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

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An increased pulmonary artery to aorta ratio is an independent determinant of mortality in moderate-to-severe COPD http://ow.ly/A12C30a0H9f

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ABSTRACT A pulmonary artery to aorta ratio (PA:A) >1 is a proxy of pulmonary hypertension. It is not known whether this measure carries prognostic information in the general population and in individuals with chronic obstructive pulmonary disease (COPD).

Between 2003 and 2006, 2197 participants from the population-based Rotterdam Study (mean±SD age 69.7±6.7 years; 51.3% female), underwent cardiac computed tomography (CT) scanning with PA:A quantification, defined as the ratio between the diameters of the pulmonary artery and the aorta. 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.

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 (hazard ratio 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.

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.

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Introduction

Chronic obstructive pulmonary disease (COPD) is a common cause of death worldwide. In Europe, ~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. Currently, the gold standard for diagnosis of pulmonary hypertension is an invasive pressure measurement in the pulmonary artery [2]. Alternatively, pulmonary hypertension may be assessed using echocardiography. However, this method has proven to be 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, more novel approach to assess pulmonary hypertension is to measure the ratio between the diameter of the pulmonary artery and that of the aorta (PA:A) using computed tomography (CT). Given its correlation with the mean pulmonary artery pressure, a PA:A >1 is suggested to be a reliable indicator of pulmonary hypertension, and may thus directly indicate a worse clinical outcome [5]. Indeed, in patients with COPD, PA:A >1 is related to an increased rate of severe exacerbations requiring hospitalisation [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 objectives and methods of the Rotterdam Study have been published in great detail previously [7]. Briefly, the Rotterdam Study includes three 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=7983), between 2000 and 2003 (n=3011) and between 2006 and 2008 (n=3932); thereafter, examinations have been conducted every 4–5 years in all cohorts. Between 2003 and 2006, all participants who visited the research centre were invited to undergo multidetector computed tomography (MDCT) study as part of a large project on vascular calcification (n=2524). 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 flow of participants included in this study.

The Rotterdam Study has been approved by the medical ethics committee of the Erasmus MC (Rotterdam) and by the Ministry of Health, Welfare and Sport of the Netherlands, implementing the "Wet Bevolkingsonderzoek: ERGO (Population Screening Act: Rotterdam Study)". All participants provided written informed consent to participate in the study and for information to be obtained from their treating physicians.

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 general practitioners, as described in detail previously [8]. Mortality data was complete up to March 2015.

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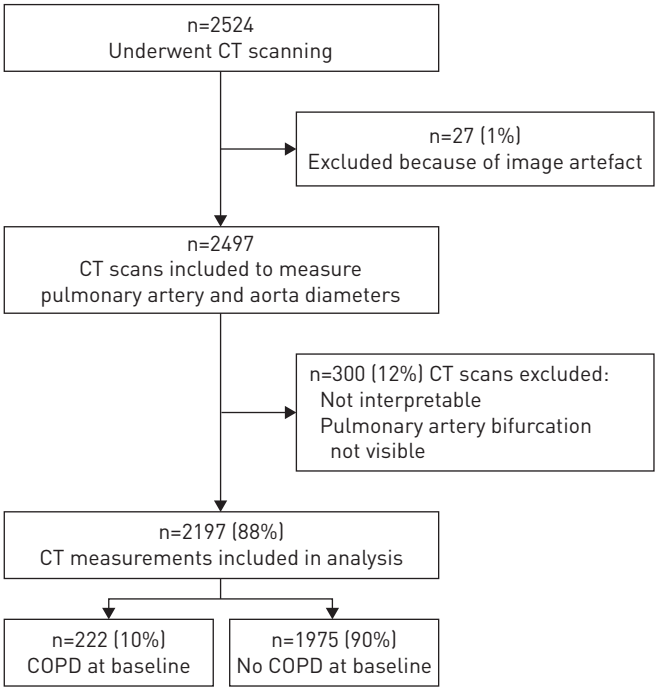


FIGURE 1 Flow chart of study participants. CT: computed tomography; COPD: chronic obstructive pulmonary disease.

Assessment of PA:A

Noncontrast CT scanning was performed using a 16-slice (n=785) or 64-slice (n=1739) MDCT scanner (Somatom Sensation 16/64; Siemens, Forchheim, Germany). An ECG-gated cardiac imaging protocol was used to visualise the heart and the proximal part of the great vessels, including the pulmonary artery and the aorta. Detailed information on the 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 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 optimised for visualisation of the heart and the great vessels. The κ-values for the inter- and intraobserver 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.

COPD diagnosis

The diagnosis of COPD was based on an obstructive prebronchodilator spirometry (forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) <0.70) according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines [10]. Spirometry was performed according to the American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines by qualified medical personnel using a portable spirometer (SpiroPro; Erich Jaeger; Hoechberg, Germany). Spirometry results that did not meet ATS/ERS criteria for acceptability were classified as not interpretable.

In the absence of an interpretable study-acquired spirometry, the medical records kept by 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 ⩾6 months (Anatomical Therapeutic Chemical classification code R03) [11]. COPD cases were 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 and moderate-to-severe COPD was defined as FEV_1/FVC <70 and FEV_1 <80% pred [10].

Covariables

Information on relevant covariables was obtained using interviews, physical examinations and blood sampling [7]. Smoking status was assessed by interview and subjects were categorised as current smoker, former smoker or never-smoker. Body mass index (BMI) was calculated by dividing body weight in

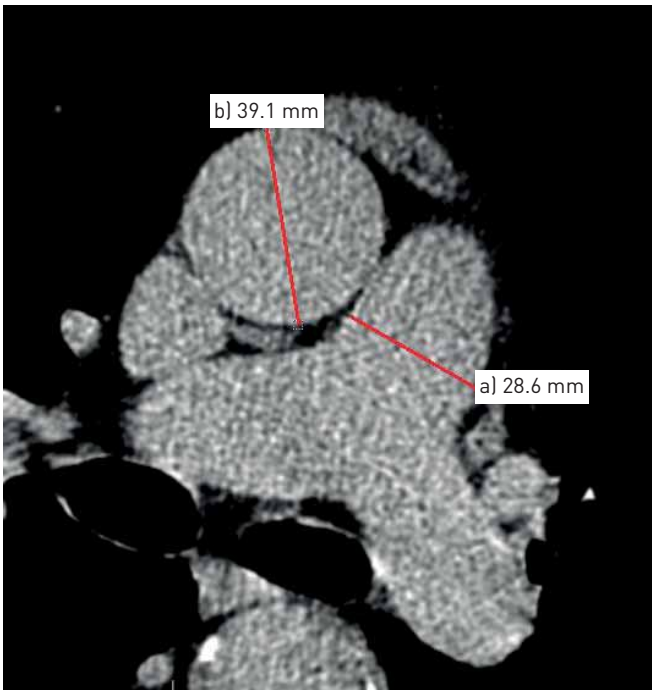


FIGURE 2 Example measurement of the diameter of a) the pulmonary artery (28.6 mm) and b) the ascending aorta (39.1 mm) at the level of bifurcation of the pulmonary artery on the same slice of a noncontrast computed tomography examination.

kilograms by height in metres squared. Obesity was defined as a BMI $\geqslant$30 kg·m^{-2}. Diabetes mellitus was defined as a fasting glucose level of $\geqslant$7.0 mmol·L^{-1} or $\geqslant$11.1 mmol·L^{-1} if fasting samples were unavailable, or use of blood glucose lowering medication [12]. Hypertension was defined as a systolic blood pressure $\geqslant$140 mmHg, a diastolic blood pressure $\geqslant$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 echocardiographers according to a standardised 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 American Society of Echocardiography/European Association of Echocardiography/Canadian Society of Echocardiography 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·s^{-1}) [14]. Pulmonary hypertension was defined as PASP >40 mmHg. Finally, diffusing capacity of the lung for carbon monoxide (D_{LCO}) per alveolar volume (V_A) (mmol·min^{-1}·kPa^{-1}·L^{-1}) was measured using the single-breath technique and was corrected for haemoglobin values. PASP and D_{LCO} 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 changed the point estimates of the univariate association with mortality by $\geqslant$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 relationship between PA:A and mortality in the individuals with COPD using the same Cox proportional hazard models. Furthermore, analyses were performed in mild and moderate-to-severe COPD. As a sensitivity analysis, we analysed the data in moderate COPD and severe COPD separately. We explored nonlinearity by using fractional polynomials and constructing quartiles of PA:A (Q1 $\leqslant$0.64, Q2

TABLE 1 Baseline characteristics of the study population

	Total population	No COPD	COPD
Subjects n	2197	1975	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
Smoking pack-years[#]	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
D_{LCOc}/V_A mmol·min^{-1}·kPa^{-1}·L^{-1}[¶]	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 diameter mm	26.0±3.7	25.9±3.6	26.7±4.1
Aorta diameter 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

Data are presented as mean±SD or %, unless otherwise stated. Entries represent original data without imputed values. In the total population, values were missing for smoking (2.2%), smoking pack-years (4.6%), body mass index (0.9%), hypertension (0.3%), diabetes mellitus (6.0%), heart failure (1.9%), left ventricular systolic function (3.4%), diffusing capacity of the lung for carbon monoxide, corrected for haemoglobin (D_{LCOc})/alveolar volume (V_A) (40.4%), pulmonary artery systolic pressure (PASP) (58.1%) and forced expiratory volume in 1 s (FEV_1) % predicted (11.3%). COPD: chronic obstructive pulmonary disease; PA:A: pulmonary artery to aorta ratio. [#]: pack-years are presented for former and current smokers only; [¶]: measurements were performed between 2009 and 2012.

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. In addition, we tested the association between a 1-SD increase in PA:A and PASP or pulmonary hypertension in COPD and non-COPD, using univariate linear regression or logistic regression models. Finally, we analysed D_{LCO}/V_A data by testing whether the mean D_{LCO}/V_A 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 D_{LCO}/V_A. This was done by adding an interaction term to the second model. Missing data on covariables were imputed using the expectation–maximisation method. We used SPSS (version 21; IBM, Armonk, NY, USA) for all analyses.

Results

Figure 1 shows the flow of the participants that were included in this study. The scanned population (n=2524) was not different from the total Rotterdam Study population [15]. The baseline characteristics of the population with interpretable PA:A measurements (n=2197) are presented in table 1. The mean±SD age was 69.7±6.7 years and 51.3% of the subjects were female. 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 2197 subjects had a ratio ⩾1. 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%) subjects died (mortality rate 23.8 per 1000 person-years, 95% CI 21.6–26.2 per 1000 person-years). The mortality rate in individuals with prevalent COPD was 51 per 1000 person-years (95% CI 40.6–63.1 per 1000 person-years). 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 using a linear model. The log relative hazards between PA:A ratio and mortality in individuals with or without COPD are plotted in figure 3. p-value for nonlinearity in those groups was 0.76 and 0.10, respectively.

TABLE 2 Mean values of diameters of aorta (A), pulmonary artery (PA) and PA:A, stratified by the presence or absence of risk factors

	Subjects	Diameter mm		PA:A
		A	PA	
Sex				
Male	1070	38.1±3.9	26.4±3.8	0.70±0.1
Female	1127	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	1635	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	1124	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	1975	36.9±3.9	26.0±3.6	0.71±0.1
Hypertension				
Present	1624	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
Diabetes mellitus				
Present	277	36.7±3.9	26.7±3.7	0.73±0.1
Absent	1786	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	2128	36.9±3.8	25.9±3.6	0.71±0.1

Data are presented as n or mean±SD. COPD: chronic obstructive pulmonary disease. [#]: the total number of COPD cases in the subgroups do not add up to the total number of COPD cases, since COPD diagnosis in 15 out of 222 subjects was confirmed after reviewing medical charts and specialist letters, but severity could not be determined.

A modest, but statistically nonsignificant 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 increase in PA:A 1.36, 95% CI 1.03–1.79

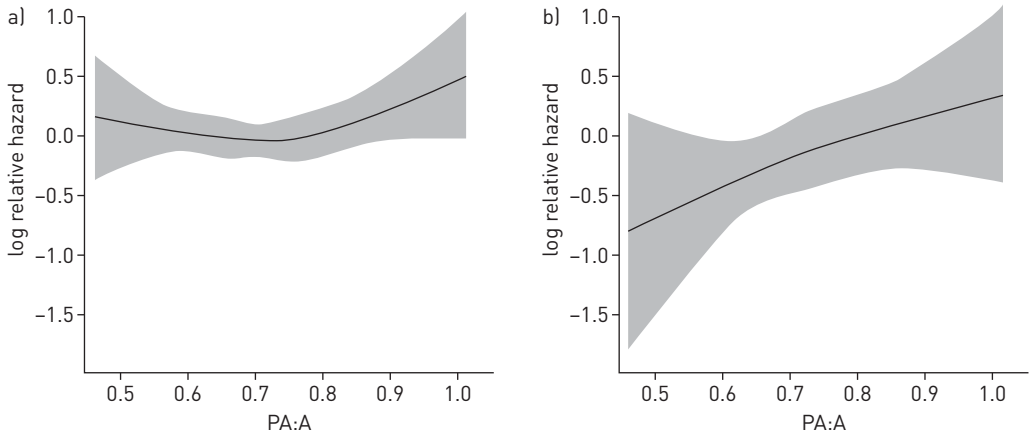


FIGURE 3 Estimates for the log relative hazard plotted against pulmonary artery (PA) to aorta (A) ratio values in a) individuals without chronic obstructive pulmonary disease (COPD) and b) individuals with COPD were derived using three restricted cubic splines, with p for nonlinearity 0.10 and 0.76 for (a) and (b), respectively.

TABLE 3 The association between pulmonary artery (PA) to aorta (A) ratio and all-cause mortality

	Subjects	Model 1[#]	Model 2[¶]
Total population[+]	2197	1.09 (1.00–1.20)	1.08 (0.98–1.18)
No COPD	1975	1.05 (0.95–1.17)	1.04 (0.93–1.15)
All COPD[§]	222	1.17 (0.98–1.40)	**1.21 (1.01–1.46)**
Mild	98	1.08 (0.77–1.52)	1.09 (0.76–1.56)
Moderate-to-severe	109	1.22 (0.94–1.58)	**1.36 (1.03–1.79)**

Data are presented as n or hazard ratio per 1-SD increase in PA:A (95% CI). Bold type represents statistical significance. COPD: chronic obstructive pulmonary disease. [#]: adjusted for age and sex; [¶]: adjusted for age, sex, body mass index, smoking, diabetes mellitus and left ventricular systolic function; [+]: model 2 additionally adjusted for COPD; [§]: the total number of COPD cases in the subgroups do not add up to the total number of all COPD cases, since COPD diagnosis in 15 out of 222 subjects was confirmed after reviewing medical charts and specialist letters, but severity could not be determined.

versus HR per 1-SD increase in PA:A: 1.09, 95% CI 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 change materially after adjustment for COPD severity by FEV_1 (litres) (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 three-fold increased risk of mortality (HR 2.78, 95% CI 1.07–7.23) compared to the subjects in the lowest PA:A quartile.

PA:A and PASP

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

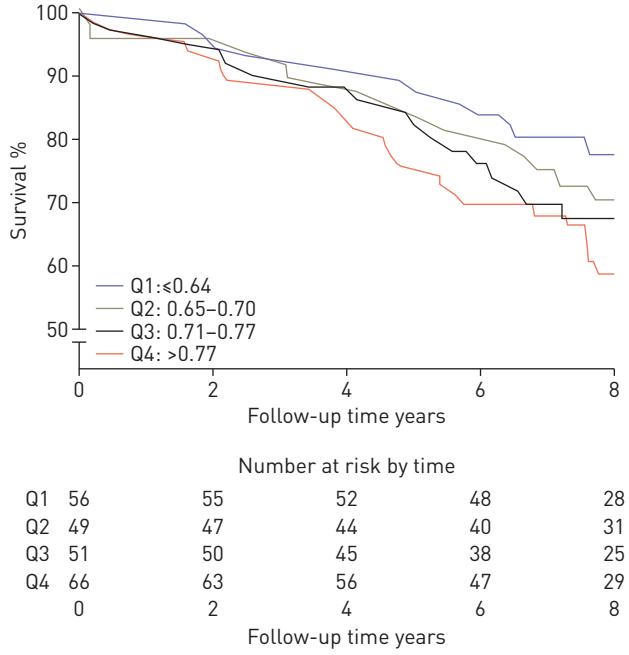
PA:A and pulmonary hypertension

The association between PA:A and pulmonary hypertension (defined as PASP >40 mmHg) were in line with the results between PA:A and PASP. PA:A was significantly associated with pulmonary hypertension in both groups. The risk of pulmonary hypertension in COPD per 1-SD increase in PA:A was OR 2.59

TABLE 4 Risk of mortality per quartile increase of pulmonary artery (PA) to aorta (A) ratio[#]

	Total population[¶]	No COPD	All COPD[+]	Mild COPD	Moderate-to-severe COPD
Subjects	2197	1975	222	98	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**

Data are presented as n or hazard ratio per quartile increase in PA:A (95% CI), unless otherwise stated. Bold type represents statistical significance. COPD: chronic obstructive pulmonary disease. [#]: adjusted for age, sex, body mass index, smoking, diabetes mellitus and left ventricular systolic function; [¶]: additionally adjusted for COPD; [+]: the total number of COPD cases in the subgroups do not add up to the total number of all COPD cases, since COPD diagnosis in 15 out of 222 subjects was confirmed after reviewing medical charts and specialist letters, but severity could not be determined.



Number at risk by time

Q1	56	55	52	48	28
Q2	49	47	44	40	31
Q3	51	50	45	38	25
Q4	66	63	56	47	29
	0	2	4	6	8

Follow-up time years

FIGURE 4 Kaplan–Meier survival curve of individuals with chronic obstructive pulmonary disease by quartiles (Q) of pulmonary artery to aorta ratio. n=222.

(95% CI 1.07–6.32), whereas the risk of pulmonary hypertension in non-COPD per 1-SD increase of PA:A was 1.86 (1.17–2.94).

PA:A and diffusing capacity of the lung

The mean *D*LCO/*V*A in COPD subjects was statistically significantly different from the mean *D*LCO/*V*A in non-COPD subjects (1.32 *versus* 1.49 mmol·min^{-1}·kPa^{-1}·L^{-1}, p<0.001).

We tested for interaction between PA:A and *D*LCO/*V*A in the Cox model to investigate whether the relationship between PA:A and mortality is different with different values of *D*LCO/*V*A, separately for individuals with COPD and without. In individuals with COPD, we observed a statistically significant interaction between PA:A and *D*LCO/*V*A (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, individuals 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 pulmonary hypertension, 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 a cut-off for normal (⩽0.9 or 1) *versus* abnormal (⩾0.9 or 1). For example, ORTAÇ ERSOY *et al.* [2] found no association between PA:A >1 and risk of mortality risk in a group of 106 patients admitted to intensive care because of an acute COPD exacerbation. In contrast, another retrospective study conducted in 1326 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 patients with very severe COPD who were undergoing evaluation for lung transplantation.

An important consideration with regard to the cut-offs in these studies is that these results are based on findings in selected groups, such as COPD patients with severe exacerbations requiring hospitalisation [2], patients with suspected ischaemic heart 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 nonsmokers, with and without various comorbidities. Importantly, only 17 out of 2197 individuals in our cohort had a PA:A ⩾1. Therefore,

instead of dichotomising 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 subjects with moderate-to-severe COPD who were in the highest quartile of PA:A were at a statistically significantly increased risk of mortality, and that this association was driven by individuals with severe COPD. Pulmonary artery pressure, and thereby pulmonary hypertension, 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 PASP per 1-SD increase in PA:A is much greater in individuals with COPD compared to those without COPD. In addition, we 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. Given that noncontrast 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, standardised data collection for COPD and mortality and the standardised, CT-based assessment of PA:A, with excellent inter- and intraobserver correlation coefficients.

Our study has some limitations. First, in individuals with COPD, analyses of cause-specific mortality as end-point were not performed due the limited number of cases per cause. Second, the observed risks of mortality may be underestimated due to a 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 generalisability 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 to tailor patient management in clinical practice.

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