

Table S1. List of ICD-10 codes identifying comorbidities during hospitalization for COPD exacerbation

COPD J41, J42, J43, J440, J441, J449
COPD exacerbation J10, J11, J13, J14, J15, J16, J18, J20, J21, J22, J46, J170, J171, J178, J440, J441, J851, J12, A481, B012, B052, B250
Bacterial pneumonia J100, J110, J12, J13, J14, J15, J16, J170, J178, J18, J851, A481
Lung cancer C34
Other malignancy C00-26, C30-33, C37-41, C43-58, C60-76
Diabetes/abnormal glucose tolerance E10-14, R703
Bone fracture/osteoporosis M80-84
Interstitial pneumonia B221, J701, J704, J841, J848, J849, J990, J991, M321, M330, M331, M332, M351
Bronchial asthma J45, J46
Bronchiectasis J40, J41, J42, J47
Pulmonary thromboembolism I26
<i>Mycobacterium</i> infection A150-154, A156-159, A161-162, A165, A168-169, A19, A310, A319
Mycotic infection A420, A43, B37, B380-382, B390-392, B400-402, B410, B420, B440, B441, B449, B460, J172
Cor pulmonare I27
Congestive heart failure E059, I46, I50, I099, I110
Ischemic heart disease I20-25
Tachycardia I47-49, R000, T818
Autoimmune disease M05, M06, M08, M30-35
Stroke I60-64
Liver dysfunction B89, B181, B182, B659, B661, K702, K703, K72, K74, K761, K762, K763, K766, K767
Renal failure E102, E112, E142, I120, N17-19
GERD K21
Constipation or ileus K56, K590
Prostate hypertrophy N40

Abbreviations: COPD, chronic obstructive pulmonary disease; GERD, gastro-esophageal reflux disease

Table S2. List of baseline characteristics, comorbidities, and treatments before and during hospitalization for COPD exacerbation

Baseline characteristics	Sex, fiscal year, season at admission, residential region, Hugh-Jones dyspnea score at admission, activities of daily living scores at both admission and discharge (Barthel Index scores), age, body mass index, smoking index, frequency of hospitalization before index hospitalization, and observation period before index hospitalization (days)
Comorbidities	Lung cancer, other malignancy, diabetes/abnormal glucose tolerance, bone fracture/osteoporosis, interstitial pneumonia, bronchial asthma, bronchiectasis, pulmonary thromboembolism, <i>Mycobacterium</i> infection, mycosis, cor pulmonale, congestive heart failure, ischemic heart disease, tachycardia, autoimmune disease, stroke, liver dysfunction, renal failure, gastro-esophageal reflux disease, constipation and/or ileus, prostate hypertrophy
Treatments	Home ventilator support, home oxygen therapy, ICS before index hospitalization, LAMAs before index hospitalization, LABAs before index hospitalization, other medications for COPD before index hospitalization, ambulance transport, corticosteroid therapy during index hospitalization, mechanical ventilation during index hospitalization, nasal tube feeding during index hospitalization, surgery under general anesthesia during index hospitalization, prescription of LAMA/LABA (fixed-dose long-acting bronchodilator combination in single inhaler), LAMA, or LABA during hospitalization, discharge to home, length of stay

Abbreviations: ICS, inhaled corticosteroids; LAMA, long-acting muscarinic receptor antagonist; LABA, long-acting beta agonist; COPD, chronic obstructive pulmonary disease

Table S3. List of drugs for the treatment of COPD and drugs used to identify COPD exacerbation in outpatient settings

Drugs for the treatment of COPD	
ICS	beclomethasone, fluticasone, budesonide, ciclesonide, mometasone
LAMA	tiotropium, glycopyrronium, umeclidinium
LABA	Salmeterol, formoterol, indacaterol, vilanterol, tulobuterol
Other medications for COPD	theophylline, acetylcysteine, ambroxol, carbocisteine, fudosteine, bromhexine, salbutamol, fenoterol, procaterol, ipratropium, oxitropium
Drugs used to identify COPD exacerbation	
Antimicrobials	benzylpenicillin, aspoxicillin, amoxicillin, ampicillin, amoxicillin/clavulanate, bacampicillin, cinoxacin piperacillin, pivmecillinam, sulbactam/ampicillin, tazobactam/piperacillin, ampicillin-cloxacillin, cefroxadine, cefaclor, cefalex, cefalotin, cefazolin, cefuroxime, cefmetazole, cefotiam, flomoxef, cefminox, cefodizime, latamoxef, sulbactam/cefoperazone, cefotaxime, cefoperazone, cefixime, ceftibuten, cefbuperazone, cefcapene pivoxil, cefteram pivoxil, cefpodoxime proxetil, cefteram pivoxil cefpirome, cefmenoxime, cefditoren, ceftazidime, ceftriaxone, cefozopran, cefepime, ceftizoxime, telithromycin, clindamycin, amikacin isepamicin, gentamicin, tobramycin, dibekacin, aztreonam, erythromycin, clarithromycin, azithromycin, josamycin, roxithromycin, aztreonam, tosufloxacin, ofloxacin, garenoxacin, levofloxacin, sitafloxacin, ciprofloxacin, tosufloxacin, norfloxacin, pazufloxacin, prulifloxacin, moxifloxacin, lomefloxacin, faropenem, biapenem, tebipenem pivoxil, panipenem/betamipron, imipenem/cilastatin, doripenem, meropenem, oseltamivir, zanamivir, peramivir, laninamivir
Systemic corticosteroids	dexamethasone, paramethasone, prednisolone, methylprednisolone, betamethasone, triamcinolone, hydrocortisone

Abbreviations: ICS, inhaled corticosteroids; LAMA, long-acting muscarinic receptor antagonist; LABA, long-acting beta agonist; COPD, chronic obstructive pulmonary disease

Table S4. Incident rate ratios and 95% confidence intervals for post-discharge frequency of outpatient antimicrobial and corticosteroid prescriptions in patients with COPD with and without asthma after 1-to-2 PS matching and stabilized IPTW in ICS withdrawal group versus control group

		Observation period	IRR	95%CI	P	
1-to-2 PS matching	With asthma	Antimicrobials	30 days	0.87	0.60 – 1.25	0.449
			1 year	0.73	0.53 – 1.00	0.047
		Corticosteroids	30 days	1.02	0.65 – 1.60	0.940
			1 year	0.86	0.57 – 1.29	0.455
	Without asthma	Antimicrobials	30 days	0.86	0.62 – 1.20	0.376
			1 year	0.74	0.56 – 0.97	0.030
		Corticosteroids	30 days	1.22	0.77 – 1.93	0.394
			1 year	0.83	0.54 – 1.28	0.407
Stabilized IPTW	With asthma	Antimicrobials	30 days	1.02	0.61 – 1.71	0.934
			1 year	0.69	0.49 – 0.96	0.030
		Corticosteroids	30 days	1.02	0.64 – 1.67	0.908
			one year	0.61	0.39 – 0.94	0.024
	Without asthma	Antimicrobials	30 days	0.73	0.55 – 0.98	0.039
			1 year	0.60	0.46 – 0.77	<0.001
		Corticosteroids	30 days	1.15	0.80 – 1.65	0.456
			one year	1.11	0.75 – 1.67	0.599

Abbreviations: COPD, chronic obstructive pulmonary disease; PS, propensity score; IPTW, inverse probability of treatment weighting; IRR, incident rate ratio; CI, confidence interval

Table S5. Baseline characteristics of COPD patients aged ≥ 40 years with and without ICS withdrawal, before and after 1-to-2 PS matching, and after stabilized IPTW

Characteristic (categorical)	All patients			1-to-2 PS matching			Stabilized IPTW		
	ICS withdrawal	Control	s.d.	ICS withdrawal	Control	s.d.	ICS withdrawal	Control	s.d.
	(N=1,091)	(N=3,307)	(%)	(N=1,016)	(N=3,069)	(%)	(N=872)	(N=2,591)	(%)
Sex (male)	82.0	77.0	-14.7	82.0	83.0	2.5	78.0	78.0	-0.2
Fiscal year									
2010	3.9	10.0	-24.0	3.9	4.2	-1.5	7.6	8.2	-2.0
2011	9.9	16.8	-20.2	9.9	10.2	-1.0	16.5	14.6	5.4
2012	13.7	20.1	-17.1	13.7	14.5	-2.4	19.6	17.7	4.8
2013	17.9	18.9	-2.6	17.9	17.2	1.9	15.7	18.5	-7.6
2014	24.9	19.6	12.8	24.9	25.8	-0.2	21.2	21.7	-1.3
2015	29.6	14.6	36.7	29.6	28.1	3.5	19.4	19.3	0.3
Season at admission									
Spring	23.4	24.7	-3.1	23.4	21.2	5.4	25.0	24.0	2.2
Summer	23.7	22.3	3.4	23.7	26.7	-6.9	23.2	23.3	-0.3
Autumn	24.5	22.9	3.8	24.5	26.2	-3.8	23.6	23.7	-0.4
Winter	28.3	30.1	-3.8	28.3	25.9	5.4	28.3	28.9	-1.4
Residential region									
Hokkaido and Tohoku	9.8	10.8	-3.0	9.8	8.3	5.3	8.6	10.8	-7.2
Kanto	31.3	35.2	-8.3	31.3	31.6	-0.6	36.1	33.7	5.1
Chubu	15.5	15.2	0.8	15.5	14.9	1.5	13.9	14.7	-2.2
Kansai	15.7	15.9	-0.5	15.7	14.4	3.9	14.8	15.6	-2.3
Chugoku, Shikoku, Kyushu, and Okinawa	27.7	22.9	10.9	27.7	30.8	-6.9	26.5	25.2	3.0
Hugh-Jones dyspnea score at admission									
1	11.8	10.0	5.8	11.8	12.3	-1.5	9.9	10.5	-2.1

2–3	33.3		32.9		0.8	33.3		35.6		-4.9	32.4		33.2		-1.7
4–5	45.4		50.9		-11.0	45.4		43.3		4.2	50.2		49.2		2.1
Missing	9.5		6.2		12.4	9.5		8.8		2.6	7.6		7.2		1.4
ADL at admission (Barthel Index score)															
100	39.4		40.0		-1.7	39.4		39.9		-1.1	36.6		40.0		-7.0
0–90	47.0		44.4		5.2	47.0		45.3		3.5	47.8		45.3		5.0
Missing	13.9		15.7		-5.0	13.6		14.8		-3.4	15.6		14.7		2.5
ADL at discharge (Barthel Index score)															
100	58.1		65.4		-15.2	58.1		57.2		1.8	59.3		62.9		-7.4
0–90	33.6		27.1		14.1	33.6		32.8		1.6	33.4		29.2		9.1
Missing	8.4		7.5		3.4	8.4		10.0		-5.6	7.3		7.9		-2.3
Smoking index															
200–599	9.0		9.8		-6.8	8.9		10.3		-5.0	9.7		10.0		-0.9
≥600	49.4		48.3		3.9	48.7		47.9		1.6	46.2		48.0		-3.6
Missing	41.6		41.9		-0.2	42.4		41.7		1.4	44.1		42.0		4.1
Characteristic (numerical)	Mean	SD	Mean	SD	s.d.	Mean	SD	Mean	SD	s.d.	Mean	SD	Mean	SD	s.d.
Age (years)	75.8	9.3	73.7	9.8	22.3	75.7	9.1	76.2	8.9	-5.2	75.1	9.4	74.2	9.8	8.9
Body mass index (kg/m ²)	20.5	3.9	21.4	4.2	-22.7	20.5	3.9	20.3	3.9	5.7	20.7	4.0	21.1	4.2	-8.1
Frequency of hospitalization before hospitalization for COPD exacerbation	0.86	1.4	0.57	1.2	20.9	0.87	1.4	0.93	1.9	-3.7	0.81	1.2	0.82	2.0	-0.7
Observation period before hospitalization for COPD exacerbation (days)	1048.4	579.5	837.4	569.0	35.9	1050.6	581.1	1032.9	602.5	3.0	903.3	572.0	910.2	588.6	-1.2

Abbreviations: ICS, inhaled corticosteroids; PS, propensity score; IPTW, inverse probability of treatment weighting; ADL, activities of daily living; COPD, chronic

obstructive pulmonary disease; s.d., standardized difference; SD, standard deviation

Table S6. Comorbidities during hospitalization and treatments for COPD with and without ICS withdrawal, before and after 1-to-2 PS matching, and after stabilized IPTW in patients aged ≥ 40 years

Comorbidity	All patients			1-to-2 PS matching			Stabilized IPTW		
	ICS withdrawal (N=971)	Control (N=2,764)	s.d. (%)	ICS withdrawal (N=904)	Control (N=1,808)	s.d. (%)	ICS withdrawal (N=872)	Control (N=2,591)	s.d. (%)
Lung cancer	0.14	0.08	20.6	0.14	0.16	-4.0	0.11	0.10	3.4
Other malignancy	0.10	0.06	12.4	0.10	0.11	-3.4	0.07	0.07	-1.2
Diabetes/abnormal glucose tolerance	0.21	0.21	0.8	0.21	0.23	-5.6	0.24	0.21	8.7
Bone fracture/osteoporosis	0.07	0.07	0.6	0.07	0.07	-1.5	0.06	0.07	-3.9
Interstitial pneumonia	0.12	0.05	25.2	0.12	0.11	0.5	0.07	0.07	2.3
Bronchial asthma	0.37	0.68	-64.6	0.37	0.39	-3.5	0.58	0.59	-1.5
Bronchiectasis	0.26	0.23	5.7	0.26	0.26	-0.4	0.22	0.23	-3.0
Pneumothorax	0.04	0.03	4.3	0.04	0.04	-1.7	0.04	0.04	2.1
Pulmonary thromboembolism	0.00	0.01	-4.4	0.00	0.00	-0.9	0.00	0.01	-0.2
<i>Mycobacterium</i> infection	0.03	0.01	10.5	0.03	0.03	-0.6	0.01	0.01	-0.8
Mycotic infection	0.02	0.02	-0.6	0.02	0.02	1.4	0.02	0.02	0.5
Cor pulmonale	0.02	0.02	1.0	0.02	0.02	3.7	0.02	0.02	1.5
Congestive heart failure	0.20	0.20	0.3	0.20	0.20	-0.2	0.21	0.20	1.7
Ischemic heart disease	0.13	0.12	2.7	0.13	0.14	-3.3	0.16	0.13	8.6
Tachycardia	0.11	0.09	5.7	0.11	0.10	3.4	0.10	0.10	-0.1
Autoimmune disease	0.05	0.03	7.7	0.05	0.03	6.9	0.04	0.04	2.9
Stroke	0.03	0.02	5.2	0.03	0.03	1.8	0.02	0.02	0.1
Liver dysfunction	0.03	0.02	5.2	0.03	0.03	-0.6	0.03	0.03	0.7
Renal failure	0.04	0.03	6.3	0.04	0.03	3.2	0.03	0.03	-1.7
GERD	0.20	0.23	-5.1	0.20	0.22	-3.5	0.23	0.23	-0.2
Constipation or ileus	0.16	0.14	4.8	0.16	0.18	-5.6	0.18	0.15	9.1
Prostate hypertrophy	0.10	0.09	4.3	0.10	0.11	-1.6	0.10	0.09	1.4
Treatment	×100 (%)	×100 (%)	s.d.	×100 (%)	×100 (%)	s.d.	×100 (%)	×100 (%)	s.d.

Before hospitalization									
Home ventilatory support	0.02	0.02	-1.3	0.02	0.02	-3.0	0.03	0.02	5.9
Home oxygen therapy	0.26	0.27	-2.6	0.26	0.26	-1.8	0.30	0.27	6.7
Both LAMA and LABA	0.24	0.20	10.5	0.24	0.22	-4.0	0.24	0.21	6.0
LAMA only	0.59	0.66	-13.5	0.59	0.58	2.4	0.65	0.65	0.3
LABA only	0.46	0.35	21.3	0.46	0.46	0.2	0.42	0.39	5.9
SABA or SAMA	0.43	0.58	-31.3	0.43	0.42	0.8	0.55	0.53	3.0
Theophylline	0.31	0.48	-36.2	0.31	0.30	2.6	0.45	0.43	4.3
Expectorants	0.75	0.76	-0.8	0.75	0.71	9.9	0.72	0.75	-7.0
Antibiotic prescriptions per 30 days	0.25	0.31	-9.6	0.25	0.22	5.6	0.28	0.29	-1.5
Macrolides per 30 days	0.12	0.19	-16.7	0.12	0.11	1.9	0.14	0.16	-3.7
TMP/SMX combination per 30 days	0.03	0.03	3.9	0.03	0.02	6.7	0.02	0.03	-2.6
Anti-MRSA drugs per 30 days	0.00	0.00	5.5	0.00	0.00	1.8	0.00	0.00	2.1
Antifungal agent per 30 days	0.00	0.00	3.1	0.00	0.00	-4.5	0.00	0.00	3.8
Medication for flu per 30 days	0.00	0.00	-5.1	0.00	0.00	0.4	0.00	0.00	-1.5
Oral corticosteroids per 30 days	0.12	0.20	-16.7	0.12	0.12	0.1	0.16	0.17	-1.9
i.v. corticosteroids per 30 days	0.06	0.16	-15.4	0.06	0.07	-3.4	0.11	0.14	-3.5
At and during hospitalization									
Ambulance transport	0.22	0.23	-3.1	0.22	0.21	2.5	0.21	0.23	-3.9
ICU admission	0.01	0.03	-7.6	0.01	0.02	-3.8	0.03	0.03	2.2
Corticosteroids	0.39	0.61	-45.1	0.39	0.37	3.4	0.52	0.54	-3.9
Aminoglycosides	0.01	0.01	-2.7	0.01	0.01	-4.4	0.01	0.01	-3.9
Carbapenems	0.14	0.13	3.4	0.14	0.15	-2.1	0.15	0.13	5.1
Anti-MRSA drugs	0.02	0.01	5.6	0.02	0.03	-4.3	0.04	0.02	12.2
Macrolides	0.24	0.34	-20.9	0.24	0.25	-1.7	0.29	0.30	-2.0
Fluoroquinolones	0.29	0.30	-1.3	0.29	0.29	0.5	0.30	0.29	1.3
Mechanical ventilation	0.06	0.06	-1.6	0.06	0.07	-5.6	0.09	0.07	7.8
Hemodialysis	0.01	0.01	6.4	0.01	0.01	4.5	0.01	0.01	-1.1
Nasal tube feeding	0.01	0.01	3.3	0.01	0.02	-4.1	0.03	0.01	12.9

Surgery under general anesthesia	0.00	0.01	-0.9	0.00	0.00	1.5	0.00	0.01	-2.9	
Prescription of LABA/LAMA	0.05	0.01	24.9	0.05	0.04	5.4	0.02	0.03	-2.8	
Prescription of LAMA	0.25	0.60	-75.1	0.25	0.25	0.2	0.50	0.50	0.4	
Prescription of LABA	0.26	0.19	16.7	0.26	0.27	-0.8	0.26	0.22	9.1	
Discharge to home	0.93	0.97	-21.1	0.93	0.92	3.1	0.94	0.95	-1.1	
Treatment (numerical)	Mean	SD	Mean	SD	s.d.	Mean	SD	Mean	SD	s.d.
Length of stay	19.2	19.6	18.8	15.9	3.4	19.3	19.9	20.3	18.0	-5.6
	19.1	20.8	19.0	15.4	4.8					

Abbreviations: PS, propensity score; IPTW, inverse probability of treatment weighting; GERD, gastro-esophageal reflux disease; ICS, inhaled corticosteroids; LAMA, long-acting muscarinic receptor antagonist; LABA, long-acting beta agonist; LABA/LAMA; fixed-dose long-acting bronchodilator combination in single inhaler; SABA, short-acting beta-agonist; SAMA, short-acting muscarinic receptor antagonist; TMP/SMX, trimethoprim-sulfamethoxazole combination; i.v., intravenous injection; ICU, intensive care unit; MRSA, methicillin-resistant *Staphylococcus aureus*; s.d., standardized difference; SD, standard deviation

Table S7. HRs and 95% CIs of re-hospitalization for COPD exacerbation or death after 1-to-2 PS matching and stabilized IPTW in the ICS withdrawal group versus control group in patients aged ≥ 40 years

		Re-hospitalization or death				
	Study population	ICS withdrawal	Control	HR	95% CI	P
1-to-2 PS matching	All	1,016	2,032	0.74	0.61–0.91	0.005
	≥ 70 years	784	1,591	0.70	0.55–0.89	0.003
	< 70 years	232	441	0.95	0.64–1.40	0.786
Stabilized IPTW	All	931	3,162	0.75	0.61–0.94	0.012
	≥ 70 years	680	2,273	0.65	0.50–0.84	0.001
	< 70 years	251	890	1.11	0.73–1.70	0.627

Abbreviations: PS, propensity score; ICS, inhaled corticosteroids; COPD, chronic obstructive pulmonary disease; IPTW, inverse probability of treatment weighting; HR, hazard ratio; CI, confidence interval

Table S8. IRRs and 95% CIs for post-discharge frequency of outpatient antimicrobial and corticosteroid prescriptions in two age groups (≥ 70 years vs. < 70 years) after 1-to-2 PS matching and stabilized IPTW in the ICS withdrawal group versus control group in the sensitivity analyses for COPD patients aged ≥ 40 years

			Observation period	IRR	95% CI	P
1-to-2 PS matching	≥ 70 years	Antimicrobials	30 days	0.82	0.62–1.09	0.168
			1 year	0.64	0.50–0.83	0.001
		Corticosteroids	30 days	0.96	0.65–1.44	0.860
			1 year	0.71	0.53–0.96	0.028
	< 70 years	Antimicrobials	30 days	1.47	0.90–2.41	0.124
			1 year	0.94	0.64–1.41	0.793
		Corticosteroids	30 days	1.34	0.86–2.10	0.192
			1 year	1.02	0.68–1.55	0.909
Stabilized IPTW	≥ 70 years	Antimicrobials	30 days	0.93	0.62–1.40	0.718
			1 year	0.63	0.49–0.83	0.001
		Corticosteroids	30 days	0.95	0.64–1.41	0.814
			one year	0.70	0.50–0.98	0.036
	< 70 years	Antimicrobials	30 days	0.89	0.63–1.28	0.553
			1 year	0.68	0.48–0.95	0.025
		Corticosteroids	30 days	1.11	0.75–1.64	0.616
			1 year	0.77	0.50–1.19	0.242

Abbreviations: COPD, chronic obstructive pulmonary disease; PS, propensity score; IPTW, inverse probability of treatment weighting; IRR, incident rate ratio; CI, confidence interval

FIGURE LEGENDS

Figure S1. Cumulative hazard curves for hospitalization for re-exacerbation or death after hospitalization for exacerbation in patients with chronic obstructive pulmonary disease (COPD) aged ≥ 65 years with or without ICS withdrawal. Results for **(A)** 1-to-2 propensity score-matched population; and **(B)** stabilized inverse probability of treatment weighted population. ICS, inhaled corticosteroids

Figure S2. Cumulative hazard curves for hospitalization for re-exacerbation or death after hospitalization for exacerbation in patients with chronic obstructive pulmonary disease (COPD) aged ≥ 40 years with or without ICS withdrawal. Results for the 1-to-2 propensity score-matched population are shown. **(A)** All patients. **(B)** Patients aged ≥ 70 years. **(C)** Patients aged < 70 years. ICS, inhaled corticosteroids

Figure S3. Cumulative hazard curves for hospitalization for re-exacerbation or death after hospitalization for exacerbation in patients with chronic obstructive pulmonary disease (COPD) aged ≥ 40 years with or without ICS withdrawal. Results for the stabilized inverse probability of treatment weighted population are shown. **(A)** All patients. **(B)** Patients aged ≥ 70 years. **(C)** Patients aged < 70 years. ICS, inhaled corticosteroids