion represent "biasing paths" (red arrows). Associations between risk stratification markers found too weak to indirectly influence outcome are marked in grey arrows.
In female patients (panel A), most risk stratification parameters interact with each other (arrows between the single parameters) and RV dysfunction on TTE/CT, tachycardia, NT-proBNP ≥ 600 pg/ml, elevated cTn (green arrows) as well as hypoxia and syncope (red arrows) were associated with an adverse outcome during the first 30 days (yellow node).
In male patients (panel B), the interaction between risk stratification markers (all arrows) was less pronounced in males compared to females. Further, only risk stratification markers directly or indirectly associated with RV dysfunction on TTE/CT (green node) affected outcome (yellow node) and include tachycardia, NT-proBNP ≥600 pg/ml and hypoxia (green arrows). Cancer and syncope did neither influence other risk stratification markers nor outcome.
Abbreviations: RV indicates right ventricular; cTn, cardiac troponin; NT-proBNP, N-terminal pro-brain natriuretic peptide.

Table 3
Prognostic performance of risk stratification markers and models for prediction of an adverse outcome in female and male normotensive patients.

Parameter	Sex	AUC (95% CI), p-value	Cut-off value	p-Value[a]	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Heart rate	Women, n = 276	0.73 (0.58–0.88), **p = 0.002**	≥ 100 beats/min	**< 0.001**	0.71 (0.47–0.87)	0.74 (0.68–0.79)	0.15 (0.09–0.24)	0.98 (0.94–0.99)
	Men, n = 220	0.69 (0.51–0.87), **p = 0.027**		**0.001**	0.58 (0.32–0.81)	0.72 (0.66–0.78)	0.11 (0.05–0.21)	0.97 (0.93–0.99)
hsTnT (pg/ml)	Women, n = 230	0.76 (0.67–0.84), **p = 0.001**	≥ 14 pg/ml	**0.001**	1.00 (0.81–1.00)	0.38 (0.32–0.45)	0.11 (0.07–0.16)	1.00 (0.96–1.00)
	Men, n = 195	0.61 (0.48–0.75), p = 0.212		0.337	0.82 (0.52–0.95)	0.35 (0.29–0.42)	0.07 (0.04–0.13)	0.97 (0.90–0.99)
NT-proBNP (pg/ml)	Women, n = 260	0.72 (0.60–0.83), **p = 0.003**	≥ 600 pg/ml	**0.019**	0.88 (0.66–0.97)	0.42 (0.36–0.48)	0.10 (0.06–0.15)	0.98 (0.93–0.99)
	Men, n = 206	0.66 (0.52–0.80), p = 0.065		**0.014**	0.83 (0.55–0.95)	0.55 (0.48–0.62)	0.10 (0.06–0.18)	0.98 (0.94–0.99)
RV/LV ratio on CT	Women, n = 154	0.75 (0.61–0.90), **p = 0.005**	≥ 1.0	0.177	0.91 (0.62–0.98)	0.31 (0.24–0.39)	0.09 (0.05–0.16)	0.98 (0.88–1.00)
	Men, n = 154	0.43 (0.23–0.63), p = 0.461		0.750	0.55 (0.28–0.79)	0.38 (0.30–0.46)	0.06 (0.03–0.13)	0.92 (0.82–0.96)
sPESI	Women, n = 280	0.74 (0.64–0.84), **p = 0.001**	≥ 1 point(s)	**0.002**	1.00 (0.82–1.00)	0.31 (0.26–0.37)	0.09 (0.05–0.14)	1.00 (0.96–1.00)
	Men, n = 221	0.74 (0.60–0.87), **p = 0.004**		**0.037**	0.92 (0.67–0.99)	0.37 (0.30–0.43)	0.08 (0.05–0.14)	0.99 (0.93–1.00)
2014 ESC guidelines algorithm	Women, n = 280	0.77 (0.68–0.86), **p < 0.001**	Intermediate-high-risk[b]	**< 0.001**	0.89 (0.67–0.97)	0.64 (0.58–0.70)	0.15 (0.09–0.22)	0.99 (0.96–1.00)
	Men, n = 221	0.55 (0.41–0.69), p = 0.533		1.000	0.31 (0.13–0.58)	0.69 (0.63–0.75)	0.06 (0.02–0.14)	0.94 (0.89–0.97)
Bova score	Women, n = 280	0.79 (0.69–0.88), **p < 0.001**	> 4 points	**< 0.001**	0.61 (0.39–0.80)	0.82 (0.77–0.87)	0.19 (0.11–0.31)	0.97 (0.94–0.98)
	Men, n = 221	0.63 (0.49–0.77), p = 0.110		0.218	0.23 (0.08–0.50)	0.88 (0.83–0.92)	0.11 (0.04–0.27)	0.95 (0.91–0.97)
Modified FAST score	Women, n = 280	0.79 (0.72–0.87), **p < 0.001**	≥ 3 points	**< 0.001**	0.89 (0.67–0.97)	0.67 (0.61–0.72)	0.16 (0.10–0.24)	0.99 (0.96–1.00)
	Men, n = 221	0.66 (0.52–0.81), **p = 0.047**		**0.027**	0.62 (0.36–0.82)	0.71 (0.64–0.76)	0.12 (0.06–0.21)	0.97 (0.93–0.99)

Abbreviations: AUC indicates area under the curve; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value; hsTnT, high-sensitive troponin T; NT-proBNP, N-terminal pro-brain natriuretic peptide; RV, right ventricle; LV, left ventricle; CT, computed tomography; sPESI, simplified Pulmonary Embolism Severity Index; ESC, European Society of Cardiology.
P-values < 0.05 are marked in bold.
[a] Chi^2-test for association between dichotomised parameters and adverse outcome.
[b] Intermediate-high-risk vs. intermediate-low-risk and low-risk.

whereas haemoptysis was more prevalent in men [12,16].

However, and in contrast to our study hypothesis, women with acute PE did not present with "atypical" symptoms such as females with ACS and CAD [1,5,8]. Thus, in the clinical judgment of initial symptoms at presentation for acute PE, the patients' sex may not require special consideration.

4.2. Sex-specific differences in the prognostic performance of risk stratification markers and models

It is increasingly acknowledged that women have lower hs-cTn plasma concentrations compared to men, regardless of the population assessed or assay applied [29]. Although the cardiovascular risk profile and thus pathophysiology of ACS differs in males and females and the use of sex-specific cut-off values has been proposed to avoid over-diagnosis of myocardial infarction in men, concerns have been raised that sex-specific cut-off values may only have a small clinical effect at the cost of increased complexity in decision-making [29,30]. Vice versa, women have higher natriuretic peptide plasma concentrations compared to men and it has been shown that lower levels of circulating androgens and the potentiating effect of exogenous female hormone therapy contribute to higher NT-proBNP concentrations in women [31]. Despite disparities in pathophysiology and disease manifestation between male and female patients with heart failure, no differences in NT-proBNP plasma concentrations were observed [32] and the use of sex-specific cut-off values is not recommended by the current ESC guidelines for the diagnosis and treatment of acute and chronic heart failure [33].

In the present study, we were able to confirm the prognostic relevance of elevated cTn and NT-proBNP plasma concentrations in normotensive patients with acute PE (Table 2). Although differences in the prognostic performance were observed in male and females (Tables 2 and 3) and the use of sex-specific cut-off values resulted in a slightly higher specificity and a better prognostic performance of the "optimised" 2014 ESC guidelines algorithm in males (Table S3 of the Supplementary material), some methodological issues of the present study deserve consideration before final conclusion should be drawn: first, the number of adverse events was small especially in subgroup analyses focussing on normotensive male and female patients resulting in large CIs and precluding multivariate analyses to correct for confounders. Second, since this is the first description of sex-related differences in the prognostic performance of risk stratification markers and models in acute PE derived in a single-centre cohort, further studies are needed to confirm the present study findings.

In the present study, RV dysfunction on TTE was more frequently diagnosed in women compared to men (56.6% vs. 44.6%, p = 0.019; Table 1); a finding in accordance with a higher prevalence of females (59.5%) in a study investigating "submassive" PE patients [14]. Moreover, evidence of RV dysfunction was associated with a higher rate of an adverse outcome in both sexes (male: 23.0% vs. 8.7%, p = 0.015; females: 32.3% vs. 3.2%, p < 0.001). For a better understanding of this observation, studies focussing on sex-related differences in RV morphology and function deserve attention: Women are known to have smaller RV mass, dimensions and volume compared to men [34–36]. However, sex-related differences in RV morphology are only insufficiently explained by a smaller body surface area in women [34,35] and are affected by hormonal status. While higher levels of androgens were related to greater RV mass and volume in both sexes, higher estradiol levels were associated with better RV systolic function in women using hormone therapy [37]. In patients with pulmonary arterial hypertension, it is increasingly understood that estrogen metabolism and signalling is a potent disease modifier [38] associated with better RV systolic function [37,39] and prognosis [40,41]. Thus, although the morphology of the female RV appears less suitable to manage the sudden increase of RV afterload due to the acute PE (indicated by a higher rate of females with RV dysfunction on TTE in the present

study), the better RV systolic function and adaptation mechanism might overcome this anatomical limitation (indicated by a comparable rate of adverse outcomes in males and females in the present study).

4.3. Sex-specific differences in 30-day outcomes

Despite sex-specific differences in the prognostic performance of risk stratification markers and models, in the present study, 30-day outcomes did not differ between males and females (Table S1 of the Supplementary material) and were not influenced by the patients' sex. This finding is in accordance with previous cohort studies reporting no differences in short- and long-term mortality in male and female PE patients [13,14,42], while studies using data from nationwide databases observed a higher short-term mortality rate in female PE patients [11,18].

Under-use of invasive procedures in female patients with CAD and ACS and of systemic thrombolysis in female patients with ischemic stroke is associated with poorer outcome [4,8,10,17]. In patients with PE, systemic thrombolysis reduces PE-related and all-cause mortality, especially in haemodynamic unstable patients [43]. Consistently, in the present study, the risk for an adverse outcome of patients classified as high- and intermediate-high-risk by the 2014 ESC guidelines algorithm was reduced by the use of reperfusion therapy in both sexes. Of note, the all-cause mortality rate remained substantial high in haemodynamic unstable patients despite reperfusion therapy (56.3% in males and 53.6% in females) indicating inclusion and analysis of a critical ill patient subgroup. Thus, and given the observational study design, conclusions on the under-use of reperfusion strategies as indicated by Stein and Matta [44] cannot be made.

5. Limitations

In addition to some methodological issues described before, the present study has further limitations that deserve consideration: First, exact information on the race of study patients was not available. However, the vast majority of patients included were Caucasians. Thus, the present study findings might not be generalizable to other populations that have significant racial/ethnic diversity. Second, since only patients with confirmed diagnosis of PE able to provide written informed consent for participation in the study were included, patients with more severe disease (e.g. sudden cardiac death due to PE) might be underrepresented in the present analysis.

6. Conclusion

In this prospective single-centre cohort study, rates of 30-day adverse outcomes did not differ between male and female patients despite sex-specific differences in the prognostic performance of risk stratification markers and models. Since no relevant sex-specific differences with regard to symptoms and initial presentation were observed, patients' sex may not require special consideration in the clinical judgment of initial symptoms at presentation for acute PE.

Key messages

- Data regarding sex-specific differences in pulmonary embolism (PE) are limited and inconsistent.
- The present prospective cohort study investigated sex-specific differences in 569 PE patients.
- Risk stratification was improved by the use of sex-specific biomarker cut-off values in male.
- No relevant sex-specific differences with regard to symptoms and acute prognosis were observed.

Author contributions

K.K. and M.L. planned the study. K.K., M.L., L.R. and A.G-A. performed the analyses. K.K. and M.L. drafted the manuscript. All authors contributed to the interpretation of the results and revision of the paper, and read and approved the final manuscript.

Acknowledgements

We thank Valerie Seeber (Center for Thrombosis and Hemostasis, University Medical Center Mainz, Germany) and Isabell Hoffmann (Institute of Medical Biostatistics, Epidemiology and Informatics (IMBEI), Mainz, Germany) for statistical assistance.

Sources of funding

This study was supported by the German Federal Ministry of Education and Research (BMBF 01EO1003 and BMBF 01EO1503). The authors are responsible for the contents of this publication.

Conflict of interest statement

None of the authors reports a relationship with industry and other relevant entities – financial or otherwise – that might pose a conflict of interest in connection with the submitted article. The following authors report financial activities outside the submitted work:

Lukas Hobohm reports having received lecture honoraria from MSD.
Gerd Hasenfuß reports having received consultancy and lecture honoraria from AstraZeneca, Corvia, Impulse Dynamics, Novartis, Servier, Berlin Chemie and Vifor Pharma; and editor honoraria from Springer International Publishing AG.
Stavros Konstantinides reports having received consultancy and lecture honoraria from Bayer, Boehringer Ingelheim, Daiichi-Sankyo, MSD and Pfizer – Bristol-Myers Squibb; and institutional grants from Actelion, Bayer, Boehringer Ingelheim, Daiichi-Sankyo and Pfizer – Bristol-Myers Squibb.
Mareike Lankeit reports having received consultancy and lecture honoraria from Actelion, Bayer, Daiichi-Sankyo, MSD and Pfizer – Bristol-Myers Squibb.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.thromres.2019.04.020.

References

[1] G. Montalescot, U. Sechtem, S. Achenbach, F. Andreotti, C. Arden, A. Budaj, R. Bugiardini, F. Crea, T. Cuisset, C. Di Mario, J.R. Ferreira, B.J. Gersh, A.K. Gitt, J.S. Hulot, N. Marx, L.H. Opie, M. Pfisterer, E. Prescott, F. Ruschitzka, M. Sabate, R. Senior, D.P. Taggart, E.E. van der Wall, C.J. Vrints, J.L. Zamorano, H. Baumgartner, J.J. Bax, H. Bueno, V. Dean, C. Deaton, C. Erol, R. Fagard, R. Ferrari, D. Hasdai, A.W. Hoes, P. Kirchhof, J. Knuuti, P. Kolh, P. Lancellotti, A. Linhart, P. Nihoyannopoulos, M.F. Piepoli, P. Ponikowski, P.A. Sirnes, J.L. Tamargo, M. Tendera, A. Torbicki, W. Wijns, S. Windecker, M. Valgimigli, M.J. Claeys, N. Donner-Banzhoff, H. Frank, C. Funck-Brentano, O. Gaemperli, J.R. Gonzalez-Juanatey, M. Hamilos, S. Husted, S.K. James, K. Kervinen, S.D. Kristensen, A.P. Maggioni, A.R. Pries, F. Romeo, L. Ryden, M.L. Simoons, P.G. Steg, A. Timmis, A. Yildirir, 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology, Eur. Heart J. 34 (38) (2013) 2949–3003.
[2] M. Schmidt, J.B. Jacobsen, T.L. Lash, H.E. Botker, H.T. Sorensen, 25 year trends in first time hospitalisation for acute myocardial infarction, subsequent short and long term mortality, and the prognostic impact of sex and comorbidity: a Danish nationwide cohort study, BMJ 344 (2012) e356.

[3] P. Appelros, B. Stegmayr, A. Terent, Sex differences in stroke epidemiology: a systematic review, Stroke 40 (4) (2009) 1082–1090.
[4] C. Milcent, B. Dormont, I. Durand-Zaleski, P.G. Steg, Gender differences in hospital mortality and use of percutaneous coronary intervention in acute myocardial infarction: microsimulation analysis of the 1999 nationwide French hospitals database, Circulation 115 (7) (2007) 833–839.
[5] A.H. Maas, Y.T. van der Schouw, V. Regitz-Zagrosek, E. Swahn, Y.E. Appelman, G. Pasterkamp, H. Ten Cate, P.M. Nilsson, M.V. Huisman, H.C. Stam, K. Eizema, M. Stramba-Badiale, Red alert for women's heart: the urgent need for more research and knowledge on cardiovascular disease in women: proceedings of the workshop held in Brussels on gender differences in cardiovascular disease, 29 September 2010, Eur. Heart J. 32 (11) (2011) 1362–1368.
[6] L. Mosca, E. Barrett-Connor, N.K. Wenger, Sex/gender differences in cardiovascular disease prevention: what a difference a decade makes, Circulation 124 (19) (2011) 2145–2154.
[7] M.F. Piepoli, A.W. Hoes, S. Agewall, C. Albus, C. Brotons, A.L. Catapano, M.T. Cooney, U. Corra, B. Cosyns, C. Deaton, I. Graham, M.S. Hall, F.D.R. Hobbs, M.L. Lochen, H. Lollgen, P. Marques-Vidal, J. Perk, E. Prescott, J. Redon, D.J. Richter, N. Sattar, Y. Smulders, M. Tiberi, H.B. van der Worp, I. van Dis, W.M.M. Verschuren, S. Binno, E.S.C.S.D. Group, 2016 European Guidelines on cardiovascular disease prevention in clinical practice: the Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR), Eur. Heart J. 37 (29) (2016) 2315–2381.
[8] L.J. Shaw, R. Bugiardini, C.N. Merz, Women and ischemic heart disease: evolving knowledge, J. Am. Coll. Cardiol. 54 (17) (2009) 1561–1575.
[9] I. Kirchberger, M. Heier, B. Kuch, R. Wende, C. Meisinger, Sex differences in patient-reported symptoms associated with myocardial infarction (from the population-based MONICA/KORA Myocardial Infarction Registry), Am. J. Cardiol. 107 (11) (2011) 1585–1589.
[10] M.J. Reeves, C.D. Bushnell, G. Howard, J.W. Gargano, P.W. Duncan, G. Lynch, A. Khatiwoda, L. Lisabeth, Sex differences in stroke: epidemiology, clinical presentation, medical care, and outcomes, Lancet Neurol. 7 (10) (2008) 915–926.
[11] S. Agarwal, D. Clark 3rd, K. Sud, W.A. Jaber, L. Cho, V. Menon, Gender disparities in outcomes and resource utilization for acute pulmonary embolism hospitalizations in the United States, Am. J. Cardiol. 116 (8) (2015) 1270–1276.
[12] K.B. McHugh, L. Visani, M. DeRosa, A. Covezzoli, E. Rossi, S.Z. Goldhaber, Gender comparisons in pulmonary embolism (results from the International Cooperative Pulmonary Embolism Registry [ICOPER]), Am. J. Cardiol. 89 (5) (2002) 616–619.
[13] A. Blanco-Molina, I. Enea, T. Gadelha, A. Tufano, A. Bura-Riviere, P. Di Micco, H. Bounameaux, J. Gonzalez, J. Villalta, M. Monreal, R. Investigators, Sex differences in patients receiving anticoagulant therapy for venous thromboembolism, Medicine (Baltimore) 93 (17) (2014) 309–317.
[14] A. Geibel, M. Olschewski, M. Zehender, M. Wilsch, K. Odening, F. Heinrich, W. Kasper, S. Konstantinides, Possible gender-related differences in the risk-to-benefit ratio of thrombolysis for acute submassive pulmonary embolism, Am. J. Cardiol. 99 (1) (2007) 103–107.
[15] D. Barrios, R. Morillo, I. Guerassimova, E. Barbero, H. Escobar-Morreale, A.T. Cohen, C. Becattini, V. Tapson, R. Yusen, D. Jimenez, Sex differences in the characteristics and short-term prognosis of patients presenting with acute symptomatic pulmonary embolism, PLoS One 12 (11) (2017) e0187648.
[16] H. Robert-Ebadi, G. Le Gal, M. Carrier, F. Couturaud, A. Perrier, H. Bounameaux, M. Righini, Differences in clinical presentation of pulmonary embolism in women and men, J. Thromb. Haemost. 8 (4) (2010) 693–698.
[17] X. Zheng, R.P. Dreyer, S. Hu, E.S. Spatz, F.A. Masoudi, J.A. Spertus, K. Nasir, X. Li, J. Li, S. Wang, H.M. Krumholz, L. Jiang, Age-specific gender differences in early mortality following ST-segment elevation myocardial infarction in China, Heart 101 (5) (2015) 349–355.
[18] T.P. Shiraev, A. Omari, R.L. Rushworth, Trends in pulmonary embolism morbidity and mortality in Australia, Thromb. Res. 132 (1) (2013) 19–25.
[19] K. Hellenkamp, J. Schwung, H. Rossmann, A. Kaeberich, R. Wachter, G. Hasenfuss, S. Konstantinides, M. Lankeit, Risk stratification of normotensive pulmonary embolism: prognostic impact of copeptin, Eur. Respir. J. 46 (6) (2015) 1701–1710.
[20] S.V. Konstantinides, A. Torbicki, G. Agnelli, N. Danchin, D. Fitzmaurice, N. Galie, J.S. Gibbs, M.V. Huisman, M. Humbert, N. Kucher, I. Lang, M. Lankeit, J. Lekakis, C. Maack, E. Mayer, N. Meneveau, A. Perrier, P. Pruszczyk, L.H. Rasmussen, T.H. Schindler, P. Svitil, A. Vonk Noordegraaf, J.L. Zamorano, M. Zompatori, D. Task Force for the, C. Management of Acute Pulmonary Embolism of the European Society of, 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism, Eur. Heart J. 35 (43) (2014) 3033–3069 (3069a-3069k).
[21] C. Bova, O. Sanchez, P. Prandoni, M. Lankeit, S. Konstantinides, S. Vanni, D. Jimenez, Identification of intermediate-risk patients with acute symptomatic pulmonary embolism, Eur. Respir. J. 44 (3) (2014) 694–703.
[22] L. Hobohm, K. Hellenkamp, G. Hasenfuss, T. Munzel, S. Konstantinides, M. Lankeit, Comparison of risk assessment strategies for not-high-risk pulmonary embolism, Eur. Respir. J. 47 (4) (2016) 1170–1178.
[23] S. Schulman, C. Kearon, S. Subcommittee on Control of Anticoagulation of the, T. Standardization Committee of the International Society on, Haemostasis, Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients, J. Thromb. Haemost. 3 (4) (2005) 692–694.
[24] E.F. Schisterman, S.R. Cole, R.W. Platt, Overadjustment bias and unnecessary adjustment in epidemiologic studies, Epidemiology 20 (4) (2009) 488–495.
[25] L. Richiardi, F. Barone-Adesi, F. Merletti, N. Pearce, Using directed acyclic graphs to consider adjustment for socioeconomic status in occupational cancer studies, J. Epidemiol. Community Health 62 (7) (2008) e14.
[26] V.P. Harjola, A. Mebazaa, J. Celutkiene, D. Bettex, H. Bueno, O. Chioncel, M.G. Crespo-Leiro, V. Falk, G. Filippatos, S. Gibbs, A. Leite-Moreira, J. Lassus, J. Masip, C. Mueller, W. Mullens, R. Naeije, A.V. Nordegraaf, J. Parissis, J.P. Riley, A. Ristic, G. Rosano, A. Rudiger, F. Ruschitzka, P. Seferovic, B. Sztrymf, A. Vieillard-Baron, M.B. Yilmaz, S. Konstantinides, Contemporary management of acute right ventricular failure: a statement from the Heart Failure Association and the Working Group on Pulmonary Circulation and Right Ventricular Function of the European Society of Cardiology, Eur. J. Heart Fail. 18 (3) (2016) 226–241.
[27] J. Textor, J. Hardt, S. Knuppel, DAGitty: a graphical tool for analyzing causal diagrams, Epidemiology 22 (5) (2011) 745.
[28] G. Meyer, E. Vicaut, T. Danays, G. Agnelli, C. Becattini, J. Beyer-Westendorf, E. Bluhmki, H. Bouvaist, B. Brenner, F. Couturaud, C. Dellas, K. Empen, A. Franca, N. Galie, A. Geibel, S.Z. Goldhaber, D. Jimenez, M. Kozak, C. Kupatt, N. Kucher, I.M. Lang, M. Lankeit, N. Meneveau, G. Pacouret, M. Palazzini, A. Petris, P. Pruszczyk, M. Rugolotto, A. Salvi, S. Schellong, M. Sebbane, B. Sobkowicz, B.S. Stefanovic, H. Thiele, A. Torbicki, F. Verschuren, S.V. Konstantinides, P. Investigators, Fibrinolysis for patients with intermediate-risk pulmonary embolism, N. Engl. J. Med. 370 (15) (2014) 1402–1411.
[29] K.M. Eggers, B. Lindahl, Impact of sex on cardiac troponin concentrations-a critical appraisal, Clin. Chem. 63 (9) (2017) 1457–1464.
[30] S.R. Motiwala, A. Sarma, J.L. Januzzi, M.L. O'Donoghue, Biomarkers in ACS and heart failure: should men and women be interpreted differently? Clin. Chem. 60 (1) (2014) 35–43.
[31] C.S. Lam, S. Cheng, K. Choong, M.G. Larson, J.M. Murabito, C. Newton-Cheh, S. Bhasin, E.L. McCabe, K.K. Miller, M.M. Redfield, R.S. Vasan, A.D. Coviello, T.J. Wang, Influence of sex and hormone status on circulating natriuretic peptides, J. Am. Coll. Cardiol. 58 (6) (2011) 618–626.
[32] S. Meyer, P. van der Meer, V.M. van Deursen, T. Jaarsma, D.J. van Veldhuisen, M.H. van der Wal, H.L. Hillege, A.A. Voors, Neurohormonal and clinical sex differences in heart failure, Eur. Heart J. 34 (32) (2013) 2538–2547.
[33] P. Ponikowski, A.A. Voors, S.D. Anker, H. Bueno, J.G. Cleland, A.J. Coats, V. Falk, J.R. Gonzalez-Juanatey, V.P. Harjola, E.A. Jankowska, M. Jessup, C. Linde, P. Nihoyannopoulos, J.T. Parissis, B. Pieske, J.P. Riley, G.M. Rosano, L.M. Ruilope, F. Ruschitzka, F.H. Rutten, P. van der Meer, M. Authors/Task Force, 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) developed with the special contribution of the Heart Failure Association (HFA) of the ESC, Eur. Heart J. 37 (27) (2016) 2129–2200.
[34] S. Kou, L. Caballero, R. Dulgheru, D. Voilliot, C. De Sousa, G. Kacharava, G.D. Athanassopoulos, D. Barone, M. Baroni, N. Cardim, J.J. Gomez De Diego, A. Hagendorff, C. Henri, K. Hristova, T. Lopez, J. Magne, G. De La Morena, B.A. Popescu, M. Penicka, T. Ozyigit, J.D. Rodrigo Carbonero, A. Salustri, N. Van De Veire, R.S. Von Bardeleben, D. Vinereanu, J.U. Voigt, J.L. Zamorano, E. Donal, R.M. Lang, L.P. Badano, P. Lancellotti, Echocardiographic reference ranges for normal cardiac chamber size: results from the NORRE study, Eur. Heart J. Cardiovasc. Imaging 15 (6) (2014) 680–690.
[35] U. D'Oronzio, O. Senn, P. Biaggi, C. Gruner, R. Jenni, F.C. Tanner, M. Greutmann, Right heart assessment by echocardiography: gender and body size matters, J. Am. Soc. Echocardiogr. 25 (12) (2012) 1251–1258.
[36] S.M. Kawut, J.A. Lima, R.G. Barr, H. Chahal, A. Jain, H. Tandri, A. Praestgaard, E. Bagiella, J.R. Kizer, W.C. Johnson, R.A. Kronmal, D.A. Bluemke, Sex and race differences in right ventricular structure and function: the multi-ethnic study of atherosclerosis-right ventricle study, Circulation 123 (22) (2011) 2542–2551.
[37] C.E. Ventetuolo, P. Ouyang, D.A. Bluemke, H. Tandri, R.G. Barr, E. Bagiella, A.R. Cappola, M.R. Bristow, C. Johnson, R.A. Kronmal, J.R. Kizer, J.A. Lima, S.M. Kawut, Sex hormones are associated with right ventricular structure and function: the MESA-right ventricle study, Am. J. Respir. Crit. Care Med. 183 (5) (2011) 659–667.
[38] T. Lahm, R.M. Tuder, I. Petrache, Progress in solving the sex hormone paradox in pulmonary hypertension, Am. J. Physiol. Lung Cell. Mol. Physiol. 307 (1) (2014) L7–26.
[39] C.E. Ventetuolo, N. Mitra, F. Wan, A. Manichaikul, R.G. Barr, C. Johnson, D.A. Bluemke, J.A. Lima, H. Tandri, P. Ouyang, S.M. Kawut, Oestradiol metabolism and androgen receptor genotypes are associated with right ventricular function, Eur. Respir. J. 47 (2) (2016) 553–563.
[40] W. Jacobs, M.C. van de Veerdonk, P. Trip, F. de Man, M.W. Heymans, J.T. Marcus, S.M. Kawut, H.J. Bogaard, A. Boonstra, A. Vonk Noordegraaf, The right ventricle explains sex differences in survival in idiopathic pulmonary arterial hypertension, Chest 145 (6) (2014) 1230–1236.
[41] A.J. Swift, D. Capener, C. Hammerton, S.M. Thomas, C. Elliot, R. Condliffe, J.M. Wild, D.G. Kiely, Right ventricular sex differences in patients with idiopathic pulmonary arterial hypertension characterised by magnetic resonance imaging: pair-matched case controlled study, PLoS One 10 (5) (2015) e0127415.
[42] S. Mansour, G. Alotaibi, C. Wu, K. Alsaleh, M.S. McMurtry, Sex disparities in hospitalization and mortality rates for venous thromboembolism, J. Thromb. Thrombolysis 44 (2) (2017) 197–202.
[43] C. Marti, G. John, S. Konstantinides, C. Combescure, O. Sanchez, M. Lankeit, G. Meyer, A. Perrier, Systemic thrombolytic therapy for acute pulmonary embolism: a systematic review and meta-analysis, Eur. Heart J. 36 (10) (2015) 605–614.
[44] P.D. Stein, F. Matta, Thrombolytic therapy in unstable patients with acute pulmonary embolism: saves lives but underused, Am. J. Med. 125 (5) (2012) 465–470.