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ORIGINAL RESEARCH

Respiratory Specialist Visits Before Admissions with COPD Exacerbation are Linked to Improved Management and Outcomes

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Purpose: Exacerbations of COPD (ECOPD) significantly impact disease progression and mortality. Visiting a respiratory specialist (RS) in proximity to the exacerbation may lead to prompt treatment and improved outcomes. We aimed to evaluate the association between an RS visit 30-days before admission and exacerbation outcomes.

Patients and methods: The prospective study included subjects that were hospitalized with ECOPD between 2017 and 2019 in 13 medical centers. Pre-admission, in-hospital, and 30-day outcomes were assessed and compared between patients with and without a 30-day RS visit, using propensity score matching. A sub-group analysis was performed based on the reason for the RS visit (emergent vs regular follow-up).

Results: Three hundred and forty-four subjects were included, and 105 (31%) had pre-admission RS visit (RS group). Before matching, indicators of severe COPD were prevalent in the RS group, while after matching there were no differences. RS visits were associated with pre-hospital initiation of short acting bronchodilators (50% vs 36%), antibiotics (30% vs 17%), and systemic steroids (38% vs 22%). The RS group had longer duration between first symptoms to hospital arrival (median 5 vs 3 days, $p < 0.01$) and shorter hospital length-of-stay (median 4 vs 5 days, $p = 0.04$). In-hospital and 30-days outcomes were similar between the groups. However, a non-emergent pre-hospital RS visit was associated with improved in-hospital and 30-day outcomes.

Conclusion: Routine RS visits could lead to correct and early treatment for ECOPD with a potential for improved outcomes. These findings highlight the need for available specialists and higher awareness.

Keywords: clinic, pulmonologist, bronchodilators, admission, diagnosis

Introduction

Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality.[1,2] While considered a chronic disease, a substantial number of patients suffer from exacerbations of COPD (ECOPD),[3,4] which frequently leads to hospital admission and to a negative impact on disease progression and mortality.[4,5] Research from recent years indicates that standard of care pharmacological and non-pharmacological long-term interventions offer opportunities to reduce exacerbations, hospitalizations, and readmissions for patients with COPD.[1,6,7] For example, treatment with triple inhaler therapy in patients with previous ECOPD was shown to be associated with improved outcomes including survival.[8,9] Although treatments specifically for ECOPD, such as short acting bronchodilators (SABD) and systemic steroids, are not considered to be associated with improvement in long-term outcomes,[10] their prompt initiation is of importance. Studies have shown that early recognition of ECOPD and initiation of treatment improves recovery and reduces the risk of hospitalization.[11,12] This aspect is especially problematic among patients and health care providers with low awareness to the disease[13] or patients deciding not to seek medical advice when new symptoms occur.

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For the reasons above, respiratory specialists (RS) have a main role in disease management, both before and during exacerbations, providing education and correct care.[14–16] The possible effects of RS follow-up after ECOPD on disease outcomes were evaluated by different studies.[4,12,17] For example, Gavish et al found a higher readmission rate among patients without an RS follow-up[12]. Still, research evaluating the significance of an RS visit before admission with ECOPD is scarce. We hypothesized that an RS visit during the short term before admission with an exacerbation could be associated with an early recognition of the event by the patients, increase the availability and use of an at-home "treatment bundle", and possibly lead to better outcomes. Therefore, we aimed to evaluate the associations between an RS visit 30-days before admission and exacerbation outcomes.

Methods

This is a prospective observational study performed in 13 medical centers across Israel between 2017 and 2019, as part of the COPD Israeli survey (COPDIS), which was discussed in detail before.[17,18] In summary, subjects admitted with ECOPD at one of the centers were approached for participation. To be included, the diagnosis of ECOPD had to be the primary admission diagnosis and verified by a respiratory specialist before enrollment. All subjects signed informed consent, completed a structured interview, and were followed during their hospitalization and 30-days after. Diagnostic criteria for COPD was a prior result of post-bronchodilator FEV1/FVC < 0.7, combined with respiratory symptoms documented by the patient or at prior medical visit. In the few cases with high suspicion but no available spirometry results, a prior pulmonologist visit that described an obstructive pattern and initiated a relevant inhaler therapy was also considered diagnostic.

The study was conducted in accordance with the declaration of Helsinki and approved by each center's institutional ethical committee. The study was performed according to STROBE guidelines.

Study Variables

The structured interviews were questionnaires performed by one of the research teams and were based on a case report form (CRF). They were comprised of questions regarding baseline and COPD-related characteristics. In cases of uncertainty, answers were validated by data from medical records. Baseline characteristics included sex, age, and comorbidities. COPD-related characteristics included long-acting inhaler treatments, prior pulmonologists visits, modified Medical Research Council (mMRC) and CAT scores (addressing their pre-exacerbation condition), and pre-admission variables, such as 30-days RS visit before admission (and reason for visit), time from symptoms to hospitalization, and home treatment initiated for ECOPD.

Clinical variables (investigations, management, and outcomes) were extracted during the hospitalization. Spirometry was not performed as part of the COPDIS, as it is not performed during exacerbations and COPDIS was an observational trial. For this work, prior forced expiratory volume in the first second (FEV1) results were only available from tests performed within the participating centers, without available access to analyze ambulatory tests. Finally, two exacerbation severity scores were calculated to validate the robustness of our matching. This analysis includes the BAP-65[19] (BUN, altered mental status, and tachycardia) and DECAF[20] scores, both validated to predict in-hospital outcomes and were without missing values in our cohort.

Pre-hospital outcomes included the initiation of ECOPD-related treatments at home by the patient and the duration from first respiratory symptoms to hospital arrival. The composite of in-hospital mortality, intubation, and transfer to the intensive care unit (ICU) was termed "in-hospital outcomes". The hospital length of stay (LOS) was analyzed as well. The composite of 30-day mortality and/or readmission was termed "30-day outcomes". Mortality was collected from an electronic database which is updated based on the Israel National death registry. Readmissions were evaluated by the research team 30-days after discharge by a follow-up call (n = 234) or by medical records when a patient was unavailable.

Statistical Analysis

Characteristics of the study cohort were compared between the subjects with an RS visit (RS group) and without (control). Continuous variables were presented as median (inter-quartile range, IQR) and compared using Mann–Whitney

test. Categorical variables were presented as total (percentage) and compared using Chi-square test. We hypothesized that there would be significant differences in baseline variables between the groups, and therefore a propensity score matching was performed using the nearest neighbor algorithm in a 1:1 ratio. The matching was based on age, sex, Charlson comorbidity score, history of heart failure, obstructive sleep apnea (OSA), prior ECOPD, mMRC above 1, and use of home oxygen. These variables were chosen by the research team based on their clinical relevance and their difference between the groups. Matching was restricted by a caliper distance of 0.01 without replacement. Outcomes were compared after matching. To further analyze the associations between RS visits and outcomes, we performed a sub-analysis, dividing the RS group between emergent visits for the ECOPD and those as part of a routine follow-up. Predictors for 30-day outcomes were assessed by logistic multivariate regression model. This model included variables found to be significant based on univariate analysis. All analyses were performed by SPSS version 28.0.

Results

The study cohort included 344 subjects, 105 (31%) visited an RS in the 30 days before admission (RS group), while 239 (69%) did not (control), as shown in Figure 1. The overall median age (IQR) was 71 (63–78), 38% were female, and 88% had ≥10 pack years smoking history. Of those with an RS visit, 45 (43%) had a routine follow-up visit, while 60 (57%) visited due to worsening symptoms as part of the ECOPD.

Comparison of baseline characteristics between the groups, before and after propensity score matching, appears in Table 1. Before matching, age and sex were similar between the groups, while the RS group had higher rates of history of heart failure, OSA, prior COPD exacerbation, an mMRC score above 1, and home oxygen use ($p < 0.01$ for all). Baseline inhaler therapy was also different before matching, with more patients using long-acting inhalers in the RS group (82% vs 60%). FEV1 was available for 248 patients, and was lower in the RS group before matching (median [IQR] 57 [36–68] vs 66 [50–78] %predicted). After matching, there were no differences in any of the baseline characteristics. In addition, all exacerbation-related variables, including the DECAF and BAP-65 scores were similar between the matched groups.

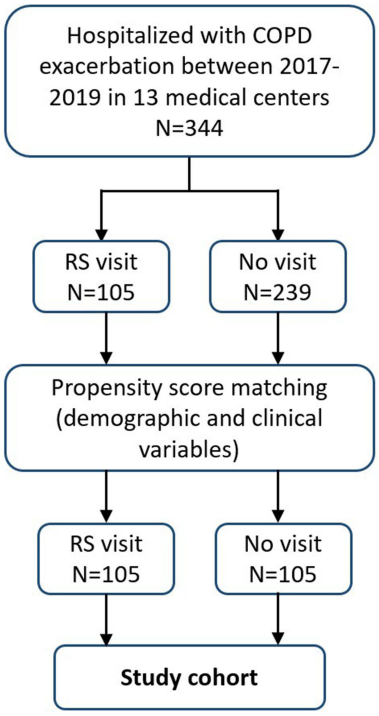

Figure 1 Study inclusion process. RS, respiratory specialist.

Table 1 Baseline Characteristics Compared Between Patients with and without 30-Day Pre-Admission RS Visit, Before and After Propensity Matching

Variable	RS Visit n=105 (%)	Unmatched Cohort		Matched Cohort	
		No Visit n=239 (%)	P^1	No Visit n=105 (%)	P^2
Age	71 (64–77)	71 (63–78)	0.84	71 (65–80)	0.47
Female sex	45 (43)	84 (35)	0.17	40 (38)	0.48
Smoking					
Past	61 (58)	111 (46)	0.07	53 (51)	0.43
Current	40 (38)	117 (49)		45 (43)	
Charlson score	5 (4–7)	5 (3–7)	0.28	6 (4–7)	0.44
Obese (BMI>30)	38 (36)	76 (32)	0.43	37 (35)	0.89
Heart failure	34 (32)	41 (17)	<0.01	30 (29)	0.55
OSA	20 (19)	18 (8)	<0.01	13 (12)	0.19
Pre-exacerbation treatment:					
Not using long-term inhaler	19 (18)	95 (40)	<0.01	34 (32)	0.08
LAMA	26 (25)	35 (14)		18 (17)	
ICS-LABA	21 (20)	51 (21)		26 (25)	
LAMA-LABA	19 (18)	30 (13)		12 (11)	
Triple therapy	20 (19)	28 (12)		15 (14)	
Prior COPD exacerbation	90 (86)	153 (64)	<0.01	93 (89)	0.40
FEV1, %predicted[a]	57 (36–68)	66 (50–78)	0.01	60 (41–71)	0.45
MMRC >1	90 (86)	155 (65)	<0.01	88 (84)	0.70
CAT score[b]	15 (10–23)	14 (10–23)	0.63	16 (10–24)	0.72
Home oxygen use	55 (52)	83 (35)	<0.01	54 (51)	0.89
Exacerbation-related variables					
Saturation <91%	61 (59)	129 (54)	0.40	66 (63)	0.48
DECAF risk score:			<0.01		0.57
Low	40 (38)	122 (51)		40 (38)	
Intermediate	26 (25)	69 (29)		32 (31)	
High	39 (37)	48 (20)		33 (31)	
BAP-65			0.54		0.56
1–2	75 (71)	160 (67)		67 (64)	
3	28 (27)	72 (30)		35 (33)	
4–5	2 (2)	8 (3)		3 (3)	
Blood eosinophils, cells/μL[c]	150 (0–200)	120 (0–200)	0.24	100 (0–200)	0.14
First CRP> 10 mg/L	54 (51)	92 (38)	<0.01	50 (48)	0.58

Notes: *P^1 – p-value for comparison in the non-matched cohort. P^2 – p- value for comparison in the matched cohort.* [a]Missing data for 28 patients in the RS group, 68 in the unmatched group, and 23 in the matched group. [b]Patients were asked to base their answers on their pre-exacerbation condition. Missing data for 22 patients in the unmatched group. [c]First blood eosinophil count result taken in the emergency department.

Abbreviations: CAT, COPD assessment test; FEV1, forced expiratory volume in the first second; ICS, inhaled corticosteroid; LABA, long-acting beta agonist; LAMA, long-acting muscarinic antagonist; MMRC, modified Medical Research Council; OSA, obstructive sleep apnea; RS, respiratory specialist.

Analysis of pre-hospital treatment, initiated by each subject at home, appears in Table 2. The RS group had higher rates of pre-hospital treatment, including short-acting bronchodilators (50% vs 36%, p = 0.04), antibiotics (30% vs 17%, p = 0.03), and systemic steroids (38% vs 22%, p = 0.01).

The duration between first respiratory symptoms to hospital arrival was longer in the RS group compared to the matched control group (median 5 [2–7] vs 3 [2–5] days, p < 0.01, Figure 2). The RS group also had shorter hospital LOS compared to the matched control group (median 4 [3–6] vs 5 [3–7] days, p = 0.04, Figure 2).

Twenty-four subjects (11%) had an in-hospital outcome, which was lower in the RS group, although not statistically significant (9% vs 14%, p = 0.13). Forty-four subjects (21%) had a 30-day adverse outcome, with similar rates between the groups (20% vs 22%). In a sub-group analysis (Figure 3), seeing an RS as part of a routine follow-up was associated

Table 2 Pre-Hospital Treatment and Exacerbation Outcomes Between Patients with and without 30-Day RS Visit Following Matching

Variable	RS Visit n=105 (%)	No Visit n=105 (%)	*P*
Home SABD	53 (50)	38 (36)	**0.04**
Home ICS	14 (13)	7 (7)	0.11
Home systemic steroids	40 (38)	23 (22)	**0.01**
Home antibiotics	31 (30)	18 (17)	**0.03**
In-hospital outcomes[a]	9 (9)	15 (14)	0.13
30-day outcomes[b]	21 (20)	23 (22)	0.73

Notes: Bold p-values stand for statistically significant results. [a]Includes in-hospital mortality, intubation, and transfer to the intensive care unit. [b]Includes 30-day mortality and re-admission.
Abbreviations: RS, respiratory specialist; SABD, short-acting bronchodilators; ICS, inhaled corticosteroids.

with a lower rate of in-hospital outcomes (2.2% vs 14%, p = 0.048) and 30-day outcomes (8.9% vs 22%, although not statistically significant, p = 0.056) compared to the control group. There were no differences in outcomes between the emergent RS visit and the control group.

We evaluated independent predictors for the composite 30-day outcomes, to identify subjects that have the highest potential to benefit from an early post-hospital RS visit (Table 3). Independent predictors for 30-day outcomes were prior ECOPD (adjusted OR 6.24, 95% CI 1.79–21.7, p < 0.01), in-hospital use of bi-level positive airway pressure (AOR 2.16, 95% CI 1.13–4.11, p = 0.02), and acute kidney injury during hospitalization (AOR 2.39, 95% CI 1.06–5.38, p = 0.04).

Discussion

In this study, by analyzing a prospective multicenter cohort of hospitalized subjects with ECOPD coupled with a propensity score matching, we assessed the potential impact of a RS visits during the 30 days before admission. We found that prior RS visits were associated with a longer duration between the first ECOPD symptoms to hospitalization and with higher rates of correct home-treatment. Subjects with prior RS visits also had shorter hospitalizations. Subjects with routine RS visit had improved outcomes, while there was no difference in outcomes among subjects with an emergent RS visits (for the ECOPD). Finally, we evaluated independent predictors for 30-day adverse outcomes, to better identify those that could possibly benefit from an early RS visit post-hospitalization.

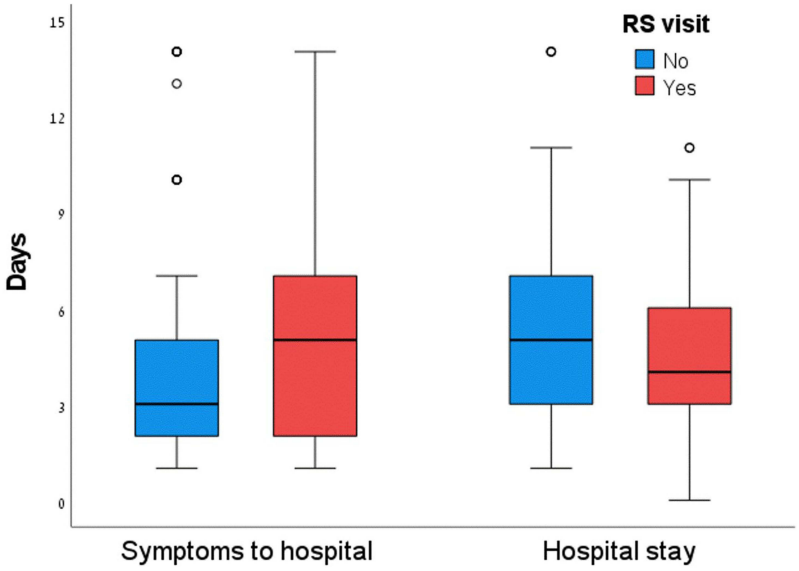

Figure 2 Time from first respiratory symptoms to hospital arrival and duration of hospital stay, compared between patients with and without prior 30-day RS visit.
Abbreviation: RS, respiratory specialist.

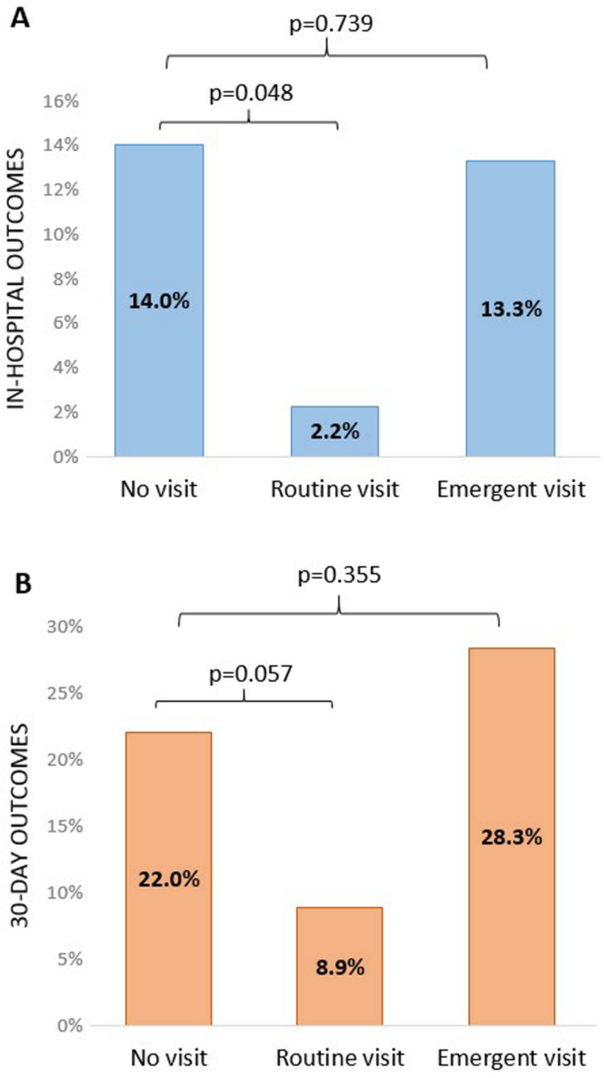

Figure 3 Sub-group analysis based on the reason for the RS visit (emergent or routine follow-up) for their association with in-hospital outcomes (panel (**A**)) and 30-days outcomes (panel (**B**)).

Prior to matching, subjects with prior RS visits had significantly higher prevalence of comorbidities and more severe COPD-related characteristics. Previous studies have shown that these variables are strong negative prognostic factors, associated with more ECOPD and hospitalizations.[21–24] That said, subjects with prior RS visits still had similar or better outcomes compared to others. This likely indicates better ambulatory treatment among those visited a specialist, which could prevent further complications or prolonged hospital stay. Moreover, the longer duration between first symptoms and hospital arrival in the RS group supports the assumption of proper ambulatory self-management. As these patients received better ambulatory treatment and still require admission, they may also represent a more severe acute disease, which further highlights the findings of our study.

By focusing on hospitalized patients, we could not evaluate the associations of RS visits in patients with ECOPD that improved and did not require hospitalization. Still, evidence exists on the general impact of RS in patients with COPD.[12] A national medical review conducted in South Korea found out that the rates of COPD exacerbation requiring admission to a general ward, emergency room, or intensive care unit were significantly lower in those with frequent outpatient visits.[25] There is also evidence that COPD care solely by a general practitioner (GP) is inferior to that by a pulmonologist. A randomized controlled trial by Aaron et al showed that an intervention by pulmonologist compared to usual care by GP (notified for the presence of COPD) resulted in lower respiratory-related health care utilization,

Table 3 Predictors for 30-Day Mortality or Readmission

Variable	Univariate		Multivariate	
	OR (95% CI)	p	AOR (95% CI)	p
Age	1.01 (0.99–1.04)	0.41	–	–
Gender	1.07 (0.59–1.95)	0.82	–	–
Charlson score	1.15 (1.02–1.31)	0.03	1.02 (0.89–1.17)	0.79
Obese	1.17 (0.63–2.15)	0.62	–	–
Prior ECOPD	8.68 (2.64–28.5)	<0.01	6.24 (1.79–21.7)	**<0.01**
MMRC >1	3.78 (1.56–9.14)	<0.01	2.35 (0.92–5.98)	0.07
Home oxygen	1.93 (1.07–3.46)	0.03	0.93 (0.48–1.81)	0.84
In-hospital oxygen	1.73 (0.91–3.29)	0.09	–	–
In-hospital BiPAP	2.78 (1.54–5.02)	<0.01	2.16 (1.13–4.11)	**0.02**
Acute kidney injury[a]	2.73 (1.34–5.54)	<0.01	2.39 (1.06–5.38)	**0.04**

Notes: Bold p-values stand for statistically significant results. [a]Defined as an increase in creatinine of ≥0.3 mg/dL from baseline.

Abbreviations: ECOPD, exacerbation of COPD; MMRC, Modified Medical Research Council; BiPAP, bi-level positive airway pressure.

improved symptoms and a higher increase in FEV1.[26] Garcia-Aymerich et al described the results of a questionnaire among patients with COPD exacerbations and showed lower rates of pharmacological and non-pharmacological treatments in patients managed by their GP and not a pulmonologist, while their disease severity was similar.[27]

Visits with RS should generally include patient education, focusing on early recognition of exacerbation, correct inhaler use, and when to seek help.[1] These factors were also chosen in a large Delphi study described by Korpershoek et al as behaviors that reduce exacerbations and their major impact on patients.[28] We unfortunately did not evaluate if patients were educated for an action plan or the interventions performed during clinic visits, although the improved prehospital treatment could indicate on such practice. Previous studies have shown that early detection of ECOPD and treatment initiation improve recovery and reduce the risk of hospitalizations.[11,12] The interaction with an RS could also facilitate self-management interventions that were found to lower respiratory-related hospital admissions.[29] Care provided by RS was shown in a systematic review from 2018 to yield direct and indirect cost reductions.[30] Considering these positive associations, there are still major gaps in the availability of RS that present a major barrier for patients.[31] This issue must be a top priority of policy makers, especially given the high rate of burnout among pulmonologists, that will only grow without adequate interventions.[32]

By evaluating 30-day outcomes (readmissions and death) after discharge, we have identified certain independent predictors to signify patients that could best benefit from an early RS visit. Similar to our findings, having recurrent exacerbations are a well-described risk factor for early adverse-events, resulting in shorter time to exacerbation and increased mortality with every additional exacerbation.[33,34] In comparison, acute kidney injury (AKI) is a less known risk factor for adverse outcomes after ECOPD, although its prognostic value is well documented in other conditions.[35] These at-risk patients could benefit from an early post-discharge follow-up and more frequent clinic visits. Predicting which patient will exacerbate is not easy, yet it could assist in personalizing the follow-up plan. Still, it is not enough, as many patients will exacerbate without seeing a pulmonologist in the months before. For these cases, flare-up clinics, available for early and fast evaluations to patients experiencing worsening respiratory symptoms, might have a similar effect, although it remains to be evaluated.

This study has limitations. First, as mentioned above, only hospitalized patients were included, a fact that limits the ability to evaluate the general impact of RS visits. Studying only hospitalized subject's likely leads to selection bias of the more severe cases, which the matching process could not entirely account for. Second, the study considered all pre-admission RS visits without isolating the specific recommendations given during the visit and the time prior to the ECOPD, which were beyond the scope of the present analysis. Third, although most clinical variables were collected prospectively, there are missing data for lung functions (which were collected retrospectively) and the study was not controlled for the RS visit, hence, could not infer on causality. There is a need to further study COPD patients from the ambulatory setting by controlled trials, in order to better evaluate the impact of RS visits on exacerbations.

Conclusions

Our study demonstrates that an early RS visit before ECOPD is associated with improved exacerbation characteristics and outcomes. This stresses the importance of making RS follow-ups available in the community and raising awareness to their importance. Further high-quality research in this field is needed to affect healthcare decision makers and introduce accessible RS clinics for subjects with high risk for exacerbations or new worsening symptoms.

Data Sharing Statement

The authors confirm that the data supporting the findings of this study are available within the article.

Ethics Approval and Consent to Participate

The study was approved by the institutional review board of each included center (Sourasky medical center, Hadassah medical center, Carmel medical center, Galilee medical center, Rabin medical center, Rambam medical center, Soroka medical center, Poriya medical center, Shaare Zedek medical center, Sheba medical center, Shamir medical center, Barzilai medical center). It was conducted in accordance with the local legislation and institutional requirements. All participants signed informed consent.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

A.B.S reports receiving personal consulting fees and lecture fees from Sanofi-Regeneron, Astrazeneca, GSK, Kamada, Boehringer Ingelheim, Roche. A.U reports personal fees from Kamada, and Boehringer-Ingelheim, outside the submitted work. All other authors report no conflicts of interest in this work.

References

1. GOLD. Global initiative for chronic obstructive lung. *Guide Health Care Prof*. 2023;1(3):261–266.
2. Safiri S, Carson-Chahhoud K, Noori M, et al. Burden of chronic obstructive pulmonary disease and its attributable risk factors in 204 countries and territories, 1990–2019: results from the global burden of disease study 2019. *BMJ*. 2022:e069679. doi:10.1136/bmj-2021-069679
3. Viniol C, Vogelmeier CF. Exacerbations of COPD. *Eur Respir Rev*. 2018;27(147):170103. doi:10.1183/16000617.0103-2017

4. Urwyler P, Abu Hussein N, Bridevaux PO, et al. Predictive factors for exacerbation and re-exacerbation in chronic obstructive pulmonary disease: an extension of the Cox model to analyze data from the Swiss COPD cohort. *Multidiscip Respir Med*. 2019;14(1):1–9. doi:10.1186/s40248-019-0168-5
5. Lüthi-Corridori G, Boesing M, Roth A, et al. Predictors of length of stay, rehospitalization and mortality in community-acquired pneumonia patients: a retrospective cohort study. *J Clin Med*. 2023;12(17). doi:10.3390/jcm12175601
6. Bollmeier SG, Hartmann AP. Management of chronic obstructive pulmonary disease: a review focusing on exacerbations. *Am J Health Syst Pharm*. 2020;77(4):259–268. doi:10.1093/ajhp/zxz306
7. Nici L, Aaron SD, Alexander PE, et al. Pharmacologic management of chronic obstructive pulmonary disease an official American thoracic society clinical practice guideline. *Am J Respir Crit Care Med*. 2020;201(9):E56–E69. doi:10.1164/RCCM.202003-0625ST
8. Lipson DA, Barnhart F, Brealey N, et al. Once-daily single-inhaler triple versus dual therapy in patients with COPD. *N Engl J Med*. 2018;378 (18):1671–1680. doi:10.1056/NEJMoa1713901
9. Rabe KF, Martinez FJ, Ferguson GT, et al. Triple inhaled therapy at two glucocorticoid doses in moderate-to-very-severe COPD. *N Engl J Med*. 2020;383(1):35–48. doi:10.1056/NEJMoa1916046
10. Venkatesan P. GOLD COPD report: 2024 update. *Lancet Respir Med*. 2024;12(1):15–16. doi:10.1016/S2213-2600(23)00461-7
11. Wilkinson TMA, Donaldson GC, Hurst JR, Seemungal TAR, Wedzicha JA. Early therapy improves outcomes of exacerbations of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2004;169(12):1298–1303. doi:10.1164/rccm.200310-1443OC
12. Gavish R, Levy A, Dekel OK, Karp E, Maimon N. The association between hospital readmission and pulmonologist follow-up visits in patients with COPD. *Chest*. 2015;148(2):375–381. doi:10.1378/chest.14-1453
13. Baiardini I, Contoli M, Corsico AG, et al. Exploring the relationship between disease awareness and outcomes in patients with chronic obstructive pulmonary disease. *Respiration*. 2021;100(4):291–297. doi:10.1159/000513953
14. Sharif R, Cuevas CR, Wang Y, Arora M, Sharma G. Guideline adherence in management of stable chronic obstructive pulmonary disease. *Respir Med*. 2013;107(7):1046–1052. doi:10.1016/j.rmed.2013.04.001
15. Jain VV, Allison R, Beck SJ, et al. Impact of an integrated disease management program in reducing exacerbations in patients with severe asthma and COPD. *Respir Med*. 2014;108(12):1794–1800. doi:10.1016/j.rmed.2014.09.010
16. Freund O, Elhadad L, Tiran B, et al. Routine in-hospital interventions during acute exacerbation of COPD are associated with improved 30-day care. *Heart Lung J Cardiopulm Acute Care*. 2024;67:114–120. doi:10.1016/j.hrtlng.2024.05.001
17. Bar-Shai A, Freund O, Ovdat T, Segel MJ, Klempfner R, Elis A. Management of acute COPD exacerbations in the internal medicine departments in Israel–a national survey. *Front Med*. 2023;10(August):1–8. doi:10.3389/fmed.2023.1174148
18. Freund O, Melloul A, Fried S, et al. Management of acute exacerbations of COPD in the emergency department and its associations with clinical variables. *Intern Emerg Med*. 2024. doi:10.1007/s11739-024-03592-w
19. Tabak YP, Sun X, Johannes RS, Gupta V, Shorr AF. Mortality and need for mechanical ventilation in acute exacerbations of chronic obstructive pulmonary disease: development and validation of a simple risk score. *Arch Intern Med*. 2009;169(17):1595–1602. doi:10.1001/archinternmed.2009.270
20. Echevarria C, Steer J, Heslop-Marshall K, et al. Validation of the DECAF score to predict hospital mortality in acute exacerbations of COPD. *Thorax*. 2016;71(2):133–140. doi:10.1136/thoraxjnl-2015-207775
21. Gulea C, Zakeri R, Quint JK. Differences in outcomes between heart failure phenotypes in patients with coexistent chronic obstructive pulmonary disease: a cohort study. *Ann Am Thorac Soc*. 2022;19(6):971–980. doi:10.1513/AnnalsATS.202107-823OC
22. Adler D, Bailly S, Benmerad M, et al. Clinical presentation and comorbidities of obstructive sleep apnea-COPD overlap syndrome. *PLoS One*. 2020;15(7):e0235331. doi:10.1371/journal.pone.0235331
23. McNicholas W, Kent M. Hypoxemia in patients with COPD: cause, effects, and disease progression. *Int J Chron Obstruct Pulmon Dis*. 2011;199. doi:10.2147/COPD.S10611
24. Lenoir A, Whittaker H, Gayle A, Jarvis D, Quint JK. Mortality in non-exacerbating COPD: a longitudinal analysis of UK primary care data. *Thorax*. 2023;78(9):904–911. doi:10.1136/thorax-2022-218724
25. Park HJ, Byun MK, Kim T, et al. Frequent outpatient visits prevent exacerbation of chronic obstructive pulmonary disease. *Sci Rep*. 2020;10 (1):6049. doi:10.1038/s41598-020-63064-x
26. Aaron SD, Vandemheen KL, Whitmore GA, et al. Early diagnosis and treatment of COPD and asthma—a randomized, controlled trial. *N Engl J Med*. 2024;390(22):2061–2073. doi:10.1056/NEJMoa2401389
27. Garcia-Aymerich J, Escarrabill J, Marrades RM, Monsó E, Barreiro E, Antó JM. Differences in COPD care among doctors who control the disease: general practitioner vs. pneumologist. *Respir Med*. 2006;100(2):332–339. doi:10.1016/j.rmed.2005.04.021
28. Korpershoek YJ, Bruins Slot JC, Effing TW, Schuurmans MJ, Trappenburg JC. Self-management behaviors to reduce exacerbation impact in COPD patients: a Delphi study. *Int J Chron Obstruct Pulmon Dis*. 2017;12:2735–2746. doi:10.2147/COPD.S138867
29. Schrijver J, Lenferink A, Brusse-Keizer M, et al. Self-management interventions for people with chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2022;1(1):CD002990. doi:10.1002/14651858.CD002990.pub4
30. Becker EA, Hoerr CA, Wiles KS, Skees DL, Miller CH, Laher DS. Utilizing respiratory therapists to reduce costs of care. *Respir Care*. 2018;63 (1):102–117. doi:10.4187/respcare.05808
31. Obaseki D, Adeniyi B, Kolawole T, Onyedum C, Erhabor G. Gaps in capacity for respiratory care in developing countries. Nigeria as a case study. *Ann Am Thorac Soc*. 2015;12(4):591–598. doi:10.1513/AnnalsATS.201410-443AR
32. Ligibel JA, Goularte N, Berliner JI, et al. Well-being parameters and intention to leave current institution among academic physicians. *JAMA Network Open*. 2023;6(12):e2347894. doi:10.1001/jamanetworkopen.2023.47894
33. Anzueto A. Impact of exacerbations on COPD. *Eur Respir Rev*. 2010;19(116):113–118. doi:10.1183/09059180.00002610
34. Whittaker H, Rubino A, Müllerová H, et al. Frequency and severity of exacerbations of COPD associated with future risk of exacerbations and mortality: a UK routine health care data study. *Int J Chron Obstruct Pulmon Dis*. 2022;17:427–437. doi:10.2147/COPD.S346591
35. Hirayama A, Goto T, Hasegawa K. Association of acute kidney injury with readmissions after hospitalization for acute exacerbation of chronic obstructive pulmonary disease: a population-based study. *BMC Nephrol*. 2020;21:116. doi:10.1186/s12882-020-01780-2