A. 研究目的

慢性閉塞性肺疾患（COPD）は予防と治療が可能な疾患であることが明らかとなった。

本邦で2000年に行われた大規模疫学調査“Nippon COPD Epidemiology (NICE) study”では、全国の35施設で、日本の人口構成に一致するように無作為に抽出された40歳以上の一般住民を対象として、健康調査記入と呼吸機能検査が施行された。10.9%（男性16.4%、女性5.0%）に呼吸機能検査による気流閉塞(1秒率<70%)が認められ、問診票から喘息と推定される被験者を除き、日本人のCOPD有病率は8.6% (男性13.1%, 女性4.4%)と推測された。さらに、NICE studyにおいて気流閉塞を認めた被験者の中でCOPDと診断されていた割合は9.4%にすぎず、多くのCOPD患者が診断されずにいる実態が明らかになった。

COPDの診断には呼吸機能検査が不可欠であるが、国民全員にスパイロメトリーを実施することは困難なため、簡易問診票によりスクリーニングを行い、COPDが疑われる症例に呼吸機能検査をすすめることが有用と考えられる。

本邦では、IPAG-COPD質問票（International Primary Care Airways Group ハンドブック）や11-Qなどの質問票の検討がなされてきたが、質問項目が多く、複雑であり普及するには問題も多い。

IPAG質問票は一般プライマリケア医のための診断の指針として作成されたハンドブックであり、合計点17点以上でCOPDが疑われる。本邦における日本語版IPAG-COPD質問票の有用性の検討では、年齢における配点（70歳以上10点）や、設定されたBMIのcut-off値（BMI<25.4, 5点）の影響から高齢者での特異度の低さが指摘されている。

近年開発されたCOPD-Population Screener (COPD-PS)は、簡単で非常に分かりやすい質問票で、米国での研究ではcut-off値が5点と設定され、簡便で有用なスクリーニングツールの候補と考えられる。しかし、医療機関受診者を対象とした米国のデータではバイアスがあり、日本語版COPD-PSを用いた場合の日本人cut-off値は全く不明であった。よって、本研究事業の一つとして、福岡県久山町住民を対象に「質問票COPD-PS日本語版における日本人cut-off値設定に関する臨床研究」を実施した。その結果、福岡県久山町住民2,357名（40～80歳）を対象とした日本語版COPD-PS質問票の解析ではcut-off値4点とすると感度67.1%、特異度72.9%、オッズ比5.49となり、気流閉塞者の鑑別に有用であった。米国での先行研究で設定されたcut-off値と日本人を対象としたcut-off値は異なるものであった。

さらに、海外で開発された質問票は日本人の文化や生活様式との相違もあるため、日本人を対象に新規のCOPDスクリーニング質問票を開発する必要がある。

B. 研究方法

鹿児島大学大学院医歯学総合研究科呼吸器内科学に本邦独自のCOPDスクリーニング質問票原案作成のため呼吸器専門医、一般臨床医、疫学専門家からなるワーキンググループを設置した。

新COPD質問票作成のための質問票原

案を概念領域 (CD: Conceptual domain)；咳嗽、喀痰、機能面、呼吸困難、身体活動性、心の問題、個人の特性の７項目に準じ、それぞれの項目ごとに複数の質問文を作成した。被験者登録施設の施設認定基準として、呼吸機能検査が可能であり、一秒率＜70%では気管支拡張薬投与後に再検査が可能であること、COPD 診断が可能であることを条件とし、登録施設を鹿児島厚生連健康管理センターおよび鹿児島大学病院とした。

本研究に関する臨床研究倫理審査申請書を作成し、鹿児島大学大学院医歯学総合研究科倫理審査委員会および鹿児島厚生連健康管理センターの疫学研究倫理審査委員会で了承を得た後に本研究を開始した。

40 歳以上 80 歳未満で鹿児島大学病院呼吸器内科および鹿児島厚生連健康管理センターを受診し本研究に同意の得られた被験者を対象とした。本研究への登録者はワーキンググループで作成した新 COPD スクリーニング質問票原案と既存の IPAG 質問票、SF-12v2 質問票に対する調査を行い、全例に呼吸機能検査を施行し、一秒率＜70%の場合は気管支拡張薬投与後に再検査を行った。信頼性の分析は無作為に登録症例の 20%以上で初回調査２週間後に質問票再調査を回収した。

統計解析はロジスティック回帰分析ステップワイズ法により COPD の予測因子となる質問項目を同定し、多変量解析により気流閉塞の予測因子となる最善の質問項目の組み合わせを決定し、点数化し独自の最終版 COPD スクリーニング質問票を作成する。

C. 研究結果

COPD スクリーニング質問票原案の開発のためのワーキンググループにより、７項目の概念定領域（咳嗽、喀痰、機能面、呼吸困難、身体活動性、心の問題、個人の特性）に基づき 19 項目 53 総質問数からなる新 COPD スクリーニング質問票原案を作成した（表１）。

本研究で開発する COPD スクリーニング質問票は一般住民を対象としており、鹿児島厚生連健康管理センターの健診受診者の登録を優先して開始した。登録期間（H26 年 4 月 22 日～H27 年 2 月 28 日）の対象者は 2,367 名であった。喘息治療中の 3 名を除外し 2,364 名を対象とした。気管支拡張薬吸入前の呼吸機能検査で $FEV_1/FVC<70\%$ を認めたが、気管支拡張薬吸入後の再検査が困難であった群（BDx 群；post-bronchodilator の 1 秒率が不明）26 名（1.1%）をさらに除外し、2,338 名を解析対象とした。AO 群（AO: airway obstruction）は 65 名 (2.7%), Non-AO 群は 2,273 名（96.2%）であり、$\%FEV_1$ に基づいた COPD 病期分類は I 期 29 名、II 期 29 名、III 期 6 名、IV 期 1 名であった（表２）。

解析対象（AO 群と Non-AO 群）の登録者背景は男女比で男性が多く偏りがみられた。両群比較において年齢、喫煙歴に明らかな有意差を認め、COPD 予測因子の項目と考えられた(表３)。一方、IPAG-COPD 質問票の一つである BMI は有意差を認めなかった。

表 1

COPD質問票

COPD の質問票作成にご協力いただきましてありがとうございます。
重複する項目がありますがよろしくお願いいたします。

名前＿＿＿＿＿＿＿＿＿＿　記入日　平成＿＿年＿＿月＿＿日

質問 1．この 1 年間に、咳が出ることがありましたか？
（一番よくあてはまるものに☑して下さい）

- ほとんど毎日 □
- 1 週間のうち 2～3 日くらい □
- 1 ヵ月のうち数日 □
- カゼをひいたときや、肺炎などにかかった時だけ □
- ほとんどない □

質問 2．以下のような状況で、咳がひどくなることがありますか？
（各項目について、"はい" か "いいえ" のうち、どちらかに☑して下さい）

	はい	いいえ
季節の変わり目	□	□
冬の寒い時期	□	□
朝起床時	□	□
クーラーの効いた部屋に入った時	□	□
台風が近づいた時	□	□
ほこりが多い時	□	□
桜島の灰が降った時	□	□
雨の日	□	□

質問 3．カゼをひいた後は、たいてい咳が 3 週間以上長引くことがありますか？

はい	いいえ
□	□

質問 4．この 1 年間に、痰が出ることがありましたか？
（一番よくあてはまるものに☑して下さい）

- ほとんど毎日 □
- 1 週間のうち 2～3 日くらい □
- 1 ヵ月のうち数日 □
- カゼをひいたときや、肺炎などにかかった時だけ □
- ほとんどない □

質問 5．以下の時に、痰が出やすいですか？
（各項目について、"はい" か "いいえ" のうち、どちらかに☑して下さい）

	はい	いいえ
朝起床時	□	□
鼻水が出ているとき	□	□

質問 6．ここ 1 年間で以下のような症状が 3 カ月以上出ることがありましたか？
（各項目について、"はい" か "いいえ" のうち、どちらかに☑して下さい）

	はい	いいえ
咳のみ	□	□
痰のみ	□	□
咳と痰	□	□

質問 7．平均して、1 日にどのくらいの量の痰が出ますか？
（一番よくあてはまるものに☑して下さい）

- まったく痰は出ません □
- 1 日に 15ml（約大さじ 1 杯）未満 □
- 1 日に 15ml（約大さじ 1 杯）以上 □

質問 8．カゼをひいていないのに、痰がからんで咳をすることがありますか？
（一番よくあてはまるものに☑して下さい）

いつも	ほとんどいつも	ときどき	まれに	ほとんどない
□	□	□	□	□

質問 9．この 1 年間で、次のような時に、息苦しさあるいは息切れを感じることがありましたか？（各項目について一番よくあてはまるものに☑して下さい）

	いつも	ほとんどいつも	ときどき	まれに	ほとんどない
じっとしている時	□	□	□	□	□
洗顔や着替えている時	□	□	□	□	□
室内を歩いている時	□	□	□	□	□
屋外の平地を歩いている時	□	□	□	□	□
軽い運動をしている時（坂を登る、階段を上がるなど）	□	□	□	□	□
比較的強い運動をしている時（重い荷物を運ぶ、走るなど）	□	□	□	□	□

質問10．次のような時に、同年代の人と比べて息切れしやすいほうですか？
（各項目について、"はい" か "いいえ" のうち、どちらかに☑して下さい）

	はい	いいえ
屋外で平地を歩いている時	□	□
軽い運動（坂を登る、階段を上がるなど）をする時	□	□
比較的強い運動（重い荷物を運ぶ、走るなど）をする時	□	□

質問11．ふだんの生活（仕事や家事など）は活動的ですか？　（1 つだけに☑して下さい）

とても活動的	活動的	あまり活動的でない	まったく活動的でない
□	□	□	□

質問12．この 1 年間で、ヒューヒューやゼーゼーを感じたことがありましたか？
（一番よくあてはまるものに☑して下さい）

- ほとんど毎日 □
- 1 週間のうち 2～3 日くらい □
- 1 ヵ月のうち数日 □
- カゼをひいたときや、肺炎などにかかった時だけ □
- ほとんどない □

質問13．次のような時に、この 1 年間で、ヒューヒューやゼーゼーを感じることがありましたか？（各項目について一番よくあてはまるものに☑して下さい）

	いつも	ほとんどいつも	ときどき	まれに	ほとんどない
夜中に、目が覚めた時	□	□	□	□	□
朝、起きた時	□	□	□	□	□
室内を歩いている時	□	□	□	□	□
屋外の平地を歩いている時	□	□	□	□	□
軽い運動をしている時（坂を登る、階段を上がるなど）	□	□	□	□	□
比較的強い運動をしている時（重い荷物を運ぶ、走るなど）	□	□	□	□	□

質問14．この 1 年間で、「あなたの日常生活が、呼吸器（肺）の症状（咳、痰、息切れなど）によってどのように影響されているか」についてうかがいます。
（各項目について、"はい" か "いいえ" のうち、どちらかに☑して下さい）

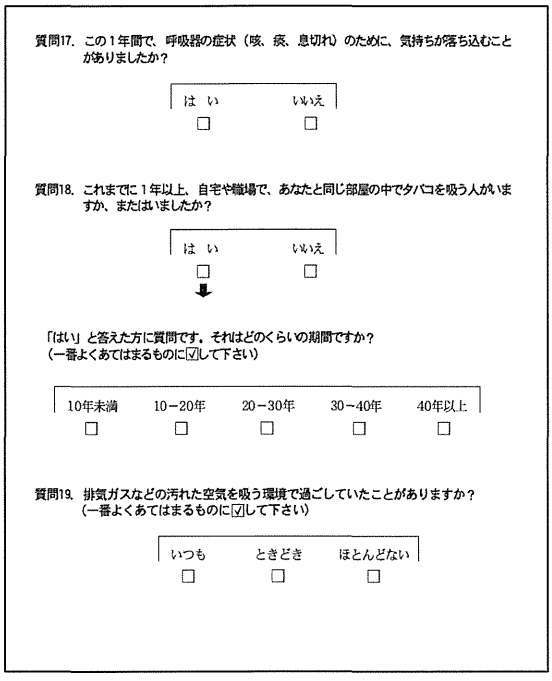
「呼吸器の症状（咳、痰、息切れ）が理由で」	はい	いいえ
目が覚めて眠れないことがある	□	□
同年代の人より歩くのが遅くなった	□	□
平地を歩いていても、立ち止まって休まなければならない	□	□
軽い運動（坂を登る、階段を上がるなど）がむずかしい	□	□
比較的強い運動（重い荷物を運ぶ、走るなど）がむずかしい	□	□

質問15．呼吸器（肺）の症状によって日常生活が制限されますか？

はい	いいえ
□	□

質問16．この 1 年間で、うまく呼吸ができずに、心配になったり、パニックになったりすることがありましたか？

はい	いいえ
□	□



質問17. この１年間で、呼吸器の症状（咳、痰、息切れ）のために、気持ちが落ち込むことがありましたか？

はい　□　　いいえ　□

質問18. これまでに１年以上、自宅や職場で、あなたと同じ部屋の中でタバコを吸う人がいますか、またはいましたか？

はい　□　　いいえ　□

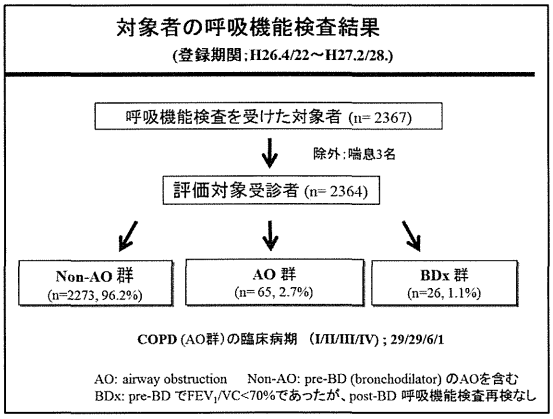
「はい」と答えた方に質問です．それはどのくらいの期間ですか？
（一番よくあてはまるものに☑して下さい）

10年未満　□　10－20年　□　20－30年　□　30－40年　□　40年以上　□

質問19. 排気ガスなどの汚れた空気を吸う環境で過ごしていたことがありますか？
（一番よくあてはまるものに☑して下さい）

いつも　□　ときどき　□　ほとんどない　□

表２



対象者の呼吸機能検査結果

(登録期間：H26.4/22～H27.2/28.)

呼吸機能検査を受けた対象者 (n= 2367)

除外：喘息3名

評価対象受診者 (n= 2364)

Non-AO 群 (n=2273, 96.2%)　AO 群 (n= 65, 2.7%)　BDx 群 (n=26, 1.1%)

COPD (AO群) の臨床病期 (I/II/III/IV) ; 29/29/6/1

AO: airway obstruction　Non-AO: pre-BD (bronchodilator) のAOを含む
BDx: pre-BD で$FEV_1/VC<70\%$であったが、post-BD 呼吸機能検査再検なし

表３

Variables		Non-AO (n=2273)	AO (n=65)	p value
Gender				
male/female		1667/606	63/2	
Age	mean ± SD	56.8 (±9.5)	63.1 (±9.5)	<0.001*
40-49		564 (25)	7 (11)	<0.001
50-59		871 (38)	15 (23)	
60-69		586 (26)	27 (42)	
70<		252 (11)	16 (25)	
Smoking status				
never/former/current		1036/793/444	8/34/23	<0.001
Pack year				
0-14		1415 (62)	13(20)	<0.001
15-24		319 (14)	8 (12)	
25-49		431 (19)	28 (43)	
50<		108 (8)	16 (25)	
BMI	mean ± SD	23.6 (±3.4)	23.5 (±3.1)	0.793*
<20		151 (7)	3 (5)	0.790
20-		340 (15)	9 (14)	
23-		728 (32)	21 (32)	
26-		759 (33)	25 (38)	
29-		294 (13)	7 (11)	

また、各質問項目の統計学検討では、COPDを予測する質問項目として、咳のみ痰のみでは有意差を認めなかったが、咳と痰を併せた質問項目で有意差を認めた（表４）。呼吸困難の項目では比較的強い運動をするときの息切れで感度が高くなる傾向があった（表５）。喘鳴に関する項目においても比較的強い運動において感度が高くなる傾向があった（表６）。

表４

Cough, Phlegm.（年齢と喫煙を補正）

Response item No (Q)	Odds ratio	95% CI	P value	Odds ratio (95% CI)
Q6この1年間で3ヶ月以上続いた症状				
咳のみ	1.9	0.8-4.3	0.140	
痰のみ	1.4	0.7-2.9	0.398	
咳と痰	2.9	1.4-5.9	**0.004**	
Q8 かぜをひいていないのに痰がからんで咳をするか				
いつも	2.6	0.3-21	**0.009**	
ほとんどいつも	2.7	0.9-7.7		**1.7 (1.0-3.0)**
ときどき	2.1	1.1-4.0		
まれに	1.5	0.8-2.9		**1 (ref)**
ほとんどない	1	ref		

表５

Dyspnea.（年齢と喫煙を補正）

No (Q)	Odds ratio	95% CI	P value	Odds ratio (95%CI)
Q9-4 屋外の平地を歩いている時に息苦しさや息切れを感じるか				
いつも	NA		**0.007**	
ほとんどいつも	NA			**3.6 (1.8-7.3)**
ときどき	2.1	0.5-9.4		
まれに	5.4	2.5-12		
ほとんどない	1	ref		**1 (ref)**
Q9-5 軽い運動をしている時に息苦しさや息切れを感じるか				
いつも	3.9	0.8-19	**0.003**	
ほとんどいつも	5.2	2.2-12		**4.0 (1.8-8.6)**
ときどき	1.2	0.5-2.5		
まれに	1.5	0.7-3.0		1 (ref)
ほとんどない	1	ref		
Q10 次の時に同年代の人と比べて息切れしやすいか（"いいえ"をreference group）				
平地を歩いている時	1.8	0.8-4.3	0.185	
軽い運動をしている時	1.9	1.1-3.3	**0.031**	
比較的強い運動をする時	1.9	1.1-3.2	**0.021**	

表 6

Wheezing, Functional Impact.（年齢と喫煙を補正）

Response item No (Q)	Odds ratio	95% CI	P value	Odds ratio (95% CI)
Q13-6 比較的強い運動をしている時、ヒューヒュー、ゼーゼー感じることがあったか				
いつも	2.9	0.4-24	<0.001	3.3 (2.0-5.6)
ほとんどいつも	4.3	1.5-12		
ときどき	3.1	1.5-6.4		
まれに	3.5	1.9-6.6		
ほとんどない	1	ref		1 (ref)
Q14 呼吸器の症状が理由で、次のようなことがあるか("いいえ"をreference group)				
目が覚めて眠れない	1.0	0.4-2.5	0.939	
同年代の人より歩きが遅い	1.8	0.8-4.0	0.124	
平地歩行時に、休まないといけない	4.2	1.6-11	0.003	
軽い運動が難しい	2.6	1.2-5.6	0.014	
比較的強い運動が難しい	2.3	1.3-3.9	0.004	

本研究結果に基づき、ワーキンググループで作成したCOPD質問票原案(draft)からCOPD予測因子として有意である、年齢、喫煙歴、咳と痰、喘鳴、息切れの5項目を最終質問項目として同定した。

D. 考察

新COPDスクリーニング質問票の開発は質問票でスクリーニングを行い、COPDが疑われる症例に呼吸機能検査をすすめることが目的である。一般住民を対象とした質問票作成を目的としており、鹿児島厚生連健康管理センターでの登録を優先しておこなった。

登録例数は2,364名であり、AO群65名、Non-AO群2,273名、BD x群26名であった。AO群は2.8%でありNICE studyで推定された本邦におけるCOPD有病率8.6%と比較し低いものであった。健診受診者では、一般住民対象と比べ健康意識の高い比較的健康な受診者が多く、また、一般住民構成と比し、比較的若年者が多く年齢の偏りも影響したと考えられる。

本邦における40歳以上の人間ドック健診者を対象としたCOPDスクリーニング効果の検討において、1秒率70%未満の気流制限例は全例の2.7%であったとする報告があり、健診受診者では一般人口モデルと比べ年齢や喫煙歴の構成比の違いが反映される可能性が高い。

AO群（COPD）の%FEV_1に基づいた病期分類ではI期とII期がそれぞれ29名であり、軽症例（I期とII期）がAO群の89.3%を占めている。軽症例では医療機関受診の機会も少ないことが予想され、一般住民を対象としたスクリーニング質問票においては、軽症例から拾い上げる感度の高さを有することが重要と考える。

WGで作成したCOPD質問票原案(draft)から最終質問票の項目として年齢、喫煙歴、咳と痰、息切れの5項目を同定した。本研究で開発するCOPDスクリーニング質問票をCOPD-Qとし、IPAG-COPD質問票、COPD-PSとの概念領域（CD: Conceptual domain）で比較すると、質問項目としてはIPAG-COPD質問票が8項目で最も多く、COPD-PSとCOPD-Qは5項目からなり簡便である（表7）。

表 7

IPAG-COPD, COPD-PS, COPD-Qの比較

Response items	IPAG	COPD-PS	COPD-Q
Age	○	○	○
Smoking history	○	○	○
Phlegm	◎	○	○
Cough	○		
Wheezing	○		○
Dyspnea		○	○
Functional impact		○	
BMI	○		
Allergy	○		

年齢と喫煙歴については、概念領域として３質問票に共通するが、年齢は IPAG-COPD 質問票と COPD-Q が 40 歳以上を対象とするのに比し、COPD-PS は 35 歳以上を対象としている。喫煙歴については、COPD-PS が pack year（0-14, 15-24, 25-49, 50<）で配点しているが、COPD-PS では喫煙数 100 本を cut-off としている。COPD-Q においては妥当性評価を行い最終的な選択肢・配点を行う予定である。咳と痰の項目については、COPD-PS と COPD-Q が咳と痰を併せた質問項目として 1 項目作成されているが、IPAG-COPD 質問票では痰のみで２項目、咳のみで 1 項目作成されている。喘鳴の項目は IPAG-COPD 質問票と COPD-Q で共通し、COPD-PS になく、息切れの項目は、COPD-PS と COPD-Q に共通し、IPAG-COPD 質問票にはない。BMI は IPAG-COPD 質問票の項目となっているが、本研究においては COPD 予測因子とし有意ではなかった。今後は最終的質問票として同定された 5 項目からなる COPD-Q を用いた他集団における妥当性の評価を行い、年齢や喫煙項目の配点や、cut-off 値の決定を行う。

E. 結論

本邦における独自の COPD スクリーニング質問票を開発するために、COPD の症状と危険因子に関連する多数の質問を作成し、健診受診者を対象にスクリーニングに最適な５項目を選定した。

本研究事業の一つとして、福岡県久山町住民を対象に「質問票 COPD-PS 日本語版における日本人 cut-off 値設定に関する臨床研究」を実施し、結果については「Validation of a COPD screening questionnaire and establishment of diagnostic cut-points in a Japanese general population: The Hisayama study.」のタイトルで Allergol Int. 2015 Jan; 64(1): 49-53.に発表した。

F. 研究発表

1. 論文発表

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G. 知的財産権の出願・登録状況
（予定を含む）

1. 特許取得
   該当なし
2. 実用新案登録
   該当なし
3. その他
   なし

Ⅳ. 研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ
隈元朋洋, 町田健太朗, 井上博雅.	COPD治療におけるコンビネーションセラピー～病態解明から最新治療まで～.	一ノ瀬正和（編）	長時間作用性気管支拡張薬 LAMA/LABA配合薬.	医薬ジャーナル	大阪	2014.8	107-14

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
内田章文, 町田健太朗, 井上博雅.	特集企画：慢性閉塞性肺疾患（Obstructive Lung Disease）「COPDの最新情報」新しい治療薬の位置付けと使い方.	日本呼吸器学会誌	3(3)	358-65	2014
Matsumoto K, Seki N, Fukuyama S, Moriwaki A, Kan-o K, Matsunaga Y, Noda N, Yoshida M, Kotso H, Takata S, Nakanishi Y, Kiyohara Y, Inoue H; Hisayama Pulmonary Physiology Study Group.	Prevalence of asthma with airflow limitation, COPD, and COPD with variable airflow limitation in older subjects in a general Japanese population: the Hisayama Study.	Respir Investig	53(1)	22-9	2014
Tsukuya G, Matsumoto K, Fukuyama S, Crawford B, Nakanishi Y, Ichinose M, Machida K, Samukawa T, Ninomiya T, Kiyohara Y, Inoue H; Hisayama Pulmonary Physiology Study Group.	Validation of a COPD screening questionnaire and establishment of diagnostic cut-points in a Japanese general population: The Hisayama study.	Allergol Int	64(1)	49-53	2015

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Original article

Prevalence of asthma with airflow limitation, COPD, and COPD with variable airflow limitation in older subjects in a general Japanese population: The Hisayama Study

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ABSTRACT

Background: Elucidating the prevalence of asthma and chronic obstructive pulmonary disease (COPD) is important for designing a public health strategy. Recent studies have discriminated a phenotype of COPD with variable airflow limitation (COPD-VAL) associated with asthma–COPD overlap syndrome. Its prevalence remains uncertain. The age and occupational distributions in the town of Hisayama and in Japan are nearly identical. Each disease's prevalence was estimated for the town's residents.

Methods: In 2008, town residents (≥40 years) were solicited to participate in a health checkup. Individuals with abnormal spirometry (forced expiratory volume in 1 s/forced vital capacity [FEV_1/FVC] < 70% and/or %FVC < 80%) were recommended for further evaluations. Two pulmonologists in a blinded fashion reviewed their medical records, including bronchodilator reversibility. Individuals with airflow limitation were classified as having asthma, COPD, COPD-VAL, or other diseases. The prevalence of each disease was then estimated.

Results: A total of 2100 residents (43.4% of residents in the age group) completed spirometry. In 455 residents with abnormal spirometry, 190 residents had further evaluations, and the medical records of 174 residents were reviewed. The prevalence of asthma with airflow limitation, COPD, and COPD-VAL, were 2.0%, 8.4%, and 0.9%, respectively. The prevalence of COPD and COPD-VAL were higher in men and smokers than in women and never-smokers. The prevalence of COPD, but not COPD-VAL or asthma, increased with age.

Conclusion: The prevalence of asthma with airflow limitation, COPD, and COPD-VAL were estimated in a population of residents (≥40 years) in Hisayama.

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1. Introduction

Asthma and chronic obstructive pulmonary disease (COPD) are major inflammatory diseases of the lung, with high and rising prevalence that disturbs the health-related quality of life of patients and imposes a substantial burden on the socioeconomic status of countries [1,2]. To design a public health strategy, it is crucial to have accurate knowledge of their prevalence. In this regard, one obstacle may be the difficult differential diagnoses, particularly in elderly residents with long-term smoking histories. Postbronchodilator spirometry and bronchodilator reversibility testing have been used to discriminate asthma from COPD, but these tests may not be effective in chronic asthma patients with airway remodeling [3]. Recent investigations have discriminated a disease phenotype of COPD with variable airflow limitation (COPD-VAL) as a cardinal feature of asthma–COPD overlap syndrome [4–7]. The risk factors are increased age, bronchial hyperresponsiveness, cigarette smoke exposure, history of asthma, and lower respiratory tract infections during infancy. Patients with overlap syndrome have an increased frequency of exacerbations and an accelerated loss of lung function [5,6]. The prevalence and risk factors in this phenotype in a general population are unknown.

The Hisayama Study is an ongoing population-based epidemiologic study designed to investigate the morbidity and mortality of cardiovascular diseases and of smoking-related diseases and their risk factors in the community in the town of Hisayama, Japan [8,9], located in a suburban area adjacent to Fukuoka City, a large urban center on Kyushu Island in the southern Japan, with a stable population of 8300 people for over 40 years. From the 1960s, the age and occupational distributions of the Hisayama population have been almost identical to those of Japan as a whole, based on data from the national census [10]. We aimed to estimate the prevalence of asthma with airflow limitation, COPD, and COPD-VAL in a general Japanese population (i.e., the PAC-J Study), and then to assess the profiles of sex, smoking history, and age distribution for the diseases. We used the term "COPD-VAL" rather than "asthma–COPD overlap syndrome" as the disease entity because the study design did not intend to obtain full lines of clinical and laboratory data to evaluate the features of overlap syndrome, other than VAL. In addition, the diagnosis of asthma was based on the documentation of airflow limitation to preclude the ambiguity of "self-reported asthma" without evidence of airflow limitation.

2. Patients and methods

In 2008, registered residents aged ≥ 40 years were solicited to participate in a town-wide health checkup, including spirometry. The residents completed a self-reported questionnaire on cigarette smoke exposure, prior diagnoses of asthma and/or COPD, and respiratory symptoms. Spirometry was performed under the guidelines of the Japanese Respiratory Society [11] using a CHESTGRAPH HI-105 spirometer (Chest, MI, Inc., Tokyo, Japan). Up to four tests were used to obtain satisfactory loop recordings. Two pulmonary physicians assessed the results by visual inspection and excluded residents without at least two satisfactory tests. Residents who had poor spirometric maneuvers were excluded from the study. Reference values for the percentage of forced expiratory volume in 1 s predicted (%FEV_1) were derived from the Japanese criteria [11]. Residents who had FEV_1/forced volume capacity (FVC) < 70% or/and %FVC < 80% were recommended for further evaluation in the outpatient clinics of pulmonary medicine at Kyushu University Hospital (Fukuoka, Japan) or Fukuoka-Higashi Medical Center (Fukuoka, Japan). Individuals who had further evaluations underwent

Abbreviations: COPD, chronic obstructive pulmonary disease; GOLD, the Global Initiative for Chronic Obstructive Lung Disease; VAL, variable airflow limitation

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spirometric evaluation, which included reversibility tests, imaging analyses, and detailed interviews regarding clinical history. For subjects with asthma or/and COPD who had taken regular medications, the reversibility test was performed after assessing periodic discontinuation of bronchodilators. Positive reversibility was defined as an increase of 200 mL and 12% or more in the FEV_1 15 min after the inhalation of salbutamol (GlaxoSmithKline, Tokyo, Japan) *via* a metered-dose inhaler with a spacer. The severity of the airflow obstruction was based on the $\%FEV_1$ in accordance with Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria (i.e., for $FEV_1 \geq 80\%$ predicted, Stage I; for $FEV_1 = 50$–79% predicted, Stage II; for $FEV_1 = 30$–49% predicted, Stage III; and for $FEV_1 \leq 30\%$ predicted, Stage IV) [12].

In 2012, the medical records of the subjects who had been further evaluated were reviewed by two pulmonary physicians (K.M. and S.F.) in a blinded fashion. Based on the review, the patients were classified as having asthma with airflow limitation, COPD, COPD-VAL, or other diseases. Asthma with airflow limitation was defined as episodic respiratory symptoms and airflow limitation that was fully reversible with a postbronchodilator FEV_1/FVC of 70% or greater. Asthma was also diagnosed in patients with airflow limitation that was not fully reversible if the patients had VAL and a clinical history compatible with asthma such as repeated episodes of dyspnea or/and wheeze, physician-diagnosed asthma, or/and medications in young adulthood. In addition, possible asthma was estimated by enumerating patients with self-reported asthma, although these patients were not included in the prevalence of asthma with airflow limitation. Chronic obstructive pulmonary disease was defined as not fully reversible airflow limitation without VAL. Variable airflow limitation was defined as an increase of 200 mL and 12% or more in the FEV_1 in the reversibility test. Chronic obstructive pulmonary disease with variable airflow limitation was defined as a not fully reversible airflow limitation with VAL and without a clinical history suggestive of asthma. If the diagnosis was inconsistent between two reviewers, a conclusive diagnosis was determined by careful discussion between the two reviewers. Based on the estimation that subjects without further evaluation would have a similar prevalence, the prevalence of each disease was calculated according to the following equation:

$$\text{The prevalence} = a \times b/c \times d$$

where a is the number of patients classified by each disease after reviewing their medical records; b is the number of subjects with abnormal spirometry at the health checkup; c is the number of subjects who received further evaluation and whose medical records were capable of being reviewed; and d is the total number of subjects who had completed spirometry in the health checkup.

The study was approved by the Institutional Review Board for Clinical Research of Kyushu University, Fukuoka, Japan (Approval date: August 6, 2007, and August 10, 2009; Approved #: 19-15 and 21-37, respectively). The study participants provided written informed consent for medical research. The values were expressed as the mean and standard deviation. Comparisons between two groups were performed using the Chi-square test or the Student t test as needed. Whether the data showed normal distribution was assessed by Shapiro–Wilk's W test. A $P<0.05$ was defined as statistically significant.

3. Results

A total of 2100 subjects (43.4%) successfully completed spirometry. Table 1 shows the subjects' characteristics. Of the 2100 subjects, 455 had an FEV_1/FVC of less than 70% or a %FVC of less than 80%; they were recommended for further evaluations (Fig. 1). Of the 455 subjects, 190 subjects had further evaluations in the clinics at Kyushu University Hospital (Fukuoka, Japan) or Fukuoka-Higashi Medical Center (Fukuoka, Japan).

The medical records of 174 subjects were processed for the study's assessments. The basic profiles of sex, smoking status, age, and spirometric measures in the health checkup were not statistically different between the individuals who

Table 1 – The subjects' characteristics.

	Number	%	FEV_1 (L)	$\%FEV_1$ (%)	FVC (L)	%FVC (%)	FEV_1/FVC (%)
Sex							
Male	890	42.4	2.49±0.66	85.1±16.3	3.35±0.70	93.9±13.9	73.9±8.6
Female	1210	57.6	1.84±0.41	95.6±14.9	2.40±0.48	100.8±13.7	76.5±6.5
Smoking history							
Never	1274	60.7	1.94±0.53	95.1±15.1	2.52±0.63	100.2±14.0	76.6±6.6
Ever	826	39.3	2.39±0.65	85.2±16.4	3.23±0.72	94.3±13.7	73.6±8.6
Age							
40–49	242	11.5	2.71±0.65	90.7±13.2	3.42±0.77	97.3±11.6	79.4±6.4
50–59	483	23.0	2.36±0.55	90.8±13.5	3.05±0.71	97.3±12.3	77.7±5.7
60–69	686	32.7	2.11±0.52	91.7±15.9	2.82±0.66	99.2±14.2	75.0±6.8
70–79	514	24.5	1.80±0.48	91.3±18.5	2.46±0.60	97.9±15.4	73.1±8.4
80–89	170	8.1	1.57±0.46	90.5±21.6	2.20±0.60	94.8±17.6	71.8±9.6
90+	5	0.2	1.61±0.81	96.1±18.0	2.23±1.03	98.7±19.7	71.6±6.3
Total	2100	100.0	2.12±0.62	91.2±16.4	2.80±0.75	97.9±14.2	75.4±7.6

Values are expressed as the mean±the standard deviation.
FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity.

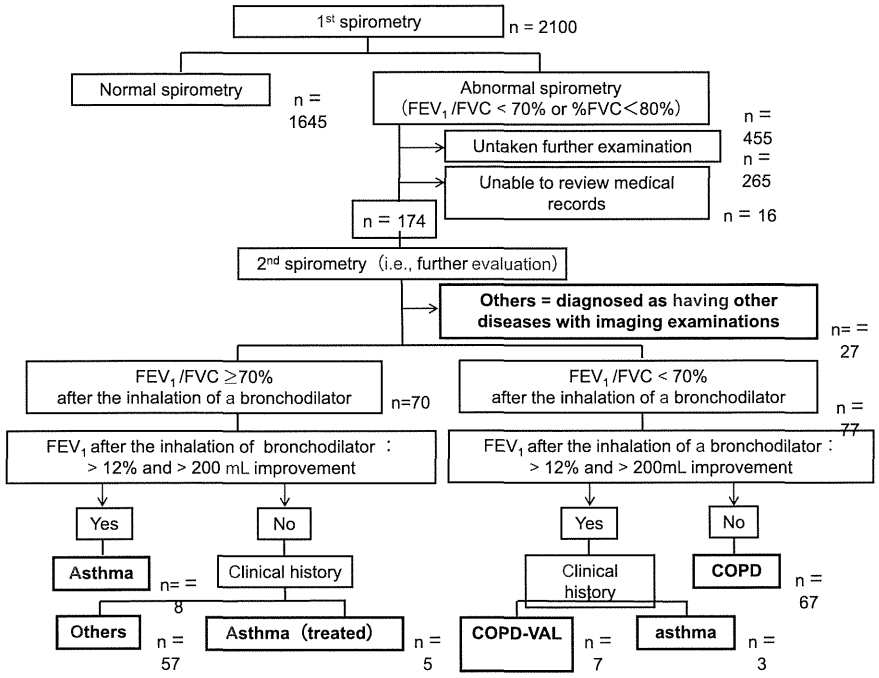

Fig. 1 – Flow diagram of the study population. COPD, chronic obstructive pulmonary disease; COPD-VAL, chronic obstructive pulmonary disease with variable airflow limitation; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity.

Table 2 – The basic profiles in the health check up of evaluatees and nonevaluatees.

	Evaluatees	Nonevaluatees	P
Subjects (no.)	174	281	
Sex (male/female)	101/73	170/111	0.604
Smoking history (ever/never)	97/77	160/121	0.803
Age (yr)	68.8±10.2	69.5±10.2	0.484
FEV_1 (L)	1.68±0.52	1.70±0.51	0.710
FEV_1, % of predicted	73.3±17.6	74.3±16.9	0.562
FVC (L)	2.54±0.72	2.55±0.71	0.953
FVC, % of predicted	88.6±18.6	88.7±17.4	0.945
FEV_1/FVC (%)	66.3±9.9	67.0±9.1	0.476

Values are expressed as the mean±the standard deviation.
Evaluatees, individuals who were available for further evaluation and whose medical records were available; nonevaluatees, individuals who did not have further evaluations or whose medical records were unavailable.
FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity.

were available for further evaluations and whose medical records were available (evaluatees, $n=174$) and residents who did not have further evaluations or whose medical records were unavailable (nonevaluatees, $n=281$) (Table 2). All subjects had spirometry, including reversibility testing. Taken together with detailed clinical histories and the results of imaging analyses, 16 residents were diagnosed as having asthma with airflow limitation; 67 residents, COPD; and 7 residents, COPD-VAL (Table 3). There was no subject with an inconsistent diagnosis that required an additional consensus between the two reviewers. Six (37.5%) of 16 patients with asthma and 13 (17.5%) of 74 patients with COPD or COPD-VAL reported a previous diagnosis of asthma or COPD in the self-reported questionnaire, which suggested that most subjects had been underdiagnosed. The remaining 84 residents were diagnosed as having other diseases (43 patients) or diagnosed as "normal" (41 residents). The other diseases included bronchiectasis, interstitial lung diseases, nontuberculosis mycobacteriosis, pneumoconiosis, diffuse panbronchiolitis, and old inflammatory changes probably due to a past history of tuberculosis. Twenty subjects had a %FVC<80% without airway obstruction. According to the documentation of airway limitation, the prevalence of asthma with airflow limitation, COPD, and COPD-VAL in residents aged ≥40 years were estimated as 2.0%, 8.4%, and 0.9%, respectively. The prevalence of self-reported asthma in the residents with or without airway limitation was 4.9% (103/2100). The prevalence of reversible airway limitation with VAL was 1.0%. The prevalence of irreversible airway limitation with VAL was 1.2%. The prevalence of "irreversible airflow limitation without VAL", but not that of "asthma with airflow limitation", "COPD-VAL", and "COPD" was 0%.

Women were more dominant among residents with asthma, compared to residents with COPD ($P<0.001$). However, they

Table 3 – The profiles of residents with asthma with airflow limitation, COPD, or COPD-VAL.

	Asthma	COPD	COPD-VAL
Subjects (no.)	16	67	7
Sex (male/female)	5/11/2014	56/11*	5/2
Smoking history (ever/never)	4/12	52/15*	5/2*
Age (yr)	66.1±12.0	72.2±8.2	59.9±9.1**
FEV_1 (L)	1.76±0.49	1.92±0.55	1.82±0.56
FEV_1, % of predicted	97.6±19.4	92.7±26.6	72.7±20.0
FVC (L)	2.69±0.61	3.23±0.72*	3.58±0.63*
FVC, % of predicted	105.8±13.6	106.7±18.8	110.6±10.8
FEV_1/FVC (%)	65.0±8.4	59.2±8.6	50.9±12.5*
pBD FEV_1 (L)	2.00±0.50	2.02±0.52	2.07±0.57
pBD FEV_1 , % of predicted	108.3±17.2	97.6±25.0	83.1±19.9
pBD FEV1/FVC (%)	70.0±7.3	60.6±7.8*	56.3±13.4*
Reversibility (mL)	242.67±87.67	73.69±77.00*	255.71±30.64**
Reversibility (%)	15.0±7.2	4.4±5.3*	15.7±6.4**
COPD stage I no. (%)		54 (80.6)	5 (71.4)
COPD stage II no. (%)		8 (11.9)	2 (28.6)
COPD stage III no. (%)		5 (7.5)	0 (0)
COPD stage IV no. (%)		0 (0)	0 (0)

Values are expressed as the mean±the standard deviation.
COPD, chronic obstructive pulmonary disease; COPD-VAL, COPD with variable airflow limitation; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; pBD, postbronchodilator.
* $P<0.05$, versus subjects with asthma with airflow limitation.
** $P<0.05$, versus subjects with COPD.

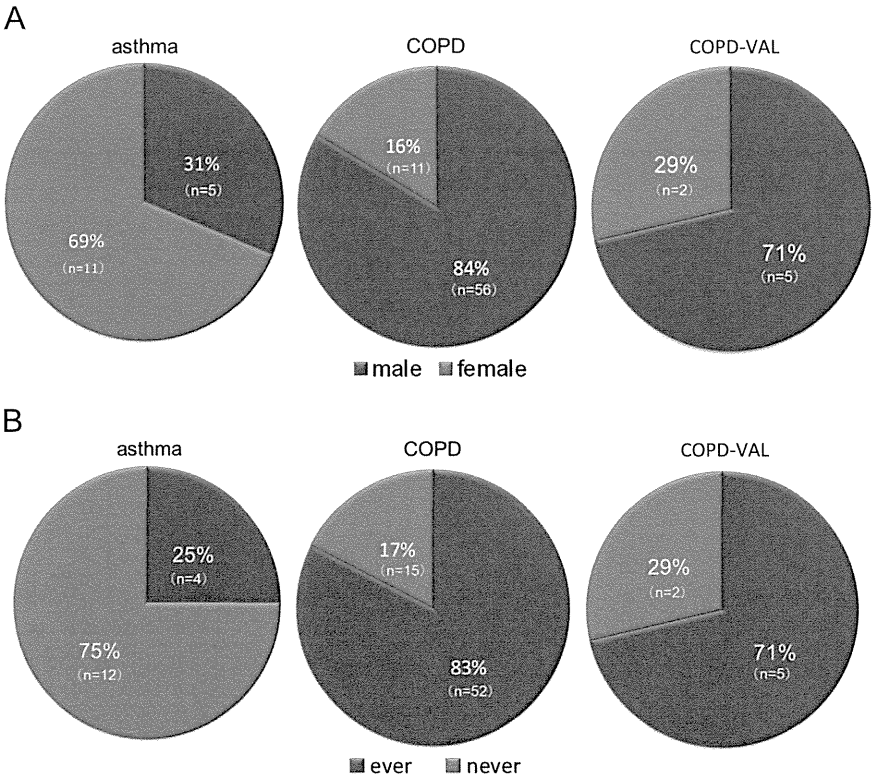

Fig. 2 – The proportion (A) by male and female sex and (B) by ever- and never-smoker in each disease phenotype. COPD, chronic obstructive pulmonary disease; COPD-VAL, chronic obstructive pulmonary disease with variable airflow limitation.

were not more dominant in comparison to residents with COPD-VAL ($P=0.073$). The sex ratio was not statistically different between individuals with COPD or COPD-VAL ($P=0.421$) (Fig. 2A). Never-smokers were more dominant among residents with asthma, compared to residents with COPD ($P<0.001$) and COPD-VAL ($P=0.036$). The ratio of ever- and never-smokers was not statistically different between residents with COPD or COPD-VAL ($P=0.639$) (Fig. 2B). Postbronchodilator airway limitation,

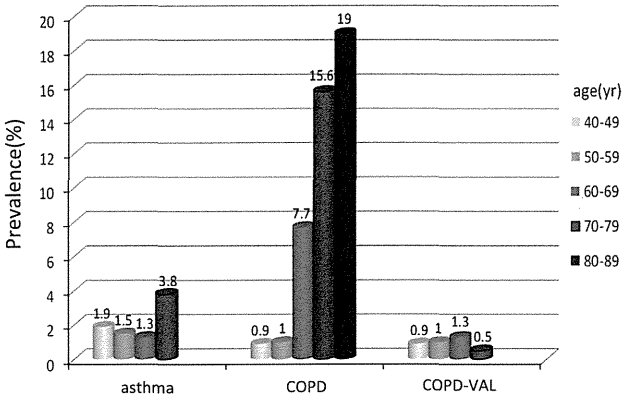

Fig. 3 – The prevalence of each disease phenotype, according to the generation. COPD, chronic obstructive pulmonary disease; COPD-VAL, chronic obstructive pulmonary disease with variable airflow limitation.

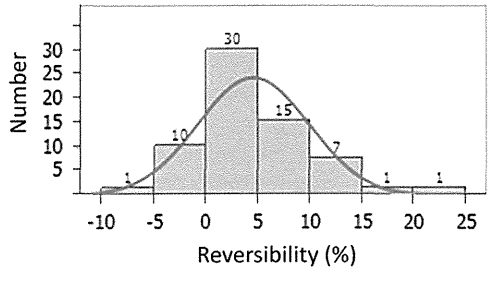

Fig. 4 – The histogram of reversibility (i.e., the percent change between the pre- and postbronchodilator FEV_1) in patients with COPD ($n=67$). The red line indicates the Gaussian curve. The validity of the normal distribution was assessed using Shapiro–Wilk's W test ($P=0.008$).

measured by the FEV_1 (% predicted) and the FEV_1/FVC, was significantly greater in the COPD and COPD-VAL groups, compared to the asthma group. In the COPD group, 80.6% of the residents were staged at GOLD stage I, whereas 71.4% of the residents in the COPD-VAL group were staged at GOLD stage I. The prevalence of COPD increased with age, but there were no any generation-associated trends for the prevalence of asthma or COPD-VAL (Fig. 3). To evaluate the profile of reversibility, a histogram of reversibility was obtained for individuals with COPD (Fig. 4). The pattern of the histogram was compatible with a normal distribution, which was confirmed by statistical analysis using Shapiro–Wilk's W test ($P=0.008$).

4. Discussion

In 2004, Fukuchi et al. [13] reported for the first time a spirometry-based study—the Nippon COPD Epidemiology (NICE) study—on the prevalence of airflow obstruction in Japan. In the NICE study conducted in 2000, the clinical, spirometric, and risk factor exposure data were collected from 2343 eligible household individuals in 18 prefectures, aged ≥40 years and demographically similar to the Japanese population. The prevalence of airflow limitation ($FEV_1/FVC<70\%$) was 10.9% in the study. The NICE study did not use reversibility testing to exclude subjects with asthma. The study accounted for this instead by defining a group of subjects with airflow limitation with possible asthma, based on self-reported diagnoses and symptoms. By excluding individuals who responded positively to any one of four asthma-compatible questions, the COPD prevalence was estimated as 8.6%.

From 2004 to 2005, a community-based approach has been conducted in Takahata, a town in the eastern part of Japan, where spirometric data were collected from 2917 residents aged ≥40 years (representing 19% of the total age-matched population) [14]. The prevalence of airflow limitation (i.e., $FEV_1/FVC<70\%$) was 10.6%. In the present study, the prevalence of asthma with airflow limitation, COPD, and COPD-VAL were 2.0%, 8.4%, and 0.9%, respectively. The summarized prevalence of the three diseases was 11.3%, and the combined prevalence of COPD and COPD-VAL was 9.3%. These values are slightly higher than those in the NICE study and the Takahata study. In this study, there were many never-smokers with COPD (17%) or COPD-VAL (29%). Many of these individuals were females. A similar result was shown by a subanalysis of the Burden of Obstructive Lung Disease (BOLD) study in which lower education levels were associated with an increased risk for COPD among female never-smokers [15]. We did not assess education levels for the study participants.

This study has several limitations regarding data interpretation. The data were collected on town residents who agreed to participate in a town-wide health checkup; they represented 43.4% of the total age-matched population. There was no assurance that the remaining residents had a similar prevalence. Because participants in health checkups tend to be highly motivated for wellbeing, nonparticipants may have different profiles, presumably with a higher disease prevalence. This assumption is supported by previous studies in which individuals in Japan underwent health checkups on one's own initiative [16–18]. The prevalence of COPD in the studies ranges 2.4–7.0%, which is less than the prevalence in the present study. On the other hand, general clinics and primary care settings in Japan report a higher prevalence of 13.6–21.9% [19,20]. However, the difference in the prevalence of airflow obstruction may be because of the difference in the age distribution. The NICE study, the Takahata study, and the present study only examined patients aged ≥40 years.

The classical disease concept of COPD involves airflow limitation without apparent reversibility in spirometry. However, recent clinical studies have revealed that a considerable proportion of patients with COPD have significant reversibility, which shows a normal distribution in the histogram [21–23]. The histogram of reversibility in patients with COPD also showed a pattern of normal distribution. The presence or absence of reversibility may have no impact on decisions regarding pharmacotherapy for COPD [24,25]. This postulation is relevant for avoiding unnecessary preclusion of therapeutic options for subpopulations of patients with COPD; however, the presence of VAL may have additional significance in deciding the content of pharmacotherapy. Gibson et al. [4] suggest that in older patients with airflow limitation, as many as one-half or more may have overlapping diagnoses of asthma and COPD, (i.e., asthma–COPD overlap syndrome) [4].

This syndrome is recognized by the coexistence of VAL in patients with incompletely reversible airflow limitation. The risk factors involve increasing age, bronchial hyperresponsiveness, cigarette smoke exposure, history of asthma, and lower respiratory infections in infancy. Residents with overlap syndrome have been excluded from clinical therapy trials; therefore, knowledge of this syndrome and optimal therapy remain unestablished [4]. The overlapping of asthma and COPD may raise a clinically important concern—whether these patients should be treated with inhaled corticosteroids in combination with long-acting bronchodilators because their asthma-associated components are expected to be steroid-sensitive.

Here, the prevalence of COPD-VAL was 0.9%, which was less than 10% of the total number of individuals with COPD (i.e., 0.9/9.3), which was far less than that of overlap syndrome reported previously [4,26].

The discrepancy may be attributable to study participant recruitment. Previous studies assessed the prevalence in residents after hospital/clinic-based recruitment, whereas the present study assessed the prevalence after a health checkup-based recruitment of the town's residents. The prevalence of overlap syndrome reportedly increases with the severity of airflow limitation. The composition of patients with airway limitation may be less severe than that in previous studies. A large proportion of patients with COPD (80.6%) and COPD-VAL (71.4%) were staged at COPD stage I, and most patients had not been diagnosed as having airflow limitation at the health checkup.

Another limitation is that the disease entity of COPD-VAL may not be identical to asthma–COPD overlap syndrome. The coexistence of VAL with incompletely reversible airway limitation is an essential feature of overlap syndrome; however, other features are also involved. We did not obtain full lines of clinical and laboratory data such as bronchial hyperresponsiveness, airway inflammation, and a history of lower respiratory infection in infancy. Thus, it was difficult to evaluate the other features of overlap syndrome. Furthermore, different definitions are used for a diagnosis of asthma–COPD overlap [4–7]. A consensus on the definition of "overlap" is mandatory. Despite these limitations, COPD-VAL showed a profile that was distinct from that of COPD because the prevalence of COPD increased with age, while no age- or generation-associated trend was noted for COPD-VAL. This finding may question the standing that VAL is a normally distributed continuous variable in COPD. Thus, if the reversibility is normally distributed, the prevalence of COPD-VAL in each generation should be similar to the prevalence of COPD without VAL.

A remaining concern is that the age- and generation-related increase of COPD prevalence may be associated with an overdiagnosis of airflow limitation in elderly patients. Table 1 shows that the mean value of the FEV_1/FVC decreased with age. There is an opinion that the presence of airflow limitation should be defined by the fifth percentile lower limit of normal (LLN) (i.e., $FEV_1/FVC < LLN$) instead of a fixed criteria (i.e., $FEV_1/FVC < 70\%$) [27,28]. An investigation of this standpoint is underway in the currently ongoing health checkup in Hisayama.

The prevalence of asthma in this study was defined by the documentation of airflow limitation and by the assessment of medical records. Patients with asthma who showed no airflow limitation at the health checkup visit would be individuals with mild asthma or well-controlled asthmatics, although these patients may occupy a large portion of asthmatics in the general population. The prevalence of "self-reported asthma" in this study was indeed 4.9%.

Postbronchodilator spirometry was performed 15 min after inhaling salbutamol, based on the guidelines of the Japanese Respiratory Society [11]. Several studies provide a rationale for using an anticholinergic agent in combination with a β_2-agonist in the reversibility test [22,29,30]. In this case, 30 min or more would be required for maximal bronchodilatation. In addition, it is well known that patients with asthma without fully reversible airflow limitation often have no acute response to bronchodilators. These patients may be classified as patients with chronic asthma or asthma with marked airway remodeling. We carefully assessed the individual medical records regarding a history compatible with asthma; however, the study design may fail to detect such patients.

In conclusion, the prevalence of asthma with airflow limitation, COPD, and COPD-VAL was 2.0%, 8.4%, and 0.9%, respectively, in residents aged ≥ 40 years from Hisayama, a town representative of the general Japanese population. The question arises as to whether these phenotypes have different clinical courses. A recent study reports no difference in the decline in the postbronchodilator FEV_1 in groups of people with asthma, asthma–COPD overlap, and COPD [31], which contrasts with previous studies that report that patients with overlap syndrome had an increased frequency of exacerbations and an accelerated loss of lung function [5,6]. The clinical relevance of COPD-VAL will be evaluated in the continuing survey of these patients.

Conflict of interest

Author Hiromasa Inoue received lecture fees from GlaxoSmithKline and Boehringer Ingelheim; his departments received donations from AstraZeneca, GlaxoSmithKline, Boehringer Ingelheim/Pfizer, and Novartis.

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Original article

Validation of a COPD screening questionnaire and establishment of diagnostic cut-points in a Japanese general population: The Hisayama study

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COPD, Chronic obstructive pulmonary disease; COPD-PS, COPD Population Screener; FEV, Forced Expiratory Volume in one second; FVC, Forced Vital Capacity; GOLD, Global Initiative on Chronic Obstructive Lung Disease; ROC, Receiver Operating Characteristic

ABSTRACT

Background: Chronic obstructive pulmonary disease (COPD) is highly prevalent worldwide. COPD is a treatable disease and it is important to identify COPD subjects, highlighting the need for an efficient screening measure. Although the COPD screening questionnaire (COPD Population Screener, COPD-PS) was developed as a screening tool, its validity is not clear in population-based studies. This study determines the validity of the COPD-PS in the general Japanese population.

Methods: All registered residents living in the town of Hisayama aged above 40 were solicited to participate in a health check-up in 2012. All subjects aged 40–79 without physician-diagnosed asthma or lung resection were recruited, and 2357 subjects with the COPD-PS recorded and valid spirometry measurements were analyzed. Persistent airflow obstruction (AO) was defined by post-bronchodilator $FEV_1/FVC < 0.7$. The sensitivity and specificity of the COPD-PS score for identifying AO was assessed by logistic regression analysis.

Results: The prevalence of AO in this population was 6.5%. The overall area under the receiver operating characteristic (ROC) curve for the continuous COPD-PS score was 0.748. A cut-point of 4-points is recommended, resulting in a sensitivity of 67.1% and specificity of 72.9% with an area under the ROC curve of 0.70. The positive predictive value was 14.6% and negative predictive value was 97.0%.

Conclusions: The COPD-PS appears to be an adequate measure for large scale screening of possible airflow obstruction requiring further testing with spirometry.

Introduction

Chronic obstructive pulmonary disease (COPD), characterized by airflow limitation that is not fully reversible and usually progressive,[1] is presently the fourth leading cause of death, and it is projected to be the third largest global cause of mortality by the year 2030.[2] COPD is high prevalent worldwide[3,4] and also in Japan,[5] and it will become one of the major health challenges. COPD is a preventable and treatable disease with some significant extrapulmonary effects,[1] and it would be important to identify these

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subjects. However, history and physical examination are poor predictors of airflow obstruction (AO)[6] and a large number of COPD patients have not yet been diagnosed.[7,8]

The diagnosis of COPD has conventionally been based on physiological pulmonary function tests using spirometry that documents the presence of airflow limitation that is not fully reversible, for which the threshold is a post-bronchodilator ratio of forced expiratory volume in one second (FEV_1) to forced vital capacity (FVC) of 0.7.[1] Spirometric testing for early detection without pre-selection of at-risk patients may result in wasting healthcare resources.[9,10] A self-administered questionnaire may identify cases with a high likelihood of showing airflow limitation and enhance the detection rate of COPD. Some COPD diagnostic questionnaires have already been reported.[11–15] Recently, a Clinician Working Group in the United States has developed a simpler and self-scored questionnaire (COPD Population Screener, COPD-PS) comprised of three COPD-related items (breathlessness, productive cough, and activity limitation), a smoking history item, and an age item.[16] They determined the validity of the COPD-PS for the identification of individuals at increased risk of airflow limitation among patients from pulmonary specialist sites and from general practice.

However, few population-based studies, especially in Asian populations, have addressed the validation of the COPD screening questionnaire. Since considerable heterogeneity in genetic background and lifestyle exists between Asian and Western populations,[17] it is of value to determine the validity of the COPD screening questionnaire in the general Japanese population. The purpose of this study was to conduct the statistical validation of the COPD-PS using the newly translated Japanese version, and to evaluate its diagnostic cut-points for diagnostic triage.

Methods

Study population

The Hisayama Study is an ongoing population-based epidemiologic study designed to investigate the morbidity and mortality of cardiovascular diseases and of smoking-related diseases and their risk factors in the community in the town of Hisayama, Japan. The town is located in a suburban area adjacent to Fukuoka City, a large urban center on Kyushu Island in the southern part of Japan. The population of the town is approximately 8000 and has been stable for more than the last 50 years. The age and occupational distributions of the Hisayama population have been almost identical to those of Japan as a whole from the 1960s to the present, based on data from the national census.[18]

Study design

The local government of Hisayama solicited all registered residents aged 40 years and older to participate in a town-wide health check-up. As there were practical difficulties in measuring lung function in elderly patients, the chosen target group for case finding in our study was aged 40–79 years. Of those who agreed to participate in the health check-up with informed consent, subjects meeting the following exclusion criteria were excluded from this study: Subjects who had physician-diagnosed asthma or lung resection. Eligible subjects were enrolled to the present study between June and October 2012.

Subjects attending their health check-up completed the Japanese version of the COPD-PS and then were administered spirometry using a CHESTGRAPH HI-105 spirometer (Chest MI, Inc., Tokyo, Japan), in addition to their usual health check-up clinical tests. Subjects were asked to perform at least three FVC maneuvers according to the recommended method.[19] Two pulmonary physicians assessed the results of flow-volume curves, and they excluded subjects with poor studied data. The highest FEV_1 and FVC values were recorded. Reference values for FEV_1% predicted were derived from Japanese criteria.[19] Subjects who had a FEV_1/FVC of less than 70% were required to have a post-bronchodilator spirometry following inhalation of 200 μg of salbutamol (GlaxoSmithKline, Tokyo, Japan) via a metered-dose inhaler. A total of 2643 subjects aged 40–79 years were recruited between June and October 2012 (65.3% of the total population in that age group). There were 2357 subjects with a COPD-PS recorded and valid spirometry measurements after excluding 105 subjects who had physician-diagnosed asthma, 22 who had lung resection, and 159 who had poor studied data. Study subjects with a post-bronchodilator $FEV_1/FVC < 70\%$ were defined as persistent AO. The severity of airflow obstruction was based upon the percent of predicted FEV_1, in accordance with Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria ($FEV_1 \geq 80\%$ predicted, mild; $50 \leq FEV_1 < 80\%$ predicted, moderate; $30 \leq FEV_1 < 50\%$ predicted, severe; $FEV_1 < 30\%$ predicted, very severe).[1]

The study protocol was approved by the Institutional Review Board for Clinical Research of Kyushu University (Number 21–37, 24–82 & 24–123) and of Kagoshima University (Number 156 & 279), and informed consent for medical research was obtained from the study subjects.

COPD-PS

The COPD-PS used in this study was translated and culturally adapted from the English version using an internationally recognized forward-backward methodology.[20] The COPD-PS contains five items; three assessing symptoms on a five-point scale, one on cigarette use (three-point scale) and one on the subject's age using four categories. Each question is scored as a 0, 1 or 2 with a summed total score ranging from 0 to 10. The completion of this questionnaire takes approximately 5 min. The COPD-PS is a self-scored questionnaire aimed to help clinicians identify patients for a full diagnostic evaluation.

Statistical analysis

Descriptive analyses [e.g., mean (standard deviation) or n (%)] were performed on the study population at baseline for the demographic characteristics of the study population and the COPD-PS. In addition to descriptive analyses, the COPD-PS items were assessed for floor and ceiling effects and missing data. Floor effect refers to a high percentage of subjects scoring the lowest scores possible while ceiling effect refers to a high percentage of subjects achieving the highest scores possible. Floor and ceiling effects must be interpreted in relation to the condition experienced by the population. Items missing more than 10% of responses were investigated.

The COPD-PS was evaluated as to its ability to correctly guide the diagnosis of obstructive lung disease. The validation of such tools is based on the predictive validity which basis comes from epidemiologic theory and methods. This key property has two major implications: Decision rules are based on scores with threshold values, and the performance should be assessed against the gold standard. The notion of a gold standard or external criteria for classifying patients is essential to evaluate the accuracy of the measure being analyzed.

The evaluation of cut-point levels was conducted through receiver operating characteristic (ROC) curve analysis and the examination of the odds ratio, sensitivity and specificity, Positive Predictive Value (PPV), Negative Predictive Value (NPV), and percent correctly classified. Analysis of variance (ANOVA) was

conducted to evaluate the COPD-PS total score, age and pack-years smoking in relation to AO status. Significance was evaluated against an alpha-level of 0.05. All statistical analyses were performed using JMP software (SAS International Inc., Cary, NC) with significance set at $P < 0.05$.

Results

Table 1 presents the characteristics of the 2357 subjects by airflow limitation category following post-bronchodilator spirometry. The majority of subjects (89.0%) showed an initial $FEV_1/FVC \geq 0.7$. Following post-bronchodilator spirometry, 6.5% were found to have AO. Almost half (47.7%) of AO subjects were classified with moderate COPD. Only 5.9% of AO subjects were classified as severe or very severe. AO subjects were older, included more men, had lower BMI, had a higher number of pack-years smoking, and had a greater proportion of former and current smokers.

Mean and median scores on the COPD-PS were higher for AO subjects. Mean values increased from 2.4 to 3.9, while the median COPD-PS score doubled from 2 with no AO to 4 with confirmed AO. The response distributions for each item on the COPD-PS are presented in Table 2. There were floor effects on items 1–3, with 48.8%–82.3% of subjects responding to the lowest score. There were no ceiling effects. There were few missing data at the item level and none at the scale level.

The overall area under the ROC curve for the continuous COPD-PS score was 0.748 (95% CI 0.706–0.789, $P < 0.001$) (Fig. 1). The COPD-PS was evaluated for the appropriateness of various cut-points (Table 3). The cut-point with the best area under the ROC curve was 4-points, with an area under the ROC of 0.70. This resulted in a sensitivity of 67.1% and specificity of 72.9%. The positive predictive value was 14.6% and negative predictive value was 97.0%. When a cut-point of 4 points was used, the crude odds ratio (OR) of COPD-PS for AO was 5.49, and the adjusted OR by gender, age, BMI, and pack-years was 1.51 (95% CI 1.29–1.76).

Table 1
Baseline characteristics.

	Non-AO†		AO†
	Pre-bd‡ $FEV_1/FVC \geq 70\%$	Pre-bd‡ $FEV_1/FVC < 70\%$	
n	2094	110	153
age	60.4 (10.5)	65.0 (10.4)	66.6 (10.4)
Male (%)	41.5	45.5	68.0
BMI (kg/m^2)	23.3 (3.4)	22.8 (3.4)	22.2 (3.4)
Pack year			
Mean (±SD)	11.5 (±19.6)	15.6 (±21.2)	31.1 (±30.6)
Median (IQR§)	0 (0–19)	0 (0–30)	26.8 (0–47.3)
Smoking status (%)			
Never	59.5	52.7	28.1
Former	25.4	24.5	35.3
Current	15.1	22.7	36.6
COPD-PS			
Mean (±SD)	2.4 (±1.4)	2.9 (±1.4)	3.9 (±1.7)
Median (IQR§)	2 (2–4)	2 (2–4)	4 (2–5)
%FVC	100.8 (13.3)	101.4 (13.4)	96.4 (13.4)
pre-bd FEV_1% predicted	95.5 (14.5)	84.8 (14.5)	74.7 (14.5)
post-bd FEV_1% predicted	NA	91.2 (15.7)	78.0 (15.7)
pre-bd FEV_1%	77.7 (6.3)	67.6 (6.3)	62.2 (6.3)
post-bd FEV_1%	NA	73.6 (8.6)	63.3 (8.6)
Reversibility (%)	NA	29.1	17.6
COPD-stage (%)			
Mild	NA	NA	46.4
Moderate	NA	NA	47.7
Severe	NA	NA	5.2
Very severe	NA	NA	0.7

† Non-AO, post-bronchodilator $FEV_1/FVC \geq 0.7$; AO, post-bronchodilator $FEV_1/FVC < 0.7$.
‡ Pre-bd, pre-bronchodilator.
§ IQR, interquartile range.

Table 2
COPD-PS item score distributions.

Item	*n* (%)
1. During The past 4 weeks, how much of the time did you feel short of breath?	
Not of the time	1940 (82.3)
A Little of the time	208 (8.8)
Some of the time	188 (8.0)
Most of the time	17 (0.7)
All the time	2 (0.1)
Missing	2 (0.1)
2. Do you ever cough up any "stuff," such as mucus or phlegm?	
No, never	1148 (48.8)
Only with occasional colds or chest infections	874 (37.1)
Yes, a few days a month	196 (8.3)
Yes, most days a week	64 (2.7)
Yes, everyday	72 (3.0)
Missing	3 (0.1)
3. I do less than I used to because of my breathing problems in the past 12 months.	
Strongly disagree	1718 (73.0)
Disagree	462 (19.6)
Unsure	123 (5.2)
Agree	43 (1.8)
Strongly agree	6 (0.2)
Missing	5 (0.2)
4. Have you smoked at least 100 cigarettes in your ENTIRE LIFE?	
No	1348 (57.2)
Yes	1006 (42.7)
Don't know	3 (0.1)
5. How old are you?	
Age 35 to 49	406 (17.2)
Age 50 to 59	558 (23.7)
Age 60 to 69	823 (34.9)
Age 70+	570 (24.2)

Discussion

In the present population-based study, the Japanese version of COPD-PS was validated in a general Japanese population. A diagnostic cut-point of 4 was selected, and the adjusted OR by gender, age, BMI, and pack-years was significantly greater than 1.0

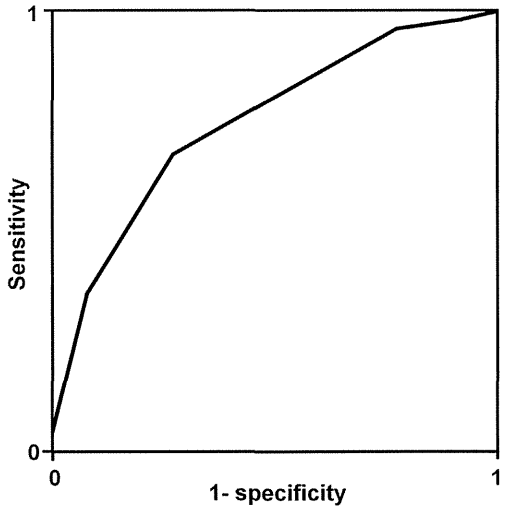

Fig. 1. Receiver Operating Characteristic (ROC) Curve of COPD-PS to discriminate between AO and non-AO states.