Pulmonary artery to aorta ratio and risk of all-cause mortality in the general population: the Rotterdam Study

ABSTRACT

Background: The pulmonary artery to aorta ratio (PA:A)>1 is a proxy of pulmonary hypertension. It is unknown whether this measure carries prognostic information in the general population and in individuals with COPD.

Methods: Between 2003-2006, 2,197 participants from the population-based Rotterdam Study (mean±SD age 69.7±6.7 years, 51.3% women), underwent cardiac CT scan with PA:A quantification, defined as the ratio between the pulmonary artery and aorta diameters. COPD was diagnosed based on spirometry or clinical presentation and obstructive lung function measured by a treating physician. Cox regression was used to investigate the risk of mortality.

Results: We observed no association between 1-SD increase of PA:A and mortality in the general population. Larger PA:A was associated with an increased risk of mortality in individuals with COPD, particularly in moderate to severe COPD (HR=1.36, 95%CI=1.03-1.79). We demonstrated that the risk of mortality in COPD was driven by severe COPD and that this risk increased with decreasing diffusing capacity.

Conclusion: Larger PA:A is not associated with mortality in an older general population, but is an independent determinant of mortality in moderate to severe COPD. Measuring PA:A in CT scans obtained for other indications may yield important prognostic information in individuals with COPD.

Key words: mortality, COPD, pulmonary hypertension, epidemiology, computed tomography, population-based

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a common cause of death worldwide. In Europe, approximately 18 per 100,000 individuals die due to COPD each year [1]. The high mortality-rate of COPD stresses the need for early identification of COPD patients at high risk of adverse outcomes, in order to guide and improve patient management.

One of the complications in the advanced stages of COPD, which is known to contribute to mortality, is pulmonary hypertension (PH). Currently, the gold standard for diagnosis of PH is an invasive pressure measurement in the pulmonary artery [2]. Alternatively, PH may be assessed using echocardiography. However, this method has proven to be often inconclusive in the advanced stages of COPD, particularly in those persons with emphysema or obesity, due to air and adipose tissue obscuring echocardiographic examination [3, 4].

An alternative, and more novel suggested approach to assess PH, is to measure the ratio between the diameter of the pulmonary artery and that of the aorta (PA:A) using computed tomography. Given its correlation with the mean pulmonary artery pressure, a PA:A larger than 1 is suggested to be a reliable indicator of PH, and may thus directly indicate a worse clinical outcome [5]. Indeed, in patients with COPD, PA:A ratios larger than 1 are related to an increased rate of severe exacerbations requiring hospitalization [6]. However, other than its relationship with exacerbations, the implications of larger PA:A remain unclear. In addition, large-scale population-based data on the utility of PA:A with regard to clinical end points in the general population and specifically in individuals with COPD are lacking. Such data may contribute to the development of targeted additional therapeutic or preventive strategies for exacerbations and mortality in COPD patients.

Therefore, in a population-based setting, we investigated the association between larger PA:A and mortality, with a specific focus on individuals with COPD.

METHODS

Setting

The present study was embedded within the Rotterdam Study, an ongoing prospective population-based cohort study aimed at investigating the occurrence and risk factors of chronic diseases in the general population. The objective and methods of the Rotterdam Study have been published in great detail previously [7]. Briefly, the Rotterdam Study includes 3 cohorts encompassing 14,926 participants aged ≥ 45 years, living in Ommoord, a well-defined suburb of the city of Rotterdam, the Netherlands. Baseline data were collected between 1990 and 1993 (n = 7,983), between 2000 and 2003 (n = 3,011), and between 2006 and 2008 (n = 3,932); thereafter, examinations

have been conducted every 4 to 5 years in all cohorts. Between 2003 and 2006, all participants that visited the research center were invited to undergo multi-detector computed tomography (MDCT)-study as part of a large project on vascular calcification (n = 2,524). The cardiac scan that was performed in this protocol was used for the assessment of PA:A. Therefore, this visit represents the baseline for the current analyses. Figure 1 shows the study flow of participants that were included in this study.

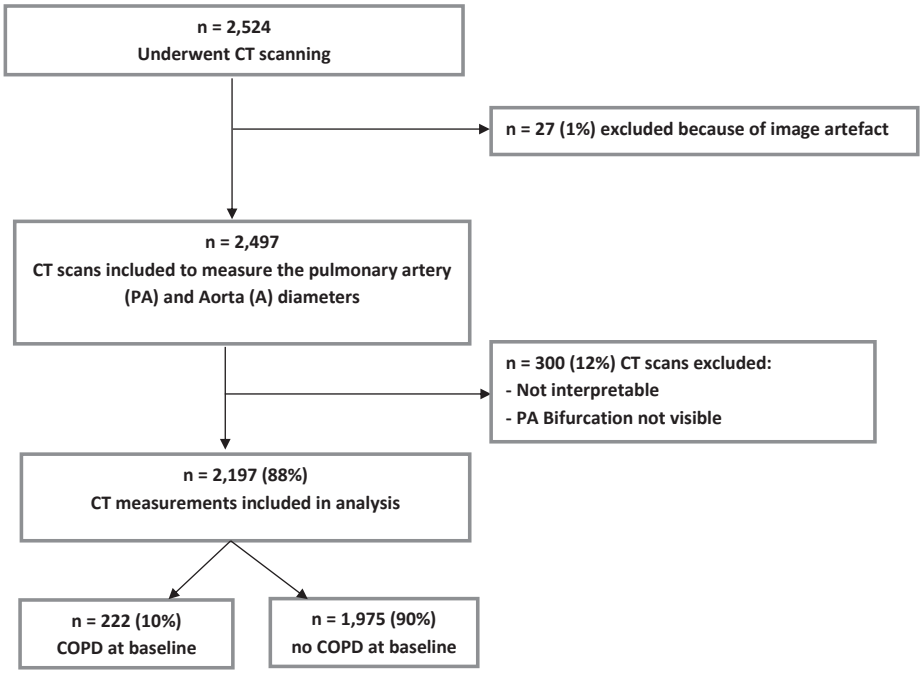

Figure 1 Flow chart of participants in the study.
COPD: chronic obstructive pulmonary disease, CT: computed tomography, n= number of individuals.

Follow-up for mortality

Information on mortality of study participants was obtained from the local municipality in Rotterdam, and additionally validated with data from medical records kept by the general practitioner's, as described in detail previously [8]. Mortality data was complete until March 2015.

Assessment of PA:A

Non-contrast CT-scanning was performed with a 16-slice (n = 785) or 64-slice (n = 1,739) MDCT scanner (Somatom Sensation 16/64, Siemens, Forchheim, Germany). An ECG-gated cardiac imaging protocol was used to visualize the heart and the proximal

part of the great vessels, including the pulmonary artery and the aorta. Detailed information on imaging parameters of this scan has been published previously [9]. Two reviewers measured the PA:A under the supervision of two radiologists. The diameters of the main pulmonary artery and of the ascending aorta were measured at the level of the bifurcation of the pulmonary artery on the same CT-image (Figure 2), according to the procedure as described by Wells et al. [6]. The reviewers were blinded to the clinical status of the participants. Additionally, no information on the status of the lungs could be obtained from the cardiac scans, given that the field-of-view was optimized for visualisation of the heart and the great vessels. The kappa values for the inter-observer and intra-observer agreement for the diameters of the pulmonary artery and the aorta (n=100) were 0.91 and 0.98, and 0.94 and 0.99, respectively.

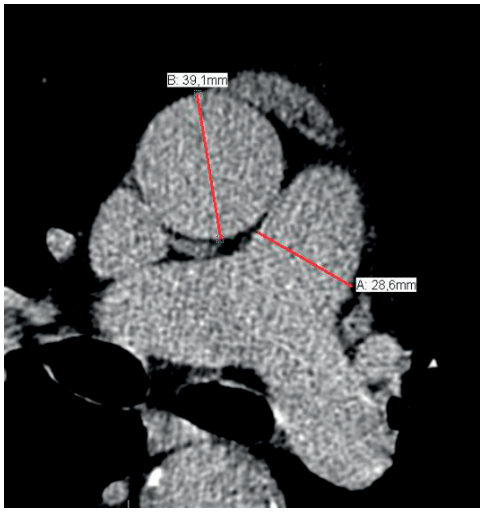

Figure 2 Measurement of the diameter of the pulmonary artery and aorta.
This figure shows an example of the measurement of the diameter of the pulmonary artery (A: 28.6mm) and of the ascending aorta (B: 39.1mm) at the level of bifurcation of the pulmonary artery on the same slice of a non-contrast CT examination.

COPD diagnosis

The diagnosis of COPD was based on an obstructive pre-bronchodilator spirometry (FEV1/FVC < 0.70) according to the Global initiative for Obstructive Lung Disease (GOLD) guidelines [10] Spirometry was performed according to the ATS/ERS guidelines by qualified medical personnel using a portable spirometer (SpiroPro; Erich Jaeger GmbH; Hoechberg, Germany). Spirometry results which did not meet ATS/ERS criteria for acceptability were classified as not interpretable.

In absence of an interpretable study-acquired spirometry, the medical records kept by the general practitioners, including outpatient clinic reports and discharge

letters from medical specialists, were reviewed for all patients who used medication for obstructive lung disease for at least six months (Anatomical Therapeutic Chemical Classification codes: R03) [11]. COPD cases were then defined as having an obstructive lung function measured by their treating physician and clinical events [11].

COPD severity groups were based on GOLD classifications, where $FEV_1/FVC<70$ and $FEV_1 > 80\%$ predicted was defined as mild COPD, while moderate to severe COPD was defined as $FEV_1/FVC<70$ and $FEV_1 < 80\%$ predicted [10].

Covariables

Information on relevant covariables was obtained using interview, physical examinations, and blood sampling [7]. Smoking status was assessed by interview and persons were categorized as current smoker, former smoker or never smoker. Body mass index (BMI) was calculated by dividing body weight in kilograms by height in meters squared. Obesity was defined as a BMI ≥ 30 kg/m^2. Diabetes mellitus was defined as a fasting glucose level of ≥ 7.0 mmol/L or ≥ 11.1 mmol/L if fasting samples were unavailable, or use of blood glucose-lowering medication [12]. Hypertension was defined as a systolic blood pressure ≥ 140 mmHg, a diastolic blood pressure ≥ 90 mmHg, or the use of blood pressure-lowering drugs. As a measure of left ventricular systolic function we used left ventricular fractional shortening at the endocardium in the parasternal long axis window (defined as left ventricular end-diastolic dimension minus left ventricular end-systolic dimension divided by the left ventricular end-diastolic dimension). For this, resting transthoracic echocardiograms were acquired by trained echo-cardiographers according to a standardized protocol. [13]. Clinical diagnosis of heart failure was based on active follow-up using the medical records of the participants [8]. Of note, the routinely collected echocardiography data in the Rotterdam Study was considered in the heart failure adjudication process. Pulmonary artery systolic pressure (PASP) was estimated from echocardiographic measurements using the recommendations by the ASE/EAE/CSE as the sum of the estimated right atrial pressure (based on inferior vena cava diameter and forced respiratory collapse) and the pressure gradient over the tricuspid valve. The pressure gradient was computed from the highest Doppler tricuspid regurgitation velocity gathered from several windows using the simplified Bernoulli equation ($4v^2$, where v is tricuspid regurgitation peak velocity in m/sec) [14]. PH was defined as having PASP > 40 mmHg. Finally, diffusing capacity of carbon monoxide per alveolar volume (DLCO/VA (mmol/min/kPa/L)) was measured by single breath technique and was corrected for haemoglobin values. PASP and DLCO were measured between 2009 and 2012.

Statistical analysis

We determined the association between PA:A (per 1-SD increase) and all-cause mortality in the general population, using Cox proportional-hazard models. For the Cox models we adjusted for covariates that were considered biologically relevant and also changed the point estimates of the univariate association with mortality by at least 10%. In the first model we adjusted for age and sex. In the second model we additionally adjusted for BMI, smoking, diabetes mellitus, left ventricular systolic function and COPD. In addition, we examined the relation between PA:A and mortality in the individuals with COPD using the same Cox proportional hazard models. Furthermore, analyses were also performed in mild and moderate to severe COPD. As a sensitivity analysis, we also analysed the data in moderate COPD and severe COPD separately. We explored non-linearity by using fractional polynomials and constructing quartiles of PA:A (Q1 ≤ 0.64, Q2 = 0.65-0.70, Q3 = 0.71-0.77 and Q4 > 0.77). The cut-offs for the PA:A quartiles were based on the study data. Finally, for the association between PA:A and all-cause mortality in individuals with COPD, we conducted a sensitivity analysis additionally adjusting for COPD severity as measured by FEV_1. We also tested the association between 1 SD increase in PA:A and PASP or PH in COPD and non-COPD, using univariate linear regression or logistic regression models. Finally, we analysed DLCO/VA data by testing whether the mean DLCO/VA was statistically significantly different between COPD and non-COPD using an independent sample t-test. Subsequently, we tested whether the risk of mortality per 1-SD increase of PA:A differs in individuals with and without COPD with different values of DLCO/VA. This was done by adding an interaction term to the second model. Missing data on covariables were imputed using the Expectation Maximization (EM) method. We used SPSS version 21 (IBM Corp, Armonk, NY, USA) for all analyses.

RESULTS

Figure 1 shows the study flow of the participants that were included in this study. The scanned population (n=2,524) was not different from the total RS population [15]. The baseline characteristics of the population with interpretable PA:A measurements (n=2,197) are presented in Table 1. The mean age was 69.7 (SD 6.7) years and 51.3% were women. The prevalence of COPD at the time of CT scanning was 10% (n=222). The 90th percentile of the PA:A in our population was 0.84. The maximum PA:A was 1.27, and only 17 out of 2,197 persons had a ratio of 1 or higher. Additional information about the diameter of the pulmonary artery, the aorta and the PA:A by disease status in the general population is presented in Table 2. During 17,751 person-years of follow-up (median: 8.8 years), 423 (19.3%) persons died [mortality rate 23.8 per 1,000 person-

Table 1 Baseline characteristics of the study population

	Total population n = 2,197		No COPD n = 1,975		COPD n = 222	
Age, years	69.7	(6.7)	69.5	(6.7)	71.2	(7.1)
Female	51.3%		52.3%		42.3%	
Ever smoker	68.5%		67.1%		81.1%	
Pack-years of smoking*	22.6	(21.5)	21.4	(21.1)	32.1	(21.6)
Body mass index, kg/m^2	27.9	(4.0)	27.9	(4.0)	27.2	(3.7)
Hypertension	73.9%		73.4%		78.4%	
Diabetes Mellitus	12.6%		11.8%		19.8%	
Heart failure	3.1%		2.5%		6.5%	
Left ventricular systolic function, %	40.0	(6.2)	40.2	(6.1)	38.1	(7.5)
DLCOc/VA, mmol/min/kPa/L†	1.5	(0.2)	1.5	(0.2)	1.3	(0.3)
PASP, mmHg†	26.0	(7.0)	25.7	(6.7)	29.2	(8.7)
FEV_1, % predicted	103.3	(19.8)	106.1	(17.7)	79.8	(21.0)
Pulmonary artery, mm	26.0	(3.7)	25.9	(3.6)	26.7	(4.1)
Aorta, mm	36.9	(3.9)	36.9	(3.9)	37.5	(3.7)
PA:A	0.71	(0.10)	0.71	(0.10)	0.72	(0.11)

DLCOc/VA: diffusing capacity of carbon monoxide per alveolar volume, corrected for haemoglobin, FEV_1: Forced expiratory volume in 1 second, PA:A: pulmonary artery to aorta ratio, PASP: Pulmonary artery systolic pressure.
Values are mean (standard deviation) for continuous variables or percentages for dichotomous variables.
Data represent original data without imputed values. In de total population missing values were present for smoking (2.2%), pack years of smoking (4.6%), body mass index (0.9%), hypertension (0.3%), diabetes mellitus (6.0%), heart failure (1.9%), left ventricular systolic function (3.4%), DLCOc/VA (40%), PASP (42%), FEV1, % pred (11.3%).
*Pack-years are presented for former and current smokers only.
† DLCOc/VA and PASP measures were performed between 2009 and 2012.

years (95% confidence interval (CI) 21.6-26.2)]. The mortality rate in individuals with prevalent COPD was 51 per 1,000 person-years (95% CI 40.6-63.1). The main causes of death in the COPD group were cardiovascular events (41.8%), bronchial carcinoma (16.4%), other malignancies (13.4%) and pulmonary complications from COPD (6.0%).

PA:A and the risk of all-cause mortality

We explored the association between PA:A and the risk of mortality by a linear model. The log relative hazard between PA:A ratio and mortality in individuals with or without COPD are plotted in Figure 3. P-value for non-linearity in those groups was 0.76 and 0.10, respectively.

Table 2 Mean values of A (aorta), PA (pulmonay artery) and PA:A, stratified by the presence of absence of risk factors (n = 2,197)

		N	Mean (SD)		
			A(mm)	PA (mm)	PA:A
Gender					
	Men	1,070	38.1 (3.9)	26.4 (3.8)	0.70 (0.1)
	Women	1,127	35.8 (3.5)	25.6 (3.6)	0.72 (0.1)
Obesity					
	Yes	562	37.6 (4.0)	27.3 (3.8)	0.73 (0.1)
	No	1,635	36.7 (3.8)	25.6 (3.6)	0.70 (0.1)
Smoking					
	Current	381	37.1 (4.0)	26.0 (3.9)	0.71 (0.1)
	Former	1,124	37.2 (3.8)	26.1 (3.6)	0.71 (0.1)
	Never	644	36.4 (3.9)	25.8 (3.7)	0.71 (0.1)
COPD					
	Prevalent*	222	37.5 (3.7)	26.7 (4.1)	0.72 (0.1)
	Mild	98	37.7 (3.8)	26.1 (4.2)	0.70 (0.1)
	Moderate to severe	107	37.5 (3.6)	27.3 (4.1)	0.73 (0.1)
	Absent	1,975	36.9 (3.9)	26.0 (3.6)	0.71 (0.1)
Hypertension					
	Present	1,624	37.2 (3.9)	26.2 (3.7)	0.71 (0.1)
	Absent	566	36.1 (3.7)	25.5 (3.6)	0.71 (0.1)
DM					
	Present	277	36.7 (3.9)	26.7 (3.7)	0.73 (0.1)
	Absent	1,786	37.0 (3.9)	25.9 (3.7)	0.71 (0.1)
Heart failure					
	Present	69	38.1 (4.7)	28.9 (4.9)	0.77 (0.1)
	Absent	2,128	36.9 (3.8)	25.9 (3.6)	0.71 (0.1)

COPD: chronic obstructive pulmonary disease; DM: diabetes mellitus; PA:A: pulmonary artery to aorta ratio; SD: standard deviation.
Data are presented in mean (SD).
* The total number of COPD cases in the sub-groups do not add up to the total number of all COPD n=222, since COPD diagnosis in 15 out of 222 was confirmed after reviewing medical charts and specialist letters, but severity could not be adjudicated.

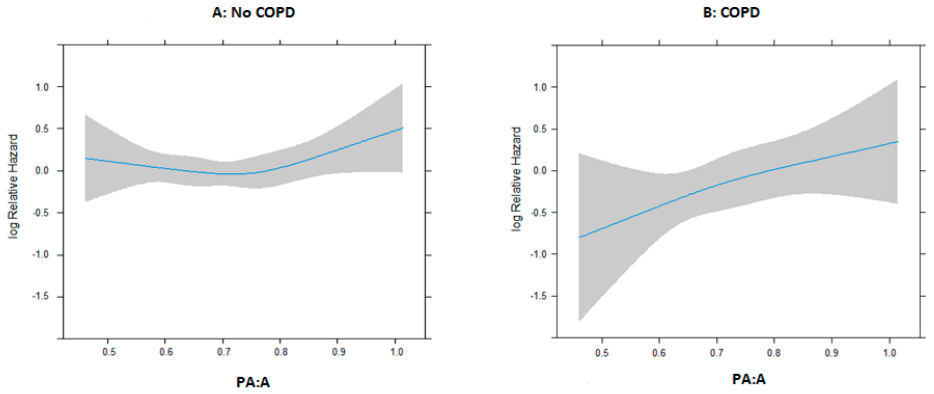

Figure 3 Log relative hazard plotted against PA:A values
Estimates for the log relative hazard in A: individuals without COPD, and B: individuals with COPD were derived using 3 restricted cubic splines, with a P for non-linearity for A = 0.10 and for B = 0.76.

A modest, but statistically non-significant association was found between PA:A with the risk of mortality in the general population (adjusted hazard ratio (HR) per 1-SD increase in PA:A: 1.08 (95%CI:0.98-1.18)) and in individuals without COPD (HR 1.04 (95% CI 0.93-1.15)) (Table 3). In persons with prevalent COPD, a larger PA:A was statistically significantly associated with a higher risk of mortality (HR per 1-SD increase in PA:A: 1.21 (95% CI 1.01-1.46)). The risk of mortality was higher in individuals with moderate to severe COPD compared to individuals with mild COPD (HR per 1-SD

Table 3 The association between PA:A and all-cause mortality.

			Hazard Ratio per 1-SD increase in PA:A (95% CI)			
			Model1*		Model2†	
Total population‡	N=2,197		1.09	(1.00-1.20)	1.08	(0.98-1.18)
No COPD	n=1,975		1.05	(0.95-1.17)	1.04	(0.93-1.15)
All COPD¶	n=222		1.17	(0.98-1.40)	**1.21**	**(1.01-1.46)**
Mild		n=98	1.08	(0.77-1.52)	1.09	(0.76-1.56)
Moderate-severe		n=109	1.22	(0.94-1.58)	**1.36**	**(1.03-1.79)**

CI: Confidence interval; COPD: chronic obstructive pulmonary disease; PA:A: pulmonary artery to aorta ratio; SD: standard deviation.
*Model1: adjusted for age and sex.
†Model2: adjusted for age, sex, body mass index, smoking, diabetes mellitus and left ventricular systolic function.
‡ Additionally adjusted for COPD in Model2.
¶ The total number of COPD cases in the sub-groups do not add up to the total number of all COPD n=222, since COPD diagnosis in 15 out of 222 was confirmed after reviewing medical charts and specialist letters, but severity could not be adjudicated.

Table 4 Risk of mortality per quartile increase of PA:A*

		Hazard Ratio (95% CI)								
PA:A quartiles		Total population†		No COPD		All COPD‡		Mild COPD		Moderate to severe COPD	
		N=2,197		N=1,975		N=222		N=98		N=109	
Q1	(≤ 0.64)	Reference		Reference		Reference		Reference		Reference	
Q2	(0.65-0.70)	0.97	(0.74-1.28)	0.93	(0.68-1.26)	1.30	(0.65-2.60)	0.46	(0.11-1.98)	1.73	(0.64-4.70)
Q3	(0.71-0.77)	1.03	(0.78-1.35)	0.93	(0.68-1.26)	1.64	(0.81-3.33)	0.91	(0.28-2.94)	1.95	(0.69-5.46)
Q4	(> 0.77)	1.19	(0.91-1.55)	1.06	(0.79-1.43)	**2.03**	**(1.06-3.88)**	1.33	(0.41-4.31)	**2.78**	**(1.07-7.23)**
P-for-trend:		0.20		0.74		**0.02**		0.62		**0.03**	

CI: confidence interval; COPD: chronic obstructive pulmonary disease; PA:A: pulmonary artery to aorta ratio.
*Adjusted for age, sex, BMI, smoking, diabetes mellitus, and left ventricular systolic function.
† Additionally adjusted for COPD.
‡ The total number of COPD cases in the sub-groups do not add up to the total number of all COPD n=222, since COPD diagnosis in 15 out of 222 was confirmed after reviewing medical charts and specialist letters, but severity could not be adjudicated.

increase in PA:A: 1.36 (95% CI 1.03-1.79) versus (HR per 1-SD increase in PA:A: 1.09 (0.76-1.56), respectively) (Table 3). Sensitivity analysis showed that the association in individuals with moderate-to-severe COPD is mainly driven by individuals with severe COPD with a HR per 1-SD increase in PA:A: 3.01 (95% CI 1.26-7.17). The association in prevalent COPD did not materially change after adjustment for COPD severity by FEV1 (L) (HR per 1-SD increase in PA:A: 1.22 (95% CI 1.02-1.48)).

Table 4 represents the results of the association of PA:A quartiles with the risk of mortality in all groups. We observed a statistically significant trend over the quartiles in persons with COPD (P-for-trend = 0.02), particularly in those with moderate to severe COPD (P-for-trend =0.03). The corresponding Kaplan-Meier curve in individuals with COPD is presented in Figure 4.

Individuals with moderate to severe COPD in the highest PA:A quartile, had an almost 3-fold increased risk of mortality (HR 2.78 (95% CI 1.07-7.23)) compared to the persons in the lowest quartile of the PA:A.

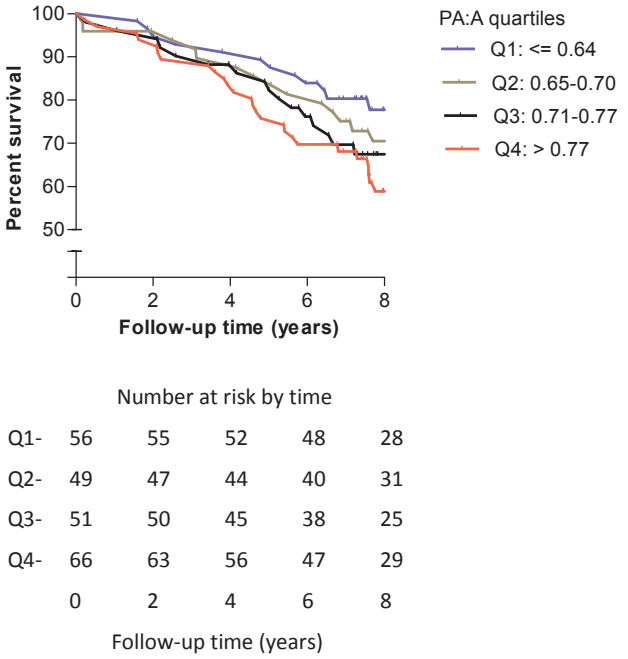

Figure 4 Kaplan-Meier survival curve of individuals with COPD (n=222) by quartiles of PA:A.

PA:A and Pulmonary Artery Systolic Pressure (PASP)

A statistically significant association was found between PA:A ratio and PASP, as estimated by echocardiography, both in non-COPD and COPD subjects. We observed that 1-SD increase of PA:A was associated with 0.61 (SE 0.23) mmHg increase in PASP in individuals without COPD (95% CI 0.16-1.06), and with 2.33 (SE 0.77) mmHg increase in PASP in individuals with COPD (95% CI 0.80-3.85).

PA:A and Pulmonary Hypertension

The association between PA:A and pulmonary hypertension (defined as PASP >40 mmHg) were in line with that between PA:A and PASP. PA:A was significantly associated with pulmonary hypertension in both groups. The risk of PH in COPD per 1-SD increase in PA:A was OR: 2.59 (95% CI 1.07-6.32), whereas the risk of PH in non-COPD per 1-SD increase of PA:A was OR: 1.86 (1.17-2.94).

PA:A and diffusing capacity of the lung

The mean diffusing capacity of the lung per alveolar volume (DLCO/VA) in COPD subjects was statistically significantly different from the mean DLCO/VA in non-COPD subjects (1.32 versus 1.49 mmol/min/kPa/L, P-value < 0.001).

We tested for interaction between PA:A and DLCO/VA in the Cox model to investigate whether the relationship between PA:A and mortality is different with different values of DLCO/VA, separately for individuals with COPD and without. In individuals with COPD, we observed a statistically significant interaction between PA:A and DLCO/VA (P-for-interaction= 0.01), while no interaction was observed in individuals without COPD (P-for-interaction= 0.14).

DISCUSSION

In this large population-based study, we observed no association between PA:A and mortality in an older general population. However, persons with COPD with higher PA:A ratios were at increased risk of mortality, particularly those with moderate to severe COPD.

To our knowledge, this is the first population-based study to investigate the association between the PA:A and mortality in the general population and in individuals with COPD, specifically. Although several studies have been performed with PA:A as proxy of PH, the variation in the use of PA:A is considerable, and the results have been inconsistent. There have been several studies that used the PA:A as a binary variable with 0.9 or 1 as cut-off for normal (< 0.9 or 1) versus abnormal (> 0.9 or 1). For example, Ersoy and colleagues [2] found no association between PA:A >1 and the risk of mortality risk in a group of 106 patients admitted to the intensive care because of an acute COPD exacerbation. In contrast, another retrospective study conducted in 1,326 patients with suspected coronary artery disease undergoing CT angiography [16], demonstrated that PA:A >0.9 was associated with an increased risk of mortality. In addition Shin et al [17], demonstrated that PA:A >1 was significantly associated with an increased risk of mortality in very severe COPD patients undergoing evaluation for lung transplantation.

An important consideration with regard to these studies cut-offs, is that these results are based on findings in selected groups such as COPD patients with severe exacerbations requiring hospitalization [2], patients with suspected ischemic heath disease [16] or patients with very severe COPD undergoing evaluation for lung transplantation [17]. In contrast to these clinic-based populations, our cohort represents the general population, including smokers and non-smokers, with and without various comorbidities. Importantly, only 17 out of 2,197 persons in our cohort had a PA:A >1. Therefore, instead of dichotomizing the PA:A on a value of 1, we analysed PA:A as a continuous measure and explored potential linear associations with risk of mortality.

We observed that PA:A was not associated with mortality in the general population and in individuals without COPD. When analysing quartiles of PA:A, we found that

only persons with moderate to severe COPD who were in the highest quartile of PA:A were at statistically significantly increased risk of mortality, and that this association was driven by individuals with severe COPD. Pulmonary artery pressure and thereby PH is known to increase in advanced COPD due to combined effects of hypoxaemia and loss of capillaries in severe emphysema [18, 19]. In this study, we demonstrated that the magnitude of increase in pulmonary arterial systolic pressures (PASP) per 1 SD increase in PA:A is much larger in persons with COPD compared to those without COPD. We also demonstrated that the risk of mortality per 1 SD increase of PA:A was most pronounced in subjects with reduced diffusing capacity of the lung, suggesting that the identified association in individuals with COPD may be driven by emphysema. Further longitudinal studies are necessary to address potential causality.

Our finding suggests that the PA:A is an independent determinant of mortality in individuals with moderate to severe COPD. Especially, given that non-contrast CT scans of the chest are often performed in current clinical practice for various indications (e.g. screening for lung cancer in subjects at risk), our finding might help in identifying persons with COPD who are at increased risk of death and thereby provide guidance for more targeted therapeutic decision making.

The strength of our study is the population-based setting and the long follow-up period, the prospective, standardized data collection for COPD and mortality, and the standardized, CT-based assessment of PA:A, with excellent inter- and intra-observer correlation coefficients.

Our study also has some limitations. First, in individuals with COPD, analyses of cause-specific mortality as endpoint were not performed due the limited number of cases per cause. Second, the observed risks of mortality may be underestimated due to healthy volunteer effect [20]. Third, although we have carefully considered the potential confounders of the association between PA:A and mortality, it is possible that part of the observed associations might be explained by residual confounding. Finally, the Rotterdam Study comprises a homogenous sample of white participants, which may limit the generalizability of our results to other ethnic groups.

CONCLUSION

Larger PA:A is an independent indicator for mortality in individuals with COPD, particularly in moderate to severe COPD. Measuring PA:A in scans, including those obtained for other indications, may yield important prognostic information usable to tailor patient management in clinical practice.

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