５．安価で且つ医療に必須な基礎的医薬品の在り方検討　分担研究

厚生労働行政推進調査事業費補助金
(政策科学総合研究事業(政策科学推進研究事業) 分担研究報告書

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研究要旨

安価で且つ医療上必須の基礎的医薬品については、費用対効果も高く、適切な医療を提供するためにも極めて重要である。平成28年度薬価制度改革において、基礎的医薬品について、試行的に対象を抗菌薬や麻薬等に限定した上で、薬価を維持する制度が導入された。本研究では、製薬企業及び医療機関に対してアンケート調査を行い、製薬企業及び医療機関が基礎的医薬品であると考える医薬品がどのようなものであるかについて一定の知見が得られた。

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Ａ．研究目的

安価で且つ医療上必須の基礎的医薬品については、費用対効果も高く、適切な医療を提供するためにも極めて重要である。平成 28 年度薬価制度改革において、基礎的医薬品について、試行的に対象を抗菌薬や麻薬等に限定した上で、薬価を維持する制度が導入された。本研究では、その他の領域の医薬品についても、諸外国の状況や我が国の医療ニーズ等を踏まえた基礎的医薬品の安定的な提供確保のための、あるべき姿を提案する。

Ｂ．方法

１．製薬企業及び医療機関への調査

本分担研究では､平成 28 年度においては、基礎的医薬品に係る製薬企業及び医療機関の考え方を整理するため、製薬企業に対する調査及び医療機関に対する調査を行った。

①　製薬企業に対する調査

製薬企業に対する調査としては、製薬企業が基礎的医薬品と考える医薬品について、日本製薬団体連合会保険薬価研究委員会の協力を得て、製薬企業各社に対して自社品目に関するアンケート調査を実施した。

調査方法としては、平成 30 年 4 月 1 日時点で薬価基準収載から 25 年を経過することとなる品目（以下、「25 年経過品目」）のうち、平成 28 年度薬価改定において基礎的医薬品選定の要件とされた項目に合致し、かつ基礎的医薬品に相応しい要件と想定される項目に合致すると企業が考える自社品目を回答するよう求め、基礎的医薬品「有」とした 150 社から回答を得た。

②　医療機関に対する調査

医療機関に対する調査としては、医療機関が基礎的医薬品と考える医薬品について、日本病院薬剤師会の協力を得て、特定機能病院に対してアンケート調査を実施した。調査方法としては、25 年経過品目のうち、各医療機関での過去 1 年間の納入歴のあるもの及び基礎的医薬品へ該当すると考えるものを回答す

るよう求めた。特定機能病院 88 施設のうち、32 施設から回答を得た。

２．海外調査

我が国における基礎的医薬品の制度に類似する海外の制度について調査を行った。

C．結果

１．製薬企業及び医療機関への調査

①　製薬企業に対する調査

約 6000 品目ある 25 年経過品目には、成分規格としては 3,578 ある。調査の結果、「25 年経過品目」に係る 3,578 成分規格のうち、基礎的医薬品に該当するものとして回答があったのは 2,402 成分規格であった。このうち、平成 28 年度薬価改定における基礎的医薬品は 218 成分規格であった。「25 年経過品目」を、「先発品」と「後発品」が掲載されている成分規格、「その他医薬品」と「後発品」が掲載されている成分規格、「先発品」のみ掲載されている成分規格、「その他医薬品」のみ掲載されている成分規格、「後発品」のみ掲載されている成分規格の５つに分類して回答数を整理した。「その他医薬品」とは、「先発品」と「後発品」の区分がない昭和 42 年 10 月以前に承認されたものであり、成分規格数が最も多いのは「その他品のみ」であった。「先発品／後発品」で構成される成分規格では、その双方から基礎的医薬品に該当すると回答があった成分規格が約半数に過ぎなかった一方、基礎的医薬品に該当すると回答があったのが後発品のみであった成分規格が４分の１あり、上述した当調査の限界が表れた結果と考えられた。

基礎的医薬品に該当するものとして回答があった 2,402 成分規格について、投与形態別、薬効分類番号（３桁）別に集計した。このうち、投与形態別の成分規格数は、内用薬が 1,400、注射薬が 648、外用薬が 345、歯科用薬が 9 という結果であった。また、平成 28 年度改定で試行的に基礎的医薬品の対象範囲とされた 600 番台（病原生物に対する医薬品）及び 800 番台（医療用麻薬）で回答があったものは、合計で 232 成分規格（内用薬：111、注射薬：117、外用薬：4）という結果であり、基礎的医薬品に該当するものとして回答があった 2,402 成分規格の約１割という結果であった。

また、基礎的医薬品に該当するものとして回答があった 2,402 成分規格について、基礎的医薬品選定の要件とされた項目及び基礎的医薬品に相応しい要件と想定される項目ごとに、合致するとの回答があった成分規格数を集計した。基礎的医薬品選定の要件とされた項目では、ほとんどの品目は複数の医療機関・薬局に納入されているとの回答であった。基礎的医薬品に相応しい要件と想定される項目では、「②実質的に新たな成分が開発されない領域」や「③新たな成分が上市されてもなお、当該疾病領域における治療のベースとして使用されている品目」に合致するとの回答が多かった。

なお、上記 2,402 成分規格に加えて「25 年経過品目」の剤形等を追加した品目として 6 成分規格の回答もあり、基礎的医薬品に該当するとした回答の総数は 2,408 成分規格であった。

このほか、詳細は別紙１に示す。

②　医療機関に対する調査

特定機能病院 88 施設のうち、32 施設から回答が得られた。一部の施設は、納入実績のみの回答であった。

基礎的医薬品に該当すると回答のあった医薬品数は、2,825 品目であり、現時点で薬価収載より 25 年が経過した医薬品の 46.6%であった。このうち、222 品目については、回答施設における納入実績（過去１年間）がなかった。

２．海外調査

海外 12 か国（アメリカ、イギリス、ドイツ、フランス、イタリア、オランダ、スウェーデン、オーストラリア、カナダ、ロシア、

中国、台湾）における関連制度の調査を行った結果、ロシア以外の国では参考とすべき制度は見つけられなかった。ロシアにおいては、「生命にとって必須かつ最重要な医薬品リストに収載された医薬品の価格の国家規制」が政府により定められており、その医薬品についてはリスト化され価格規制の対象となっている。

詳細は別紙２に示す。

D．考察

製薬企業及び医療機関に対する調査により、製薬企業及び医療機関が基礎的医薬品であると考える医薬品がどのようなものであるかについて一定の知見が得られた。特に、製薬企業が基礎的医薬品であると考える医薬品については、昭和 42 年 10 月以前に承認された医薬品が約半数を占めることや、平成 28 年度薬価制度改革で基礎的医薬品の対象とされた品目は、全体の１割程度を占めることなどが明らかになった。

海外調査の結果からは、ロシア以外の国では参考とすべき制度は見つけられず、ロシアにおいては一部の医薬品が価格規制の対象となっていることが明らかになった。ただし、ロシアにおける価格規制の目的は、薬価の不採算対策というよりは、価格の上限を設定するもののようであると考えら得る。

E．結論

製薬企業及び医療機関が基礎的医薬品であると考える医薬品がどのようなものであるかについて一定の知見が得られた。引き続き、基礎的医薬品の在り方について、更なる調査・検討を進める必要がある。

F．健康危機情報

特に無し。

G．研究発表

1. Yamauchi Y, Yasunaga H, Hasegawa W, Sakamoto Y, Takeshima H, Jo T, Matsui H, Fushimi K, Nagase T. Effect of outpatient therapy with inhaled corticosteroids on decreasing in-hospital mortality from pneumonia in patients with COPD. *Int J Chron Obstruct Pulmon Dis* 2016; 11: 1403-11.

2. Yamauchi Y, Yasunaga H, Sakamoto Y, Hasegawa W, Takeshima H, Urushiyama H, Jo T, Matsui H, Fushimi K, Nagase T. Mortality associated with bone fractures in COPD patients. *Int J Chron Obstruct Pulmon Dis* 2016 Sep 21;11:2335-2340.

H．　知的財産権の出願・登録状況

特に無し。

別紙１

製薬業界における調査

製薬企業が基礎的医薬品と考える医薬品について、日本製薬団体連合会保険薬価研究委員会の協力を得て、製薬企業各社に対して自社品目に関するアンケート調査を実施した。

調査方法としては、平成 30 年 4 月 1 日時点で薬価基準収載から 25 年を経過することとなる品目（以下、「25 年経過品目」）のうち、平成 28 年度薬価改定において基礎的医薬品選定の要件とされた項目（表１）に合致し、かつ基礎的医薬品に相応しい要件と想定される項目（表２）に合致すると企業が考える自社品目を回答するよう求め、基礎的医薬品「有」とした 150 社から回答を得た。

表１　平成 28 年度薬価改定　基礎的医薬品選定の要件とされた項目

（平成 27 年 12 月 2 日　厚生労働省医政局経済課事務連絡を参考）

・ガイドラインに記載されていること
・WHO Model of Essential Medicines に記載
・複数の医療機関・薬局に納入されていること

表２　基礎的医薬品の要件に相応しいと想定される項目（複数の項目に合致する場合も可）

①天然・生体由来で代替品がない領域の品目（例：血液製剤、麻薬など）
②実質的に新たな成分が開発されない領域の品目（例：生理食塩液、透析液など）
③新たな成分が上市されてもなお、当該疾病領域における治療のベースとして使用されている品目
④災害等に備えて備蓄が求められている品目（通常使用されないために、廃棄を前提に製造している品目／業界団体で災害時の安定供給マニュアルを整備している品目）
⑤製剤として日本薬局方に収載されている品目（第十七改正日本薬局方において局方収載された品目も含む。）
⑥①～⑤以外に基礎的医薬品の対象と考える理由がある品目（理由を別途記載）

回答には、いわゆる先発医薬品と後発医薬品の関係に当たる品目が多く含まれることを考慮し、集計は、成分、投与形態、剤形、規格が同一の「成分規格」単位とした。

※「成分規格」

品目名	成分名	規格単位	
ベンザリン錠５	ニトラゼパム	５ｍｇ１錠	1 成分規格
ネルボン錠５ｍｇ	ニトラゼパム	５ｍｇ１錠	

品目名	成分名	規格単位	
ベンザリン錠５	ニトラゼパム	５ｍｇ１錠	2 成分規格
ベンザリン錠１０	ニトラゼパム	１０ｍｇ１錠	

なお、当調査は薬価基準に収載されている品目を有する全ての企業に対して実施したものではない。また、以下に示す調査結果は各企業の考えを集計したものであり、同一成分規格に複数の品目が存在するケースにおいて、基礎的医薬品に合致するか否か、あるいは表２に該当する項目について、必ずしも全ての企業の回答が一致した訳ではない。その場合、いわば各社回答の「最大公約数」として集計せざるを得なかったことを付記する。

調査の結果、「25 年経過品目」に係る 3,578 成分規格のうち、基礎的医薬品に該当するものとして回答があったのは 2,402 成分規格であった。このうち、平成 28 年度薬価改定における基礎的医薬品は 218 成分規格であった。「25 年経過品目」を、「先発品」と「後発品」が掲載されている成分規格、「その他医薬品」と「後発品」が掲載されている成分規格、「先発品」のみ掲載されている成分規格、「その他医薬品」のみ掲載されている成分規格、「後発品」のみ掲載されている成分規格の５つに分類して回答数を整理した（表３）。「その他医薬品」（表３「その他品」）とは、「先発品」と「後発品」の区分がない昭和 42 年 10 月以前に承認されたものであり、成分規格数が最も多いのは「その他品のみ」であった。「先発品／後発品」で構成される成分規格では、その双方から基礎的医薬品に該当すると回答があった成分規格が約半数に過ぎなかった一方、基礎的医薬品に該当すると回答があったのが後発品のみであった成分規格が４分の１あり、上述した当調査の限界が表れた結果と考えられた。

表３　基礎的医薬品業界調査結果　カテゴリー構成　　単位：成分規格数

成分規格内カテゴリー構成		先発品／後発品	その他品／後発品	先発品のみ	その他品のみ	後発品のみ	計
25 年経過品目		237	195	1,044	1,793	309	3,578
回答数	基礎的医薬品　有	224	153	※1 726	1,157	※2 142	2,402
	先発品、後発品双方	121					
	その他品、後発品双方		80				
	先発品のみ	50					
	その他品のみ		54				
	後発品のみ	53	19				

※1：うち 21 成分規格は、先発医薬品は基礎的医薬品と回答していないが、収載より 25 年を経過していない後発医薬品について回答があったもの。

※2：うち 1 成分規格は、25 年経過している後発品は基礎的医薬品と回答していないが、収載より 25 年を経過していない後発医薬品について回答があったもの。

基礎的医薬品に該当するものとして回答があった 2,402 成分規格について、投与形態別、薬効分類番号（３桁）別に集計した（表４）。このうち、投与形態別の成分規格数は、内用薬が 1,400、注射薬が 648、外用薬が 345、歯科用薬が 9 という結果であった。また、平成 28 年度改定で試行的に基礎的医薬品の対象範囲とされた 600 番台（病原生物に対する医薬品）及び 800 番台（医療用麻薬）で回答があったものは、合計で 232 成分規格（内用薬：111、注射薬：117、外用薬：4）という結果であり、基礎的医薬品に該当するものとして回答があった 2,402 成分規格の約 1 割という結果であった。

表４　基礎的医薬品業界調査結果　　薬効分類別　　単位：成分規格数

薬効分類番号	25 年経過品目	基礎的医薬品「有」回答数
内 100 番台	374	265
内 200 番台	587	372
内 300 番台	220	124
内 400 番台	81	51
内 500 番台	521	453
内 600 番台	139	98
内 700 番台	49	24
内 800 番台	17	13
内用薬計	1,988	1,400
注 100 番台	95	64
注 200 番台	181	118
注 300 番台	345	231
注 400 番台	98	66
注 600 番台	207	114
注 700 番台	71	52
注 800 番台	15	3
注射薬計	1,012	648
外 100 番台	132	86
外 200 番台	338	217
外 300 番台	15	8
外 400 番台	4	1
外 600 番台	4	2
外 700 番台	66	29
外 800 番台	3	2
外用薬計	562	345
歯 200 番台	16	9
歯科用薬計	16	9
総　　計	3,578	2,402

また、基礎的医薬品に該当するものとして回答があった 2,402 成分規格について、基礎的医薬品選定の要件とされた項目（表１）及び基礎的医薬品に相応しい要件と想定される項目（表２）ごとに、合致するとの回答があった成分規格数を集計した（表５）。基礎的医薬品選定の要件とされた項目では、ほとんどの品目は複数の医療機関・薬局に納入されているとの回答であった。基礎的医薬品に相応しい要件と想定される項目では、「②実質的に新たな成分が開発されない領域」や「③新たな成分が上市されてもなお、当該疾病領域における治療のベースとして使用されている品目」に合致するとの回答が多かった。

表５　基礎的医薬品業界調査結果　　項目別回答　　単位：成分規格数

項目		回答数
表１	ガイドラインに記載	1,726
	WHO Model of Essential Medicines に記載	493
	複数の医療機関・薬局に納入	2,366
表２	①天然・生体由来で代替品がない領域の品目	584
	②実質的に新たな成分が開発されない領域の品目	931
	③新たな成分が上市されてもなお、当該疾病領域における治療のベースとして使用されている品目	872
	④災害等に備えて備蓄が求められている品目	320
	⑤製剤として日本薬局方に収載されている品目	737
	⑥①～⑤以外に基礎的医薬品の対象と考える理由がある品目	128

なお、上記 2,402 成分規格に加えて「25 年経過品目」の剤形等を追加した品目として 6 成分規格の回答もあり、基礎的医薬品に該当するとした回答の総数は 2,408 成分規格であった。

別紙 2

千葉大学医学部附属病院薬剤部
鈴木貴明

基礎的医薬品に関する調査結果報告（海外における同様の制度）

１．基礎的医薬品に類似する海外の制度について

本邦における基礎的医薬品についての制度構築に関し、他国に参考となる制度が存在するかを文献により調査した。

利用する文献資料等が少なく詳細な調査と言えるほどの情報量はなかったが、下記の国に関する薬価制度について調査を行った。

・アメリカ
・イギリス
・ドイツ
・フランス
・イタリア
・オランダ
・スウェーデン
・オーストラリア
・カナダ
・ロシア
・中国
・台湾

各国の保険制度や薬価制度が各国で異なる背景があり、参考とすべき制度は見つけられなかった。この中では、複数の国で医薬品の価格が自由設定であったり、参照価格というものを用いて決められているようであった。したがって、国が一方的に薬価として価格決定しているわけではないので、採算面を考慮した対応が製薬企業側にはある程度可能な状況であると思われる。唯一ロシアだけは「生命にとって必須かつ最重要な医薬品リストに

収載された医薬品の価格の国家規制」が政府により定められており、その医薬品についてはリスト化され価格規制の対象となっているようである（詳細不明）。しかしロシアは医薬品の価格水準が最も高い国の一つであり、この規制は薬価の不採算対策というよりむしろ価格の上限を定めるもののようである。その他、アジア諸国の中ではエッセンシャルドラッグについては価格リストが作成されているケースがあるようだが詳細はわからなかった。

２．PubMed、メディカルオンラインでの検索

有用な情報を得ることはできなかった。

３．今後の予定

他にも有用な文献がないか引き続き検索をする。

４．参考文献

・諸外国の薬剤給付制度と動向（薬事日報社）
・世界の薬価・医療保険制度早引き書（技術情報協会）

研究成果の刊行に関する一覧表

雑誌

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ORIGINAL RESEARCH

Effect of outpatient therapy with inhaled corticosteroids on decreasing in-hospital mortality from pneumonia in patients with COPD

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Background and objectives: Inhaled corticosteroids (ICS) and long-acting inhaled bronchodilators (IBD) are beneficial for the management of COPD. Although ICS has been reported to increase the risk of pneumonia in patients with COPD, it remains controversial whether it influences mortality. Using a Japanese national database, we examined the association between preadmission ICS therapy and in-hospital mortality from pneumonia in patients with COPD.

Methods: We retrospectively collected data from 1,165 hospitals in Japan on patients with COPD who received outpatient inhalation therapy and were admitted with pneumonia. Patients were categorized into those who received ICS with IBD and those who received IBD alone. We performed multivariate logistic regression analysis to examine the association between outpatient ICS therapy and in-hospital mortality, adjusting for the patients' backgrounds.

Results: Of the 7,033 eligible patients, the IBD alone group (n=3,331) was more likely to be older, have lower body mass index, poorer general conditions, and more severe pneumonia than the ICS with IBD group (n=3,702). In-hospital mortality was 13.2% and 8.1% in the IBD alone and the ICS with IBD groups, respectively. After adjustment for patients' backgrounds, the ICS with IBD group had significantly lower mortality than the IBD alone group (adjusted odds ratio, 0.80; 95% confidence interval, 0.68–0.94). Higher mortality was associated with older age, being male, lower body mass index, poorer general status, and more severe pneumonia.

Conclusion: Outpatient inhaled ICS and IBD therapy was significantly associated with lower mortality from pneumonia in patients with COPD than treatment with IBD alone.

Keywords: inhaled corticosteroids, bronchodilators, in-hospital mortality, pneumonia, COPD

Introduction

COPD is the third leading cause of death in the world.[1] COPD is characterized by persistent airflow restriction, which is associated with chronic airway inflammation.[2] Mainstream treatments for COPD, as recommended by international guidelines,[3] are mainly inhaled bronchodilators (IBD), including long-acting β stimulants and long-acting muscarinic antagonists, to improve respiratory function and reduce respiratory symptoms,[4–6] and inhaled corticosteroids (ICS) to reduce the frequency of exacerbations and improve the quality of life in patients with severe COPD.[5,7,8] However, regular treatment with ICS does not modify the long-term decline of respiratory functions and mortality in COPD.[9,10] Combination therapy with ICS and IBD is recommended for patients with severe COPD symptoms and frequent exacerbations.[3]

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Recently, combination treatment with more than one long-acting IBD, consisting of long-acting β stimulants and long-acting muscarinic antagonists without ICS, has been reported to be more effective in improving respiratory function and symptoms,[11–13] and preventing exacerbations in severe COPD[14] than use of IBD alone. In addition, withdrawal of ICS from treatment with triple combination therapy, consisting of long-acting β stimulants, long-acting muscarinic antagonists, and ICS, does not change the risk of exacerbations.[15] This suggests that combined IBD treatment would be as effective in preventing exacerbations as triple combination therapy. Thus, the benefits of ICS in the treatment of COPD have been questioned, particularly because of the adverse side effect of ICS-caused pneumonia.

Lower respiratory infections, such as pneumonia, often occur in COPD and are known to cause COPD exacerbations, increasing the risk of mortality.[16,17] In addition, recent clinical studies and meta-analyses have reported that ICS use increases the occurrence of pneumonia.[18–21] Other studies have produced conflicting results regarding the rate of mortality from pneumonia in patients with COPD using ICS as outpatients.[18,22–24] Thus, it is important and useful for the management of COPD to clarify the association between ICS and mortality from pneumonia in patients with COPD.

This study aimed to examine the association between ICS and mortality from pneumonia in patients with COPD by comparing in-hospital mortality between those who received ICS with IBD and those who received IBD alone.

Methods

Database

We used the Japanese diagnosis procedure combination database, which contains administrative claims data and discharge abstract data from approximately 7,000,000 inpatients per year from around 1,100 hospitals across Japan. The database also includes the outpatient data of patients admitted to 426 hospitals. The database does not include data about those patients who only received outpatient treatment.

The inpatient database contains details of the primary diagnosis on admission, comorbidities present on admission, and complications occurring during hospitalization. These are recorded with the appropriate International Classification of Disease and Related Health Problems, 10th revision (ICD-10) codes accompanied by text in Japanese. This database also contains the following information on admission: dates of admission and discharge; intensive care unit admission during hospitalization; discharge status; the patient's age, sex, body height, and weight; severity of dyspnea based on the Hugh-Jones dyspnea scale;[25,26] levels of consciousness based on the Japan Coma Scale;[27,28] activities of daily life on admission converted to the Barthel index;[29] and severity of pneumonia based on age, dehydration, respiratory failure, orientation disturbance, and low blood pressure (A-DROP) score.[30] Details of the Hugh-Jones dyspnea scale, the Japan Coma Scale, the Barthel index, and the A-DROP score are described in the "Supplementary materials". The database also includes data on the medication and procedures the patients received during hospitalization, for example, the administration of systemic corticosteroids and intubation/mechanical ventilation. The outpatient data contain information that includes prescription dates and the names of the drugs prescribed.

This study was approved by the Institutional Review Board of The University of Tokyo. The board waived the requirement for the patients' written informed consent because of the anonymous nature of the data.

Patient selection

Inclusion criteria for this study were as follows: 1) patients aged over 40 years, 2) those who were admitted to hospital for pneumonia (ICD-10 codes, J10–J18, J69) as the primary diagnosis between July 1, 2010 and March 31, 2013, 3) those who had a secondary diagnosis of COPD (J41–44); and 4) those who received IBD.

We excluded 1) patients who received ICS alone; 2) those who had other obstructive ventilatory impairments, including bronchiectasis (J47) and diffuse panbronchiolitis (J21); and 3) those who had pneumonia recorded as a complication during hospitalization, to preclude hospital-acquired and ventilator-associated pneumonia (J95).

Categorization by inhaled therapy

The IBD administered included tiotropium, glycopyrronium, acridinium, umeclidinium, salmeterol, formoterol, indacaterol, and vilanterol. The ICS administered included fluticasone, budesonide, mometasone, and beclomethasone. Patients who received any ICS with any IBD were defined as the ICS with IBD group. Patients who received one or more IBD but did not receive any ICS were defined as the IBD alone group.

A-DROP score

We used the A-DROP scoring system to evaluate the severity of pneumonia. This system was established by the Japanese Respiratory Society and is similar to the CURB-65 system used by the British Thoracic Society.[30] The severity of

pneumonia was classified into four classes using the A-DROP score: mild, 0 points; moderate, 1–2 points; severe, 3 points; and extremely severe, 4–5 points.

Outcomes

The primary outcome of this study was all-cause in-hospital mortality. The secondary outcomes were length of stay, length of intensive care unit stay, requirement for intubation/mechanical ventilation, duration of mechanical ventilation, and mortality in patients who underwent mechanical ventilation during their hospital stay.

Analysis

We used the chi-square test to compare proportional data, the two-sample *t*-test to compare average values, and the Mann–Whitney *U*-test to compare the median values between groups. We performed multivariate logistic regression analyses to assess the association between ICS use and in-hospital mortality with adjustment for patients' backgrounds, while also adjusting for within-hospital clustering by means of generalized estimation equations. The threshold for significance was $P<0.05$. We performed all statistical analysis using SPSS statistics for Windows, version 22.0 (IBM Corporation, Armonk, NY, USA).

Results

We identified 7,033 patients with COPD (aged ≥40 years) who were treated with outpatient inhaled therapy and were admitted to the hospital with pneumonia. Of them, 3,702 patients were treated with ICS and IBD, and 3,331 patients were treated with IBD alone. The patients' characteristics are shown in Table 1. A-DROP scores in the ICS and IBD group

Table 1 Clinical characteristics of patients on admission

	Total (n=7,033) (%)	ICS with IBD (n=3,702) (%)	IBD alone (n=3,331) (%)	*P*-value
Age (years)[a]	76.3 (8.4)	75.7 (8.4)	77.0 (8.4)	<0.001
Sex (male)	6,315 (89.8)	3,281 (88.6)	3,034 (91.1)	0.001
BMI (kg/m^2)				<0.001
<18.5	3,316 (47.1)	1,831 (49.5)	1,485 (44.6)	
18.5–24.9	2,499 (35.5)	1,247 (33.7)	1,252 (37.6)	
25.0–29.9	492 (7.0)	266 (7.2)	226 (6.8)	
≥30.0	51 (0.7)	18 (0.5)	33 (1.0)	
Missing	675 (9.6)	340 (9.2)	335 (10.1)	
Dyspnea scale by Hugh-Jones classification				<0.001
I	607 (8.6)	301 (8.1)	306 (9.2)	
II	897 (12.8)	460 (12.4)	437 (13.1)	
III	1,071 (15.2)	574 (15.5)	497 (14.9)	
IV	1,913 (27.2)	1,095 (29.6)	818 (24.6)	
V	1,754 (4.9)	922 (24.9)	832 (25.0)	
Unclassified	791 (11.2)	350 (9.5)	441 (13.2)	
Activity of daily living by Barthel index				<0.001
Completely independent	2,275 (32.3)	1,247 (33.7)	1,028 (30.9)	
Partially independent	1,064 (15.1)	604 (16.3)	460 (13.8)	
Partially dependent	1,295 (18.4)	681 (18.4)	614 (18.4)	
Completely dependent	1,163 (16.5)	534 (14.4)	629 (18.9)	
Missing	1,263 (17.6)	636 (17.2)	600 (18.0)	
Level of consciousness by Japan Coma Scale				<0.001
Clear	6,338 (90.1)	3,398 (91.8)	2,940 (88.3)	
Dull	541 (7.7)	240 (6.5)	301 (9.0)	
Somnolence	100 (1.4)	41 (1.1)	59 (1.8)	
Coma	53 (0.8)	23 (0.6)	30 (0.9)	
Pneumonia severity by A-DROP score				<0.001
Mild	416 (5.9)	222 (6.0)	194 (5.8)	
Moderate	3,349 (47.6)	1,808 (48.8)	1,541 (46.3)	
Severe	978 (13.9)	501 (13.5)	477 (14.3)	
Extremely severe	301 (4.3)	122 (3.3)	179 (5.4)	
Missing	1,989 (28.3)	1,049 (28.3)	940 (28.2)	

Notes: [a]Mean (SD). The two-sample *t*-test was used to compare average values between groups. The chi-square test was used to compare proportional data between groups. The threshold for significance was a value of $P<0.05$.

Abbreviations: A-DROP, age, dehydration, respiratory failure, orientation disturbance, and low blood pressure; BMI, body mass index; IBD, inhaled bronchodilators; ICS, inhaled corticosteroids; SD, standard deviation.

Table 2 Patient comorbidities on admission

	Total (n=7,033) (%)	ICS with IBD (n=3,702) (%)	IBD alone (n=3,331) (%)	*P*-value
Asthma	1,872 (26.6)	1,379 (37.3)	493 (14.8)	<0.001
Interstitial pneumonia	323 (4.6)	125 (3.4)	198 (5.9)	<0.001
Lung cancer	719 (10.2)	261 (7.1)	458 (13.7)	<0.001
Congestive heart failure	1,223 (17.4)	597 (16.1)	626 (18.8)	0.003
Arrhythmia	331 (4.7)	157 (4.2)	174 (5.2)	0.052
Cerebrovascular disease	299 (4.3)	151 (4.1)	148 (4.4)	0.450
Chronic liver disease	86 (1.2)	38 (1.0)	4 (1.4)	0.114
Chronic renal failure	133 (1.9)	61 (1.6)	72 (2.2)	0.114

Notes: The chi-square test was used to compare proportional data between groups. The threshold for significance was a value of $P<0.05$.
Abbreviations: IBD, inhaled bronchodilators; ICS, inhaled corticosteroids.

were significantly lower, and therefore their pneumonia was less severe, than in the IBD alone group.

Comorbidities on admission are presented in Table 2. The percentage of asthma was higher in the ICS and IBD group than in the IBD alone group. The percentages of interstitial pneumonia, lung cancer, and congestive heart failure were lower in the ICS and IBD group.

The outcomes are shown in Table 3. All-cause in-hospital mortality in the ICS and IBD group was 8.1%, which was significantly lower than that in the IBD alone group (13.2%). Length of stay in the ICS and IBD group was shorter than that in the IBD alone group. The difference in the results for intensive care unit admission or requirement for mechanical ventilation was not significant between the groups. In-hospital mortality in patients who required mechanical ventilation was significantly lower in the ICS and IBD group (31.9%, n=100/313) than in the IBD alone group (39.7%, n=129/325).

The results of multivariate logistic regression analysis for all-cause in-hospital mortality associated with pneumonia in patients with COPD are shown in Table 4. Outpatient treatment with ICS and IBD was significantly associated with lower mortality than IBD treatment alone, even after adjustment for the patients' backgrounds. Higher mortality was associated with being male, lower body mass index (BMI), severe dyspnea, poorer activities of daily living scores, and more severe pneumonia. Higher mortality was also associated with having interstitial pneumonia and lung cancer, whereas lower mortality was associated with having asthma.

Discussion

We demonstrated that in-hospital mortality associated with pneumonia in patients with COPD was significantly lower in patients treated with combined ICS and IBD therapy than IBD alone.

Previous studies have reported that the use of ICS in patients with COPD increased the occurrence of serious pneumonia requiring hospitalization.[18–21] However, the association between ICS use and mortality from pneumonia in patients with COPD has remained controversial. One study demonstrated that the use of ICS was associated with an increased risk of hospitalization for pneumonia and subsequent death.[18] Several studies have reported that the use of ICS had no impact on outcomes in patients with COPD admitted with pneumonia.[19,21,22] Other studies have demonstrated that ICS use was associated with a decreased risk of mortality, after adjusting for potential confounders, including age, sex,

Table 3 Clinical course and outcomes

	Total (n=7,033) (%)	ICS with IBD (n=3,702) (%)	IBD alone (n=3,331) (%)	*P*-value
Death, n (%)	742 (10.6)	301 (8.1)	441 (13.2)	<0.001
Length of stay (days), median (IQR)	15 (10–25)	14 (10–23)	15 (10–26)	<0.001
Systemic corticosteroids, n (%)	20 (0.3)	12 (0.3)	8 (0.2)	0.509
ICU admission, n (%)	151 (2.1)	81 (2.2)	70 (2.1)	0.803
ICU stay (days), median (IQR)	5 (2–10)	5 (1.5–10)	4.5 (2–12)	0.577
Mechanical ventilation, n (%)	638 (9.1)	313 (8.5)	325 (9.8)	0.058
Length of MV (days), median (IQR)	8 (2–23)	7 (2–20.5)	8 (2.5–25)	0.202
Deaths among patients under MV (n=638); n (%)	229 (35.9)	100 (31.9)	129 (39.7)	0.042

Notes: The chi-square test was used to compare proportional data between groups. The Mann–Whitney U-test was used to compare the median values between groups. The threshold for significance was a value of $P<0.05$.
Abbreviations: IBD, inhaled bronchodilators; ICS, inhaled corticosteroids; ICU, intensive care unit; IQR, interquartile range; MV, mechanical ventilation.

Table 4 Multivariate logistic regression analysis for in-hospital mortality

	Adjusted odds ratio	95% Confidence interval		*P*-value
IBD alone	Reference			
ICS and IBD	0.80	0.68	0.94	0.007
Age (years)				
40–64	Reference			
65–74	1.51	1.04	2.20	0.033
75–84	1.36	0.93	1.99	0.116
>85	2.12	1.40	3.24	<0.001
Sex				
Male	Reference			
Female	0.66	0.48	0.90	0.008
BMI (kg/m^2)				
<18.5	2.26	1.84	3.46	<0.001
18.5–24.9	Reference			
25–29.9	0.75	0.47	1.18	0.216
≥30	1.26	0.38	4.18	0.749
Missing	2.49	1.93	3.22	<0.001
Dyspnea classification				
I	Reference			
II	0.72	0.34	1.54	0.394
III	1.21	0.70	2.09	0.290
IV	1.86	1.08	3.20	0.026
V	4.08	2.42	6.86	<0.001
Unspecified	4.55	2.68	7.71	<0.001
Level of consciousness				
Clear	Reference			
Dull	1.29	0.98	1.70	0.073
Somnolence	2.28	1.50	3.48	<0.001
Coma	2.96	1.57	5.59	0.001
Activity of daily living				
Completely independent	Reference			
Partially independent	0.97	0.67	1.40	0.871
Partially dependent	1.55	1.12	2.14	0.009
Completely dependent	3.03	2.21	4.16	<0.001
Missing	1.44	1.03	2.01	0.033
Severity of pneumonia				
Mild	Reference			
Moderate	1.52	0.72	3.19	0.270
Severe	2.83	1.29	6.20	0.010
Very severe	7.41	3.24	16.95	<0.001
Missing	3.10	1.48	6.49	0.003
Systemic corticosteroids	0.96	0.24	3.84	0.948
Comorbidities				
Asthma	0.57	0.45	0.73	<0.001
Interstitial pneumonia	1.92	1.29	2.86	0.001
Lung cancer	3.57	2.74	4.65	<0.001
Chronic heart failure	1.24	1.00	1.54	0.047
Arrhythmia	1.10	0.74	1.63	0.639
Cerebrovascular disease	0.72	0.48	1.10	0.128
Chronic liver disease	0.95	0.39	2.33	0.918
Chronic renal failure	1.37	0.77	2.43	0.292

Notes: The multivariate logistic regression analyses were used to assess the association between ICS use and in-hospital mortality. The threshold for significance was a value of $P<0.05$.

Abbreviations: BMI, body mass index; IBD, inhaled bronchodilators; ICS, inhaled corticosteroids.

and comorbidities.[23,24] Furthermore, some of the previous studies[18,19] subjected the COPD patients who were taking inhaled therapy and evaluated the mortality of pneumonia, and the others[22–24] subjected the COPD patients who were admitted with pneumonia and evaluated the effects of prior use of ICS on mortality; these latter studies were compatible with our study. However, these studies were limited because they did not adjust for the severity of pneumonia.[23,24] Our study confirmed that the outpatient usage of ICS was associated with lower mortality than nonusage of ICS, even after adjusting

for several confounders, including pneumonia severity. This indicates that treatment with ICS has protective effects against pneumonia-related mortality in patients with COPD.

A possible explanation for the association between ICS and decreased mortality is that corticosteroids produce anti-inflammatory effects by modulating inflammatory mediators. ICS may suppress the inflammatory response in the airway, which spreads to cause systemic inflammation.[31] It may reduce systemic inflammation by blocking excessive inflammation and the harmful effects this causes during infections.[32]

Our study demonstrated that A-DROP scores in patients receiving outpatient ICS treatment were lower than those not receiving ICS. A previous study with a relatively small sample size (n=490) demonstrated that ICS use was not associated with pneumonia severity.[22] Another previous study demonstrated that the use of ICS was associated with a lower degree of pleural inflammatory effusion,[33] suggesting that ICS has a protective effect against the progression of pneumonia and related complications. Because ICS has been reported to reduce bacterial invasion into the airway epithelium in an experimental model[34] and has the potential to reduce inflammation, prior use of ICS may lead to less severe pneumonia. Our study suggests that ICS may have protective effects against the progression of pneumonia in patients with COPD.

The association between ICS and mechanical ventilation has also been controversial.[22,24] Our study demonstrated that the percentage of patients requiring mechanical ventilation was lower in the ICS and IBD group than in the IBD alone group, although this result was not significant. Furthermore, the mortality from pneumonia in patients with COPD requiring mechanical ventilation was significantly lower in the ICS and IBD group than in the IBD alone group. These results also suggest that ICS may have protective effects against pneumonia and pneumonia-related mortality in patients with COPD.

Comorbidity of asthma was associated with decreased mortality in this study. Recently, comorbid asthma and COPD have been recognized as asthma–COPD overlap (ACO).[35] As patients with ACO have lower health-related quality of life, frequent exacerbations, and often require hospitalization,[36,37] patients with ACO have been suggested to have a poorer long-term prognosis, when compared with patients having asthma or COPD alone. However, recent studies have demonstrated that ACO patients have better short-term mortality, compared with COPD alone.[38,39] Our present study is consistent with the previous reports that comorbid asthma and COPD were associated with better prognosis.

Higher mortality was associated with worse general conditions at admission, including lower BMI, more severe dyspnea grade, lower level of consciousness, and poorer activities of daily life. The findings of this study were compatible with the previous study demonstrating the mortality of pneumonia in patients with COPD.[26] Further, missing data in the covariants, such as BMI and activities of daily life at admission, were also associated with higher mortality in this study. Because patients with severe conditions might not be able to get their body height and weight measured or their physical activities evaluated at admission, missing data of BMI and activities of daily life might indicate the more severe general conditions.

This study has several limitations. First, the database did not contain information on the degree of airflow limitation, such as details of pulmonary function tests and COPD severity. However, the grade of dyspnea was used as a covariant of respiratory condition in this study, as a previous study had shown that dyspnea grade reflects respiratory function.[40] Second, the database did not contain information related to the dosages of the medications used. Thus, we cannot evaluate the association between mortality and the dose of ICS.

Conclusion

Outpatient inhaled therapy with ICS and IBD was associated with lower mortality from pneumonia in patients with COPD than IBD treatment alone. ICS may have protective effects against pneumonia and help prevent pneumonia-related mortality in patients with COPD.

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Disclosure

The authors report no conflicts of interest in this work.

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Supplementary materials

Methods

Hugh-Jones dyspnea scale

The Hugh-Jones dyspnea scale is a system for grading dyspnea severity, established by Hugh-Jones and Lambert in 1952.[1] It is similar to the Medical Research Council's breathlessness scale, and is widely used in Japan.[2] The dyspnea scale is defined as follows: 1) the patient's breathing is as good as that of other people of their age and build when working, walking, and climbing hills or stairs; 2) the patient is able to walk on level ground at the pace of normal people of their age and build but is unable to maintain that pace when climbing hills or stairs; 3) the patient is unable to keep up with normal people of their age and build on level ground but is able to walk ~1.6 km or more at their own speed; 4) the patient is unable to walk more than ~50 m on level ground without resting; 5) the patient is breathless when talking or undressing or is unable to leave home because of breathlessness; (unspecified) the patient is unable to be classified into the above grades because of bedridden status.

Japan Coma Scale

The Japan Coma Scale is a system widely used in Japan[3] for assessing patients' levels of consciousness and is reported to correlate well with the Glasgow coma scale.[4] The Japan Coma Scale is defined as follows: one-digit codes (1–3) are given to patients who are conscious without any stimuli; two-digit codes (10–30) are assigned to patients who could be aroused by some stimuli; and three-digit codes (100–300) are given to patients in coma.

Barthel index

The Barthel index is a system for grading the activities of daily life, assessing functional status and the ability to perform daily activities.[5] It consists of ten factors: feeding, bathing, grooming, dressing, bowels, bladder, toilet use, transfer, mobility, and stairs. Scores range from 0 to 20, with a score of 20 indicating total independence, lower scores indicating increasing dependence, and 0 signifying complete dependence. It should be noted that changes of more than two points (10%) in the total score accurately reflect changes in functional status.[6] We categorized patients into four groups according to their score: completely independent (20); partially independent; (19–14); partially dependent (13–7); and completely dependent (6–0).

BMI categories

BMI categories were assigned based on the World Health Organization classifications of underweight (<18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2), and obese (≥ 30.0 kg/m^2).

A-DROP scores

The severity of pneumonia was evaluated using A-DROP scores, which use a six-point scale (0–5) to assess the clinical severity of community-acquired pneumonia. This scale was established by the Japanese Respiratory Society and is reportedly similar to the CURB-65 system of the British Thoracic Society.[7] The A-DROP score consists of the following parameters: 1) age (male ≥ 70 years, female ≥ 75 years), 2) dehydration (blood urea nitrogen ≥ 21 mg/dL), 3) respiratory failure ($SaO_2 \leq 90\%$ or $PaO_2 \leq 60$ mmHg), 4) orientation disturbance (confusion), and 5) low blood pressure (systolic blood pressure ≤ 90 mmHg). The severity of pneumonia was classified into four categories using the A-DROP score: mild, 0 points; moderate, 1–2 points; severe, 3 points; and extremely severe, 4–5 points.

ICD-10 codes of comorbidities

Comorbidities on admission were identified using ICD-10 codes: asthma (J45 and J46), interstitial pneumonia (J84), lung cancer (C34), congestive heart failure (I50), cardiac arrhythmia (I44 and I45, I47–I49), cerebrovascular disease (I60–I69), chronic liver disease (K70 and 71, K73 and 74, K76), and chronic renal failure (N18).

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ORIGINAL RESEARCH

Mortality associated with bone fractures in COPD patients

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Background and objective: COPD is well known to frequently coexist with osteoporosis. Bone fractures often occur and may affect mortality in COPD patients. However, in-hospital mortality related to bone fractures in COPD patients has been poorly studied. This retrospective study investigated in-hospital mortality of COPD patients with bone fractures using a national inpatient database in Japan.

Methods: Data of COPD patients admitted with bone fractures, including hip, vertebra, shoulder, and forearm fractures to 1,165 hospitals in Japan between July 2010 and March 2013, were extracted from the Diagnosis Procedure Combination database. The clinical characteristics and mortalities of the patients were determined. Multivariable logistic regression analysis was also performed to determine the factors associated with in-hospital mortality of COPD patients with hip fractures.

Results: Among 5,975 eligible patients, those with hip fractures (n=4,059) were older, had lower body mass index (BMI), and had poorer general condition than those with vertebral (n=1,477), shoulder (n=281), or forearm (n=158) fractures. In-hospital mortality was 7.4%, 5.2%, 3.9%, and 1.3%, respectively. Among the hip fracture group, surgical treatment was significantly associated with lower mortality (adjusted odds ratio, 0.43; 95% confidence interval, 0.32–0.56) after adjustment for patient backgrounds. Higher in-hospital mortality was associated with male sex, lower BMI, lower level of consciousness, and having several comorbidities, including pneumonia, lung cancer, congestive heart failure, chronic liver disease, and chronic renal failure.

Conclusion: COPD patients with hip fractures had higher mortality than COPD patients with other types of fracture. Surgery for hip fracture was associated with lower mortality than conservative treatment.

Keywords: COPD, hip fractures, in-hospital mortality, surgical treatment

Introduction

COPD is the third leading cause of death worldwide.[1] COPD is often accompanied by multiple comorbidities that are associated with systemic inflammation related to COPD and affect mortality in COPD patients.[2] Osteoporosis is one of the major comorbidities in COPD[3,4] and is reported to be associated with poor health status in COPD patients.[2] Osteoporosis leads to a greater risk of bone fractures, including hip, vertebral, shoulder, and forearm fractures. Hip fracture is the most common type of fracture in elderly patients[5] and is a well-known risk factor for increased mortality.[6–9] Previous studies have reported that hip fractures, as well as vertebral and shoulder fractures, were associated with increased mortality in the general population.[7–10]

COPD patients have bone fragility because of osteoporosis and weakness of skeletal muscle related to reduced physical activity. These patients have been encouraged to improve their physical activity,[11,12] as physical activity has been reported to reduce

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all-cause mortality in COPD patients.[13] However, physical activities may increase the risk of falls and fall-related injuries. Several studies have also demonstrated an association between mortality and chronic respiratory disease in patients with hip fractures,[14–16] but previous studies investigating mortality related to hip fractures in COPD patients have been limited because of small sample sizes.[17,18]

To our knowledge, there have been no studies of mortality related to bone fractures, including hip, vertebral, shoulder, and forearm fractures, in COPD patients. This study investigated the clinical characteristics and mortality of COPD patients with bone fractures using a national inpatient database in Japan. In addition, the factors associated with in-hospital mortality of COPD patients with hip fractures were investigated.

Methods

Database

The Diagnosis Procedure Combination database, a national inpatient database in Japan, includes administrative claims data and hospital discharge data.[19] The Diagnosis Procedure Combination database includes data on the following: primary diagnosis on admission; comorbidities present on admission; complications occurring during hospitalization, recorded with the *International Classification of Disease and Related Health Problems, 10th Revision (ICD-10)* codes accompanied by text data in Japanese; patient discharge status including outcomes; and operative procedures during hospitalization. The database also contains the following information on admission: patient age and sex; body height and weight; level of consciousness based on the Japan Coma Scale; and activities of daily life represented by the Barthel Index.

This study was approved by the Institutional Review Board of the University of Tokyo. The board waived the requirement for patients' informed consent because of the anonymous nature of the data.

Patient selection

We retrospectively collected data for patients aged 40 years and older who were admitted to hospital with bone fracture as the main diagnosis on admission, had a diagnosis of COPD, and were discharged between July 1, 2010 and March 31, 2013 (Figure 1). Bone fracture on admission was identified

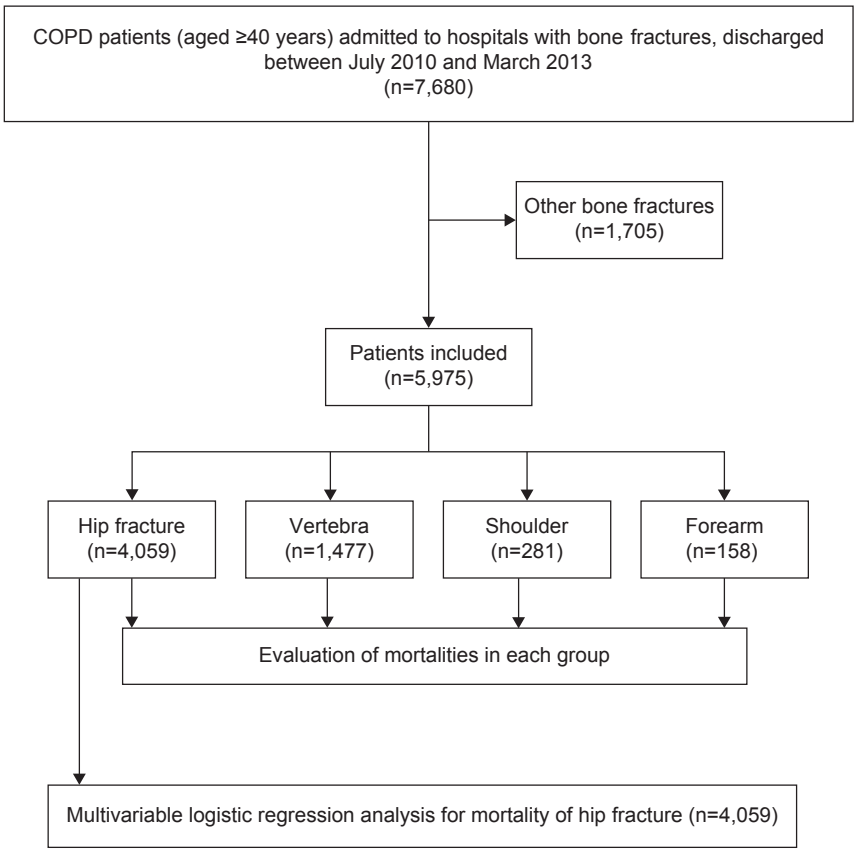

Figure 1 Flowchart showing the inclusion and exclusion criteria of this study.

with ICD-10 codes. Hip fracture included fracture of the proximal femur (S720, S721, and S722). Vertebral fracture included fracture of the thoracic and lumbar vertebra (S220, S221, and S320). Shoulder fracture included fracture of the clavicle, scapula, and proximal humerus (S420, S421, and S422). Forearm fracture included fracture of the distal forearm (S525 and S526). The diagnosis of COPD was based on physician-diagnosed COPD, and having COPD on admission was identified with ICD-10 codes (J41, J42, J43, and J44). Patients who were injured in traffic accidents were excluded (V01x–V99x).

Outcomes

The primary outcome of this study was all-cause in-hospital mortality.

Statistical analysis

We used the χ^2 test to compare proportions, analyses of variance followed by a post hoc Bonferroni test to compare mean values, and the Kruskal–Wallis test to compare median values between groups. Multivariable logistic regression analysis was used to assess the association between patient-level factors and mortality after adjustment for within-hospital clustering by means of a generalized estimation equation. The threshold for significance was $P<0.05$. Statistical analyses were performed using SPSS Statistics for windows, version 22.0 (IBM Corp., Armonk, NY, USA).

Results

Patient characteristics on admission

A total of 5,975 COPD patients (aged ≥40 years) were admitted to the hospital with bone fractures, 4,059 (67.9%) with a hip fracture, 1,477 (24.7%) with a vertebral fracture, 281 (4.7%) with a shoulder fracture, and 158 (2.6%) with a forearm fracture. Patient characteristics are listed in Table 1. The mean age of the COPD patients with a bone fracture was 81.2 years, and mean body mass index (BMI) was 19.7 kg/m^2. Patients with hip fractures were significantly older (83.2 years), had lower BMI (19.3 kg/m^2), and had poorer general condition than those with other types of fracture. Patients with a forearm fracture were significantly younger, had normal BMI, and were in better condition compared with the other groups.

Comorbidities on admission are listed in Table 2. Major comorbidities in COPD patients with bone fracture were pneumonia, asthma, congestive heart failure, ischemic heart disease, and cerebrovascular disease. The proportions of pneumonia, congestive heart failure, and cerebrovascular disease were higher in the hip fracture group than the other fracture groups.

The clinical course and outcomes are listed in Table 3. Mortality in the hip, vertebral, shoulder, and forearm groups was 7.4%, 5.2%, 3.9%, and 1.3%, respectively. Length of hospital stay in the hip fracture group was significantly longer than in the other fracture groups. In the hip fracture group,

Table 1 Clinical characteristics of COPD patients on admission

	Total		Hip		Vertebra		Shoulder		Forearm		*P*-value
	n=5,975	(%)	n=4,059	(%)	n=1,477	(%)	n=281	(%)	n=158	(%)	
Age (years)[a]	82.1 (8.2)		83.2 (7.9)		80.7 (7.5)		77.4 (10.2)		75.3 (9.0)		<0.001
40–79	1,874	(31.4)	1,069	(26.3)	567	(38.4)	136	(48.4)	102	(64.6)	
≥80	4,101	(68.6)	2,990	(73.7)	910	(61.6)	145	(51.6)	56	(35.4)	
Sex											<0.001
Male	3,122	(52.3)	2,087	(51.4)	845	(57.2)	150	(53.4)	40	(25.3)	
Female	2,853	(47.7)	1,972	(48.6)	632	(42.8)	131	(46.6)	118	(74.7)	
BMI (kg/m^2)[a]	19.7 (3.7)		19.3 (3.6)		20.2 (3.9)		20.7 (3.9)		22.0 (4.3)		<0.001
<18.5	2,198	(36.8)	1,609	(39.6)	478	(32.4)	82	(29.2)	29	(18.4)	
18.5–24.9	2,753	(46.1)	1,814	(44.7)	701	(47.5)	145	(51.6)	93	(58.9)	
≥25.0	440	(7.4)	227	(5.6)	152	(10.3)	31	(11.0)	30	(19.0)	
Missing	584	(9.8)	409	(10.1)	146	(9.9)	23	(8.2)	6	(3.8)	
Level of consciousness											<0.001
Clear	5,410	(90.6)	3,601	(88.7)	1,392	(94.2)	263	(93.6)	154	(97.5)	
Drowsy	533	(8.9)	431	(10.6)	81	(5.5)	17	(6.0)	4	(2.5)	
Coma	31	(0.5)	26	(0.6)	4	(0.3)	1	(0.4)	0	(0.0)	
Activities of daily living											<0.001
Independent	1,067	(17.9)	406	(10.0)	383	(25.9)	162	(57.7)	116	(73.4)	
Dependent	3,654	(61.2)	2,762	(68.0)	796	(53.9)	73	(26.0)	23	(14.6)	
Missing	1,254	(21.0)	891	(22.0)	298	(20.2)	46	(16.4)	19	(12.0)	

Notes: [a]Data expressed as mean (standard deviation). Missing refers to lack of data.
Abbreviation: BMI, body mass index.

Table 2 Patient comorbidities on admission

	Total		Hip		Vertebra		Shoulder		Forearm		*P*-value
	n=5,975	(%)	n=4,059	(%)	n=1,477	(%)	n=281	(%)	n=158	(%)	
Pneumonia	500	(8.4)	389	(9.6)	94	(6.4)	14	(5.0)	3	(1.9)	<0.001
Asthma	692	(11.6)	437	(10.8)	196	(13.3)	31	(11.0)	28	(17.7)	0.005
Interstitial pneumonia	97	(1.6)	56	(1.4)	38	(2.6)	3	(1.1)	0	(0.0)	0.005
Lung cancer	184	(3.1)	108	(2.7)	65	(4.4)	9	(3.2)	2	(1.3)	0.005
Congestive heart failure	674	(11.3)	496	(12.2)	151	(10.2)	19	(6.8)	8	(5.1)	0.001
Ischemic heart disease	605	(10.1)	411	(10.1)	143	(9.7)	27	(9.6)	24	(15.2)	0.183
Arrhythmia	302	(5.1)	223	(5.5)	62	(4.2)	10	(3.6)	7	(4.4)	0.149
Cerebrovascular disease	569	(9.5)	419	(10.3)	120	(8.1)	20	(7.1)	10	(6.3)	0.018
Chronic liver disease	88	(1.5)	61	(1.5)	24	(1.6)	0	(0.0)	3	(1.9)	0.199
Chronic renal failure	149	(2.5)	115	(2.8)	28	(1.9)	5	(1.8)	1	(0.6)	0.074

3,220 (79.3%) patients received surgical treatment. Mortality in the surgically treated hip fracture group was 5.3%, while that in the conservatively treated hip fracture group was 15.4%.

The results of the multivariable logistic regression analysis of factors associated with mortality in COPD patients with hip fractures are listed in Table 4. Higher mortality was associated with male sex, lower BMI, and lower level of consciousness on admission. Surgical treatment of hip fracture was associated with lower mortality compared with conservative treatment (adjusted odds ratio, 0.43; 95% confidence interval, 0.32–0.56; $P<0.001$). Comorbidities of pneumonia, interstitial pneumonia, lung cancer, congestive heart failure, chronic liver disease, and chronic renal failure were also associated with higher mortality in COPD patients with hip fracture.

Discussion

This retrospective study, using data from a national inpatients database in Japan, established that COPD patients with hip fractures had higher in-hospital mortality than COPD patients with other types of bone fractures. Hip fracture patients were also older and had lower BMI than patients with other types of fracture. In the hip fracture group, patients who underwent surgical treatment had significantly lower mortality than those who received conservative treatment. Higher mortality was associated with male sex, lower BMI, lower level of consciousness on admission, and several comorbidities.

Previous studies have shown that hip fractures were associated with increased mortality in elderly patients;[5–8] COPD was also reported to be associated with increased mortality in patients with hip fracture.[14–17] Thus, mortality associated with hip fractures in COPD patients was expected to be high, and this was confirmed in this study. In-hospital mortality of COPD patients with a vertebral fracture was also higher than in patients with shoulder or forearm fractures. Vertebral fractures have also been reported to be associated with increased mortality in the general population.[9] A previous study demonstrated that long-term mortality in spine fracture patients was as high as that of patients with hip fractures.[10] Another recent study reported that vertebral fractures in COPD patients were associated with an increase in long-term mortality.[20] These findings suggest that COPD patients should take care to prevent osteoporotic fractures, particularly hip and vertebral fractures.

Our study demonstrated that the prevalence of hip fracture was more frequent in male COPD patients than female COPD patients. However, hip fracture is well known to be

Table 3 Clinical course and outcomes

	Total		Hip		Vertebra		Shoulder		Forearm		*P*-value
	n=5,975	(%)	n=4,059	(%)	n=1,477	(%)	n=281	(%)	n=158	(%)	
Death	389	(6.5)	299	(7.4)	77	(5.2)	11	(3.9)	2	(1.3)	<0.001
Length of stay, days[a]	31 (20–50)		34 (22–53)		29 (19–47)		23 (12–36)		12 (5–12)		<0.001
With surgery	3,476	(58.2)	3,220	(79.3)	63	(4.3)	165	(58.7)	88	(55.7)	<0.001
Death[b]	177	(5.1)	170	(5.3)	3	(4.8)	4	(2.4)	0	(0.0)	0.055
Without surgery	2,499	(41.8)	839	(20.7)	1,474	(95.7)	116	(41.3)	70	(44.3)	
Death[c]	212	(8.6)	129	(15.4)	74	(5.2)	7	(6.1)	2	(2.9)	<0.001

Notes: [a]Median (interquartile range); [b]percentage among patients with surgery; [c]percentage among patients without surgery.

Table 4 Multivariable logistic regression analysis of COPD patients with hip fractures (n=4,059)

	aOR	95% CI	*P*-value
Age (years)			
40–79	Ref		
≥80	1.21	0.89–1.66	0.229
Sex			
Male	Ref		
Female	0.42	0.32–0.56	<0.001
BMI (kg/m^2)			
<18.5	2.10	1.58–2.79	<0.001
18.5–24.9	Ref		
≥25.0	0.63	0.27–1.45	0.276
Missing	2.47	1.64–3.70	<0.001
Level of consciousness			
Clear	Ref		
Drowsy	1.36	0.91–2.03	0.137
Coma	3.70	1.36–10.07	0.010
Activity of daily living			
Independent	Ref		
Dependent	1.12	0.71–1.78	0.954
Missing	0.94	0.55–1.58	0.805
Surgery with anesthesia			
Yes	0.43	0.32–0.56	<0.001
Comorbidities			
Pneumonia	4.65	3.47–6.23	<0.001
Asthma	1.04	0.64–1.68	0.713
Interstitial pneumonia	4.47	2.12–9.41	<0.001
Lung cancer	2.47	1.33–4.59	0.004
Congestive heart failure	1.95	1.40–2.72	<0.001
Ischemic heart disease	1.41	0.95–2.09	0.090
Arrhythmia	1.45	0.89–2.38	0.140
Cerebrovascular disease	0.84	0.52–1.36	0.480
Chronic liver disease	2.60	1.17–5.77	0.019
Chronic renal failure	1.88	1.00–3.53	0.050

Note: Missing refers to lack of data.
Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; Ref, reference; BMI, body mass index.

more frequent in females than males in general population.[5,21] This discrepancy might be explained based on the frequency of male COPD patients and the existence of osteoporosis as one of the comorbidities of COPD. Our previous study demonstrated that males were four times more likely to suffer from COPD than females.[22] Furthermore, COPD frequently coexists with osteoporosis, which leads to bone fracture. Thus, hip fracture in male COPD patients might be more frequent than in female COPD patients.

This study demonstrated that mortality of hip fracture patients who underwent surgery was 5.3%. A previous study demonstrated that short-term mortality of surgically treated hip fracture patients in general populations was around 1%–2%,[23] whereas that in COPD patients was reported to be around 12%;[18] this indicates that surgical treatment for hip fracture in patients with COPD had more perioperative complications and higher mortality.[18] The mortality in this study was higher than that reported in the general population, and compatible with previous findings.[18]

This study also demonstrated that mortality in COPD patients with hip fractures who underwent surgery was significantly lower than that of patients who underwent conservative treatment (15.4%), after adjustment for patient backgrounds. A previous report demonstrated that urgent scheduling of hip fracture surgery in COPD patients was associated with lower mortality,[18] and it was confirmed by this study. To the best of our knowledge, there are no previous reports regarding mortality in conservatively treated hip fractures in COPD patients. However, this study indicates that surgical treatment should be recommended for COPD patients with hip fractures, rather than conservative treatment.

Mortality in COPD patients with hip fractures was also found to be associated with several comorbidities, including pneumonia, interstitial pneumonia, lung cancer, congestive heart failure, and chronic liver disease. Previous studies demonstrated that congestive heart failure and poor renal function were associated with higher mortality in patients with hip fractures,[16,18] and these findings were consistent with this study. Therefore, treatments for comorbid diseases may be crucial for the management of COPD patients to reduce the risk of bone fractures in such patients.

Limitations

There are several limitations in this study. First, our database does not contain parameters of pulmonary function tests, which could evaluate airflow limitation and indicate the severity of COPD. Therefore, we could not evaluate the association between mortality and severity of COPD. Second, the database does not contain information related to osteoporosis, such as bone mineral density and treatment. Therefore, we could not investigate the association between mortality and osteoporosis in COPD.

Conclusion

In conclusion, mortality was highest in COPD patients with hip fractures, followed by those with vertebral fractures. Surgically treated hip fractures were associated with lower mortality in COPD patients, compared with conservative treatment. Pneumonia and congestive heart failure were also associated with higher mortality in COPD patients with hip fracture. The study indicates that COPD patients should take care to prevent bone fractures, especially hip and vertebral fractures; nevertheless, such patients are generally encouraged to maintain or increase physical activities to improve their prognosis.

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Disclosure

The authors report no conflicts of interest in this work.

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