# Remote patient monitoring and machine learning in acute exacerbations of COPD: A dual systematic literature review and narrative synthesis

Henry Mark Granger Glyde, Caitlin Morgan, Tom M A Wilkinson, Ian T Nabney, James W Dodd

Submitted to: Journal of Medical Internet Research
on: August 24, 2023

# *Table of Contents*

# Remote patient monitoring and machine learning in acute exacerbations of COPD: A dual systematic literature review and narrative synthesis

Henry Mark Granger Glyde[1] BSc; Caitlin Morgan[2] MBChB, MRCP(UK), BSc; Tom M A Wilkinson[3]; Ian T Nabney[4]; James W Dodd[2]

[1]EPSRC Centre for Doctoral Training in Digital Health and Care, University of Bristol Bristol GB
[2]Academic Respiratory Unit, Translational Health Sciences, Bristol Medical School, University of Bristol Bristol GB
[3]My mHealth and Clinical and Experimental Science, University of Southampton Southampton GB
[4]School of Computer Science, Electrical and Electronic Engineering and Engineering Maths, University of Bristol Bristol GB

**Corresponding Author:**
Henry Mark Granger Glyde BSc
EPSRC Centre for Doctoral Training in Digital Health and Care, University of Bristol
2nd Floor, Learning and Research Southmead Hospital
Bristol
GB

## *Abstract*

**Background:** Acute exacerbations of chronic obstructive pulmonary disease (AECOPD) are associated with high mortality, morbidity and poor quality of life and constitute a substantial burden to patients and healthcare systems. New approaches to prevent or reduce the severity of AECOPD are urgently needed. Internationally, this has prompted increased interest in the potential of remote patient monitoring (RPM) and digital medicine. RPM refers to the direct transmission of patient-reported outcomes, physiological, and functional data including heart rate, weight, blood pressure, oxygen saturation, physical activity, and lung function (spirometry) directly to healthcare professionals through automation, web-based data entry or phone-based data entry. Machine learning has the potential to enhance RPM in COPD by increasing the accuracy and precision of AECOPD prediction systems.

**Objective:** Here we conduct a dual systematic review of RPM randomised controlled trials (RCT) in AECOPD and machine learning studies combined with RPM to predict AECOPD. We review the evidence and concepts behind RPM and machine learning and go on to discuss the strengths, limitations, and clinical utility of available systems. We have generated a list of recommendations needed to deliver patient and healthcare system benefits.

**Methods:** A comprehensive search strategy, encompassing the SCOPUS and Web Of Science databases was used to identify relevant studies. Two independent reviewers conducted study selection, data extraction, and quality assessment, with discrepancies resolved through consensus. Data synthesis involved a narrative synthesis and reporting followed PRISMA guidelines.

**Results:** RPM, and in particular the incorporation of machine learning appears to have the potential to improve the predictive capabilities of RPM for AECOPD significantly. Advances in RPM and machine learning require a greater focus on patient co-design, identification and clinical validation of the optimal physiological, behavioural and environmental sensors.

**Conclusions:** This focus of research should ultimately result in randomised controlled trials set against usual care to provide an evidence base for their safety, efficacy and cost-effectiveness which could, once present transform outcomes through the widespread implementation of new approaches to care.

(JMIR Preprints 24/08/2023:52143)
DOI: https://doi.org/10.2196/preprints.52143

### Preprint Settings

1) Would you like to publish your submitted manuscript as preprint?

✓ **Please make my preprint PDF available to anyone at any time (recommended).**
Please make my preprint PDF available only to logged-in users; I understand that my title and abstract will remain visible to all users.

Only make the preprint title and abstract visible.
No, I do not wish to publish my submitted manuscript as a preprint.

2) If accepted for publication in a JMIR journal, would you like the PDF to be visible to the public?

✓ **Yes, please make my accepted manuscript PDF available to anyone at any time (Recommended).**
Yes, but please make my accepted manuscript PDF available only to logged-in users; I understand that the title and abstract will remain v
Yes, but only make the title and abstract visible (see Important note, above). I understand that if I later pay to participate in <a href="http

# Original Manuscript

# Remote patient monitoring and machine learning in acute exacerbations of COPD: A dual systematic literature review and narrative synthesis

Henry M. G. Glyde[1,2], Caitlin Morgan[2], Tom M.A. Wilkinson[3], Ian T. Nabney[4], James W. Dodd[2]

[1]EPSRC Centre for Doctoral Training in Digital Health and Care, University of Bristol, Bristol, UK
[2]Academic Respiratory Unit, Translational Health Sciences, Bristol Medical School, University of Bristol, Bristol, UK
[3]Clinical and Experimental Science, University of Southampton, Southampton, UK
[4]School of Engineering Mathematics and Technology, University of Bristol, Bristol, UK

**Corresponding author**

Dr Henry Glyde

**Adress**

Academic Respiratory Unit
2nd Floor, Learning and Research
Southmead Hospital
Westbury-on-Trym
Bristol BS10 5NB
United Kingdom

**Phone**

07843037078

**Fax**

N/A

**Email address**

henry.glyde@bristol.ac.uk



**Abstract**

# Background

Acute exacerbations of chronic obstructive pulmonary disease (AECOPD) are associated with high mortality, morbidity and poor quality of life and constitute a substantial burden to patients and healthcare systems. New approaches to prevent or reduce the severity of AECOPD are urgently needed. Internationally, this has prompted increased interest in the potential of remote patient monitoring (RPM) and digital medicine. RPM refers to the direct transmission of patient-reported outcomes, physiological, and functional data including heart rate, weight, blood pressure, oxygen saturation, physical activity, and lung function (spirometry) directly to healthcare professionals through automation, web-based data entry or phone-based data entry. Machine learning has the potential to enhance RPM in COPD by increasing the accuracy and precision of AECOPD prediction systems.

# Objective

Here, we conduct a dual systematic review. The first review focuses on randomised controlled trials (RCTs) where RPM was used as an intervention to treat or improve AECOPD. The second review examines studies that combined machine learning with RPM to predict AECOPD. We review the evidence and

concepts behind RPM and machine learning and go on to discuss the strengths, limitations, and clinical utility of available systems. We have generated a list of recommendations needed to deliver patient and healthcare system benefits.

## Methods

A comprehensive search strategy, encompassing the SCOPUS and Web Of Science databases was used to identify relevant studies. Two independent reviewers conducted study selection, data extraction, and quality assessment, with discrepancies resolved through consensus. Data synthesis involved evidence assessment using CASP checklist and a narrative synthesis. Reporting followed PRISMA guidelines.

## Results

These narrative syntheses suggest that 57% of the RCTs for RPM interventions fail to achieve the required level of evidence for better outcomes in AECOPD. However, the integration of machine learning into RPM demonstrates promise for increasing the predictive accuracy AECOPD and therefore early intervention.

## Conclusions

This review suggests a transition towards the integration of machine learning into RPM for predicting AECOPD. We discuss particular RPM indices that have the potential to improve AECOPD prediction and highlight research gaps concerning patient factors and the sustained adoption of RPM. Furthermore, we emphasise the importance of a more comprehensive examination of patient and healthcare burdens associated with RPM, along with the development of practical solutions.

# Introduction

Chronic obstructive pulmonary disease (COPD) is a disease defined by airway obstruction, airway inflammation, and in some cases parenchymal destruction (emphysema). COPD accounts for 55% of all chronic respiratory diseases [1] and is characterised by intermittent periods of significantly worsening symptoms known as exacerbations [2]. After a severe exacerbation, the in-hospital mortality is 6.7% [3]. Subsequently, the average mortality rates at 3 and 6 months stand at 18% and 26%, respectively, with a notable 50% mortality rate observed at 3.6 years [3, 4]. Exacerbations increase airway and systemic inflammation, disease progression and a reduction in quality of life [5–11]. It is estimated that exacerbations in COPD account for 45% of COPD-related costs [12]. Patients who suffer frequent acute exacerbations of COPD (AECOPD) have more primary care interactions, increased emergency department (ED) presentations, increased hospitalisations, and increased admissions to the Intensive Care Unit (ICU) [13]. A recent research priority-setting partnership in COPD found the highest-rated issue by patients or carers to be ‘identify better ways to prevent exacerbations’ [14]. The researchers highlighted the importance of predicting and preventing exacerbations.

There is evidence to suggest that reducing delays in treatment and correct identification of exacerbations can reduce the severity of exacerbations, improve health-related quality of life (HRQL), and reduce recovery time after an exacerbation. Wilkinson *et al.* found that a longer time to treatment in AECOPD was associated with an increase in recovery time of exacerbation symptoms [15]. Moreover, they demonstrated that a greater number of correctly identified exacerbations treated by a physician resulted in a better HRQL as seen in the lower total St George’s Respiratory Questionnaire (SGRQ) scores.

Remote Patient Monitoring (RPM) is a method of healthcare delivery that uses wearable devices and sensors to gather patient data outside of traditional healthcare settings. Using RPM, data becomes available that may provide a more detailed picture of the patient’s health. The patient, along with a team of healthcare professionals, can review this data to promptly identify changes in the patient's health status, enabling early detection of potential exacerbations and facilitating timely intervention. Nevertheless, the current role of RPM in managing AECOPD remains uncertain. While some studies indicate potential benefits, others show no significant effects. Therefore, conducting a systematic review and synthesising existing evidence becomes crucial to comprehend the current state of the art. This assessment is essential for defining the next steps in the development and testing of technology to address this global health challenge. Notably, leveraging machine learning approaches on the gathered data holds promise in enhancing RPM's predictive capabilities. Thus, a comprehensive review is imperative to assess the current progress in this field.

In this dual systematic review, we aim to identify diverse approaches to remote monitoring for exacerbation intervention and prediction. We integrate insights from both machine learning and remote clinical monitoring perspectives. We investigate advancements that machine learning offers, analyse the labelling of exacerbations, scrutinise study designs, examine types of RPM, and explore various approaches to applying machine learning in the context of RPM. This approach allows us to provide a more comprehensive and novel understanding of digitally enabled AECOPD interventions.

# Methodology

We conducted two systematic literature searches in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [16].

## Search strategy

The searches were conducted between April and May 2023 in 2 electronic databases (Scopus and Web of Science) covering publications since the databases began. For Scopus this includes records dating back to 1788 and for Web of Science the database covers literature dating back to the early 1900s. The first search strategy included search strings in the three main areas: COPD, RPM (telemedicine, telemonitoring, remote patient monitoring, real-time monitoring, telehealth, mhealth, digital health), study design (intervention, trial) and outcome (exacerbation frequency, exacerbation duration, ED presentations, hospital admissions, hospital readmissions, primary care interaction, healthcare costs, quality of life, days in hospital). The second search strategy also included COPD and RPM but did not include study design and instead of outcome, the search term was machine learning modelling (machine learning, deep learning, prediction models, algorithms). The full search strategies for each database are presented in the Multimedia Appendix. Articles published in peer-reviewed journals or conference proceedings were considered for review. We did not include abstracts, dissertations, systematic reviews, or case studies.

## Study selection

To be included in the first search, studies were required to (1) specifically examine the use of RPM in COPD:

(2) be a randomised controlled trial (RCT), (3) have an exacerbation-related outcome variable i.e. hospital admissions, exacerbation frequency; HRQL, (4) be published between the start date of each electronic database and May 2023, (5) be full freely available articles, (6) be published in English.

For the second search, fewer studies were available, therefore, studies were not required to (2) be an RCT and instead of including (3) an exacerbation-related outcome variable, studies were required to incorporate (7) a form of AI modelling, usually machine learning algorithms for exacerbation prediction.

Papers were excluded from the study for any one of the following reasons: (a) the study is a systematic literature review, (b) the study did not include one outcome related to either (3) (first search), or (7) (second search), (c) the focus of the intervention was behaviour change (physical activity, medication adherence, inhaler technique) or remote rehabilitation (usually pulmonary rehabilitation) rather than remote monitoring, (d) the main study outcome was cost and does not include patient-related outcomes.

Machine learning studies were intentionally excluded from the first search. This decision was guided by the unique emphasis of each search: the first centered on RPM with clinical monitoring, while the second focused on RPM with an emphasis on machine learning.

Two authors independently assessed the results obtained from the first literature search. Articles were screened in four steps: first, duplicates were removed, and then the title, abstract, and keywords were screened. Articles were screed on the inclusion and exclusion criteria outlined above. If authors could not determine suitability during the screening, full-text articles were accessed for inclusion criteria and exclusion criteria. Full-text articles were excluded for not reporting outcomes for COPD patients or the accuracy of COPD exacerbation prediction separately (in the case of studies with multiple diseases).

Remote monitoring studies were not included in the review if they reported on remote monitoring as an alternative to hospitalisation for exacerbation treatment, did not include the specifics of the RPM use, or they focused on the diagnosis of AECOPD rather than prediction.

## Evidence Assessment and Narrative Synthesis

In the process of narrative synthesis, the initial step involved the identification and documentation of comparator groups. The lead author identified and documented comparator groups, capturing patient numbers, age, sex, and $FEV_1$. Subsequently, the lead recorded the specific RPM indices used in these studies, providing insight into the monitored parameters. These results are detailed in the Multimedia Appendix. The RPM index, including its percentage occurrence in studies and the average study duration, can be found in Figures 2 and 5. The lead identified and described the method of detection or prediction of AECOPD. This encompasses flagging/clinical oversight or the application of machine learning approaches. Lastly, outcomes/effect sizes were described, documenting key measures such as hospitalisations, HRQL, and performance metrics like sensitivity and accuracy. The results from the narrative synthesis can be found in the Multimedia Appendix, which the remaining authors checked.

For the initial search, we use the Critical Appraisal Skills Programme (CASP) RCT checklist. This tool is designed to systematically assess the validity, results, and relevance of randomised controlled trials, helping us gauge the quality of the evidence. Questions 9 and 11 were omitted from the evaluation as they are not relevant to this assessment. Studies satisfying 90% of the criteria were designated as having the highest level of evidence (strongest evidence). Those meeting 80% were categorised as strong evidence, while those meeting 70% were classified as moderate evidence. Studies fulfilling 60% of the criteria were considered to have limited evidence. For the second search, we used the CASP cohort checklist to assess cohort study quality. Questions 7 and 12 were excluded due to their lack of relevance. As in the first search, studies meeting 90%, 80%, 70%, and 60% of the criteria were categorised as strongest, strong, moderate, and limited quality, respectively. The resulting rankings are visualised in Figures 3 and described in the results.

# Results

We screened and analysed data from April to May 2023. Through the first systematic search, we identified 216 studies, extending from 1998 to 2023. Of these, 28 were included in the review [17-44] (Figure 1).

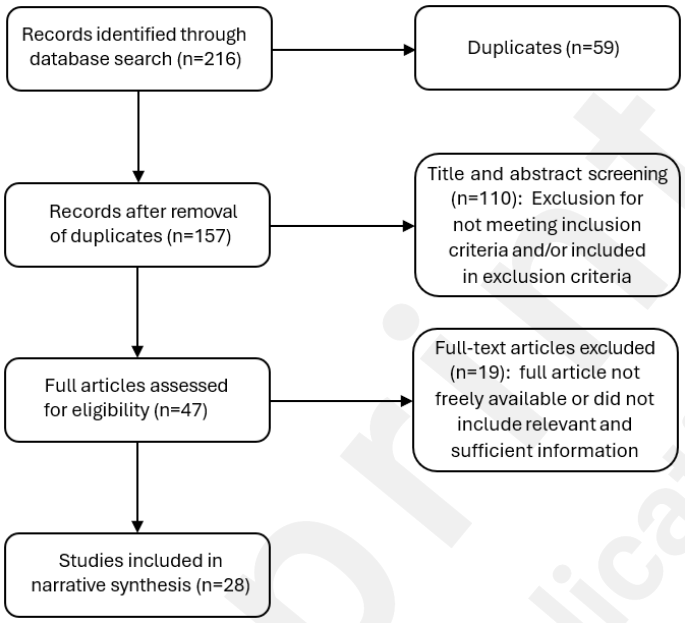



Figure 1: Search procedure for randomised controlled trials where remote patient monitoring was used as an intervention to treat or improve AECOPD.

To identify the distribution and duration of studies and RPM indices identified in our first search, we visualised the data using a dual-axis plot (Figure 2). On the x-axis, each RPM index is represented. The left y-axis (blue bar chart) indicates the percentage of studies in which each index appears, while the right y-axis (red points) shows the average duration of these studies. This visualisation facilitates a comprehensive comparison between the prevalence and the duration of the studies associated with each RPM index.

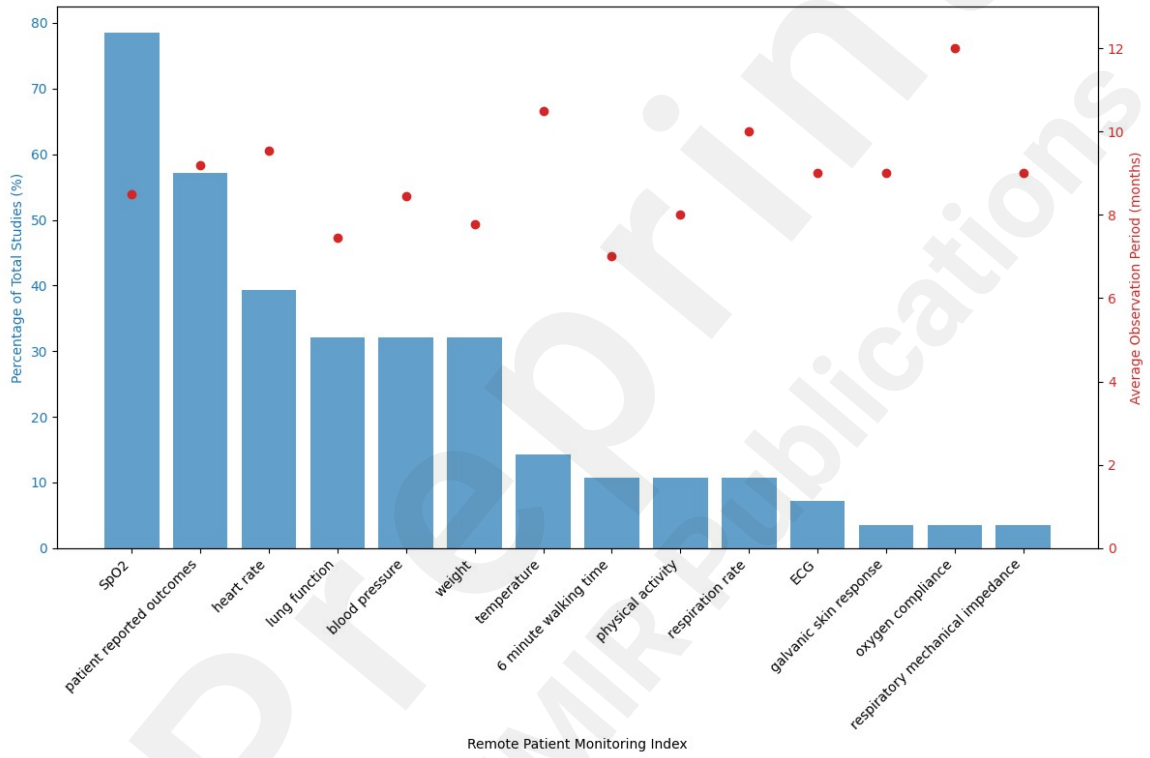



Figure 2: Distribution of RPM Indexes and Average Study Duration for the first search. The figure illustrates the percentage of total studies each RPM index appears in, alongside the average duration of these studies.

We constructed a figure to present the outcomes and rankings derived from the CASP RCT checklist evaluation of the RCTs identified in our first search (Figure 3). The figure is divided into two columns: the left column displays RCTs showing some improvement in clinical outcomes, while the right column shows RCTs with limited or no improvement. Within each column, studies are ranked by the strength of evidence, from limited evidence at the bottom to the strongest evidence at the top. Each section indicating evidence strength includes the number of RCTs, with the specific studies cited below this label.

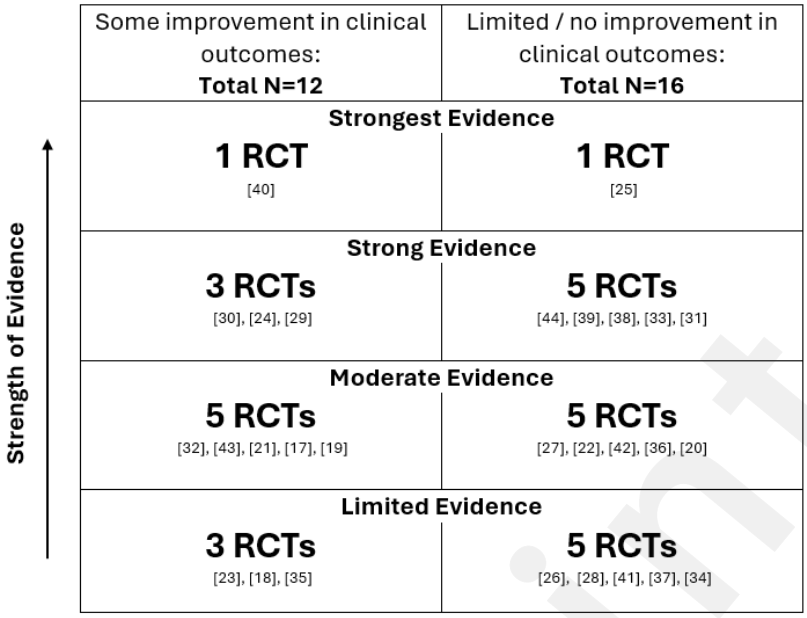



Figure 3: CASP RCT Checklist Rankings of RCTs on RPM in COPD. This figure presents the rankings of RCTs on RPM in COPD according to the CASP RCT checklist.

A detailed breakdown of the RCT characteristics, method of intervention delivery, and outcomes are available in Multimedia Appendix.

The second systematic literature review search identified 350 articles, extending from 2005 to 2023. Of these, 23 were included in the review [45-68] (Figure 4).

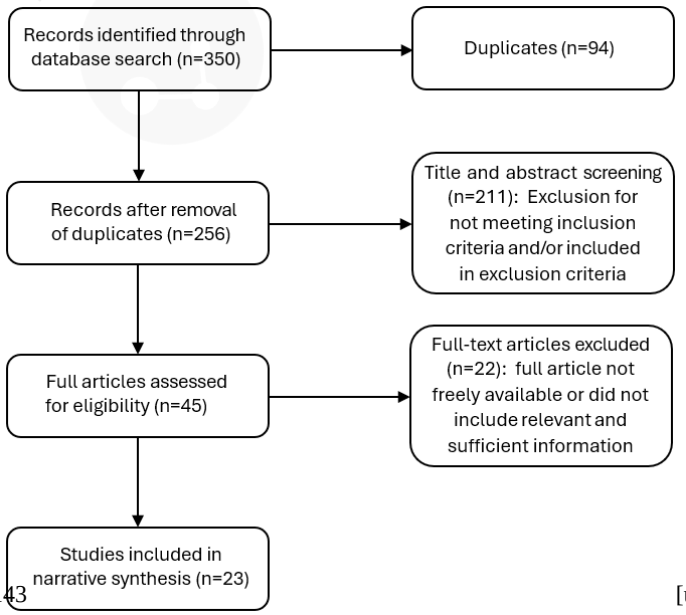


Figure 4: Search procedure for empirical studies on RPM and machine learning to predict AECOPD.

To identify the distribution and duration of studies and RPM indices identified in our second search, we visualised the data using a dual-axis plot (Figure 5). On the x-axis, each RPM index is represented. The left y-axis (blue bar chart) indicates the percentage of studies in which each index appears, while the right y-axis (red points) shows the average duration of these studies. This visualisation facilitates a comprehensive comparison between the prevalence and the duration of the studies associated with each RPM index.

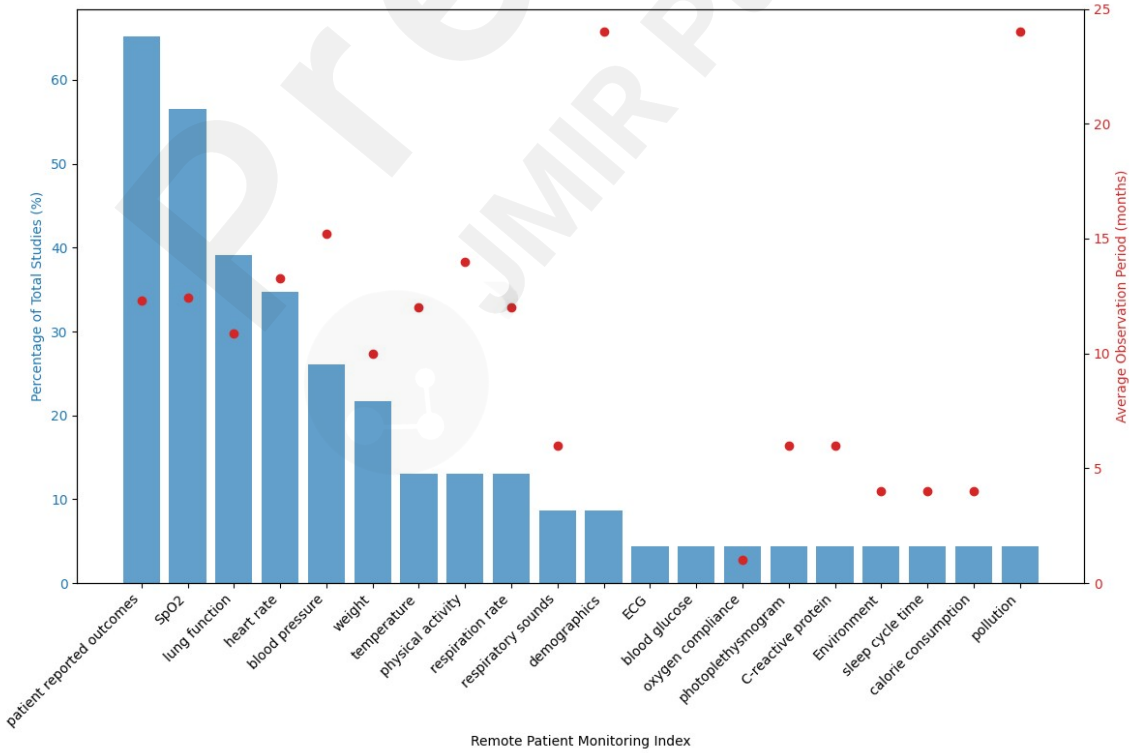


Figure 5: Distribution of RPM Indexes and Average Study Duration for the second search. The figure illustrates the percentage of total studies each RPM index appears in, alongside the average duration of these studies.

The studies identified in the second search were ranked according to the CASP cohort checklist. The ranking is categorised by the quality of the study as follows: strongest (studies [52], [58-61]), strong (studies [51], [55], [54], [57], [64-68]), moderate (studies [48-50], [53], [56]), and limited (studies [45-47], [62], [63]). This categorisation helps in clearly delineating the quality across the identified studies. A detailed breakdown of the machine learning study characteristics, method of intervention delivery, and outcomes are available in Multimedia Appendix.

## Remote patient monitoring for intervention or management of AECOPD

Our analysis revealed a tendency among RCTs towards non-improvement or demonstrate a lack of statistical significance in indicators of improvement in exacerbation management (Figure 2).

Both Jang *et al.* and Kruse *et al.* systematic reviews identified that RPM often does not show a significant improvement in patient outcomes [69, 70]. This may stem from the diversity of study approaches, as emphasised by Kruse *et al*.: “high variability between the articles and the ways they provided telemonitoring services created conflicting results from the literature review”. The varied study designs make comparisons challenging and likely contribute to the diverse reported success levels in the literature. Furthermore, the burden of frequent monitoring may impact the effectiveness of RPM, as the commonly employed approaches are often resource-intensive and burdensome for both patients and clinicians, thereby hindering widespread adoption.

## Remote patient monitoring and machine learning for AECOPD prediction

Machine learning, a subset of artificial intelligence, centers on leveraging data and algorithms to enable mathematical models for learning without direct instruction. In the context of predicting AECOPD, most studies employing machine learning concentrate on assessing accuracy and related performance metrics based on retrospective data. This stands in contrast to efforts using RPM exclusively, which primarily aim at identifying improvements in patient outcomes through RCT. This makes the comparison of these two interrelated fields of research challenging especially with regard to the indication of improving health outcomes for patients. Nevertheless, the narrative synthesis revealed that machine learning in conjunction with RPM facilitates highly accurate AECOPD prediction (Figure 4).

Orchard *et al.* compared machine learning with traditional symptom-counting algorithms in RPM for COPD exacerbation risk [59]. They found that machine learning "outperforms existing predictive algorithms". On a dataset from 135 patients over 363 days, basic symptom-counting algorithms had limited accuracy (AUROC of 0.60 and 0.58). Testing in real-world scenarios reduced the algorithms' performance to no better than random decision making. Machine learning models achieved the best AUROC of 0.74, exposing traditional algorithms' notable shortcomings, including low accuracy and frequent false positives. This highlights machine learning's potential to significantly enhance RPM accuracy in identifying and predicting COPD exacerbations.

So far two patient facing studies have been complete using machine learning for AECOPD prediction and intervention. The first tool evaluated was ACCESS [61], which demonstrated 97.4% sensitivity but lower specificity at 65.6%. In an RCT, ACCESS didn't significantly impact weeks without exacerbations or hospital admissions [61]. The second tool evaluated was the COPDPredict™ app that used PRO, FEV1, and CRP, predicting AECOPD with 97.9% sensitivity and 84.0% specificity [65]. For 6 months, COPDPredict™ reduced hospitalisations by 98%, but lower specificity resulted in 458 false positives, potentially hindering implementation. Using blood CRP levels for diagnosis/prediction may be impractical in real-world scenarios due to cost and access, indicating the need for the development of low-cost at-home biomarker sensors. COPDPredict™ identified exacerbations earlier than clinician-defined episodes, while ACCESS required major symptoms for two consecutive days, potentially delaying timely intervention. Furthermore, the low PPV of ACCESS may have affected the trust of the patient-user and reduced the interventions effectiveness.

## Machine learning approaches

5 papers used neural networks for AECOPD prediction [48, 50, 58, 59, 68]. Neural networks excel at classification and prediction tasks due to their ability to model complex nonlinear relationships and automatically learn relevant features from data. Furthermore, neural networks can use transfer learning for efficient knowledge reuse, exhibit robustness to noisy data, and generalise well to new, unseen examples.

Nunavath *et al.* used a recurrent neural network (RNN), a subtype of artificial neural networks, for exacerbation prediction [58]. RNNs, commonly employed in ordinal or temporal problems, generally demand substantial data for optimal performance. In this study, with a dataset of 96 patients and approximately 7300 records collected over two years, data augmentation was applied to expand the training data, allowing the application of RNN, potentially resulting in a more potent, robust model for accurate. Heijden *et al.* [46] used Bayesian network algorithms to predict COPD exacerbations, offering advantages in incorporating prior knowledge, handling missing data through probabilistic inference, and providing interpretability by representing dependencies among variables. These models, known for their interpretability, are well-suited for dynamic environments like RPM. In studies by Fernandez-Granero, Sanchez-Morillo, and Leon-Jimenez [51, 56], different machine learning methodologies were employed in 2015 and 2017. The 2017 analysis, using an RF classifier, demonstrated the benefits of ensemble learning and reduced overfitting compared to the SVM model in 2015. This analysis also used the Markov chain Monte Carlo (MCMC) method and feature subset selection (FSS) for imputing missing data, contributing to improved model performance. Additionally, Logistic Regression (LR) was used by Shah *et al.* and Kronborg *et al.* [55, 57]. The models created in Shah et al.'s study encountered a notable trade-off between sensitivity and specificity (possibly stemming from challenges in data quality) and the model in Kronborg *et al.* achieved an AUROC of 0.74, suggesting LR's limitations in capturing complex non-linear relationships. Researchers should consider diverse approaches, acknowledging their strengths and limitations. Ensemble methods enhance robustness, Bayesian Networks offer interpretability, and techniques like bootstrapping and data augmentation can improve data quality.

## Study design

The studies identified in systematic searches exhibit heterogeneity in duration, sample size, and outcomes, influencing both RPM interventions and machine learning model development and testing.

Study durations vary from 3 months to 1 year impacting AECOPD events due to seasonality. Machine learning interventions may face challenges in generalising beyond specific months. Small studies with 10-30 participants may restrict the capture of exacerbations and hinder model generalisability to larger populations. While recruiting frequent exacerbators can help, it may lead to more false positives in less exacerbation-prone populations. Furthermore, smaller samples will limit diversity of age, sex, ethnicity, socioeconomic status, disease severity, exacerbation frequency, and time since diagnosis. Diverse participants are crucial to validate intervention effectiveness.

Many studies use machine learning with data from interventional studies or RCTs to develop predictive models. The success of these studies is typically gauged by the accuracy/predictive capability of the generated models. While this is a crucial initial step to evaluate exacerbation prediction potential, relying solely on machine learning from RCT conditions may restrict applicability to real-world settings and diminish model accuracy. RCTs, conducted in controlled environments with specific criteria, might not fully capture real-world variability and complexity. Despite these difficulties, RCTs offer advantages, particularly in COPD, where a gold standard diagnostic test for

AECOPD is lacking. RCT data often involve rigorous testing, enhancing the certainty of accurately modelling true AECOPD events.

Defining and labelling exacerbations is a complex aspect of predicting AECOPD. It involves determining what qualifies as an exacerbation in the data, which presents significant challenges. Various methods exist for defining exacerbations, including patient-reported symptoms, clinician diagnosis, medication usage, hospitalisation, or a combination of these criteria. Each approach has its advantages and drawbacks. Patient-reported symptoms and medication use are categorised as "symptom-based," capturing all exacerbations efficiently but lacking oversight and verification with objective measures. Clinician diagnosis and hospitalisation fall into the "event-based" category, with the former possibly being symptom-based if verified remotely. While clinician diagnosis is the gold standard, it can be resource intensive. An alternative is to use hospitalisation which offers clinician diagnosis but may overlook milder events managed at home.

The challenge in labeling exacerbations lies in accurately distinguishing between exacerbation events and periods of stable health during machine learning model training. Failure to do so prevents the identification of the prodromal period and may lead to the misclassification of moments of symptom relief as stable health rather than ongoing exacerbations. To address this, an algorithmic approach is necessary, involving the delineation of data windows. Typically, these windows are created by capturing 14 days of exacerbation-free periods, a duration commonly recognised as the time it takes for an exacerbation to develop after the onset of symptoms. Failure to implement an effective label indicates an AECOPD prediction model may be ineffective in real-world application.

## Patient factors

Patient engagement and monitoring burden are crucial in RPM. Many studies in this review rely on daily use of multiple sensors and PRO, yet still show high engagement. However, this may be influenced by the controlled research setting, providing extra attention and support, and motivating participants to engage. These studies often include rigorous monitoring and alerts for missed days. To assess real-world patient engagement, long-term data-gathering studies are often needed.

The burden of daily monitoring is frequently overlooked in interventions and model development studies, despite high adherence. Concerns arise about time and effort, impacting daily life. Daily self-monitoring involves tracking symptoms, vital signs, medication adherence, and lifestyle factors, potentially causing anxiety and stress. Some patients, with co-morbidities or limited digital access, may struggle with devices or apps, leading to frustration and non-adherence. Patient and Public Involvement (PPI) research is needed to understand user burden, develop strategies, and identify sensor

types minimising burdens for increased long-term RPM adoption.

## A review of indices in remote patient monitoring

The main types of data collected are physiological measures (BP, HR/PR, RR, weight, SpO2, and temperature), functional measures (lung function, PA), PRO (dyspnea, sputum, sleep quality, depression, anxiety, HRQL), self-report (physiological measures, medication-usage, exacerbation history, demographics, and medical history), and meteorological data.

## Physiological measures

In a systematic review, Buekers *et al.* identified 71 papers measuring SpO2 in COPD patients before exacerbations, revealing predictive limitations due to scant information on implementation and performance [71]. Milkowska-Dymanowska *et al.* noted a significant SpO2 decrease before exacerbation, distinguishing it from SBP, DBP, or HR [72]. Shah *et al*'*s* findings indicated that SpO2 (AUROC: 0.658) outperformed PR (AUROC: 0.578) in predicting exacerbations, highlighting SpO2's superiority, while SBP and HR/PR might offer some predictive capability [55]. Mohktar *et al.* emphasised weight as an essential feature for AECOPD prediction [52]. Dinesen *et al.* conducted an RCT which incorporated weight changes for clinical monitoring [21]. Their intervention reduced hospitalisation, affirming weight's role in early AECOPD detection. Heijden, Velicova, and Lucas established a dependency between exacerbation and body temperature [73]. RCT studies by Ho *et al.* and Pedone *et al.* reported positive patient outcomes using body temperature as an index for exacerbation monitoring [30, 24]. Shah *et al.* found that mean RR increased by 2 in the prodromal period leading to an exacerbation [55]. However, a feasibility study by Chau *et al.*, employing RR to monitor patients, did not demonstrate improvements in patient outcomes, possibly due to inherent study design limitations [74]. Burton, Pinnock, and McKinstry observed a mean SpO2 drop from 93.6% to 92.4% at exacerbation onset and Shah *et al.* found a decrease from 94% to 93% in the prodromal period, enhancing AECOPD predictive models [75, 55]. Despite these findings, Burton, Pinnock, and McKinstry identified weak associations between physiological variables and exacerbation episodes, underscoring the need for improved algorithms or additional features for early event detection.

## Functional measures

FEV1, or forced expiratory volume in 1 second, serves as a crucial measure captured by a spirometer for diagnosing and monitoring obstructive lung diseases. Digital spirometry holds the potential to be a potent predictor of AECOPD. Limited data on lung function deterioration shortly before exacerbations exist, but Watz *et al.* through their post hoc analysis observed FEV1 decline two weeks before an exacerbation in the WISDOM clinical trial [76], highlighting spirometry's utility in identifying exacerbations. Patel *et al.* demonstrated spirometry's predictive capability, achieving a sensitivity of 97.9% and specificity of 84.0% for AECOPD when combined with CRP and PRO [65].

Physical activity (PA), though infrequently used, offers a burdenless monitoring approach. Pedone *et al.,* in their RCT, incorporating PA as a measure, showed a significant reduction in exacerbation events [24]. Chawla *et al.* found that lower PA in the first week after discharge increased the likelihood of 30-day all-cause readmissions [77]. Wrist-worn wearables measuring PA, prevalent through smartwatches, provide a useful, unobtrusive tool for monitoring for exacerbation prediction. While not a direct alternative to spirometry for lung function, they offer continuous monitoring without user engagement.

## Patient-reported outcomes (PRO)

PRO is typically obtained through patient inputs into a digital diary, involving daily responses to yes/no or graded questions. Graded inquiries may include assessing chest tightness on a scale of 0 to 5. The rationale for incorporating PRO in RPM is robust. The CAT, an eight-question validated tool [78], shows a positive correlation with COPD exacerbation risk [79]. A one-unit increase in CAT score signals an 8% higher risk of exacerbation [80]. Similar associations exist for other PRO measures, such as the mMRC dyspnea scale [11]. Most of the RCTs included in this review commonly use PRO as part of RPM. However, many of these studies do not show significant improvements in exacerbation-related outcomes. This might be attributed to the frequent use of non-validated, study-specific questionnaires for assessing PRO. To potentially enhance outcomes, a recommended shift would be from employing non-validated questionnaires to prioritising validated measures, such as the CAT.

## Biological measures

Exacerbations in COPD correlate with various biomarkers, with CRP being extensively studied [81-84]. Patel *et al.* showcased CRP's efficacy in COPDPredict™, emphasising its high sensitivity and specificity. However, limited CRP use in prediction models stems from challenges in deploying widespread systems with frequent point-of-care testing. Potential solutions include at-home finger-prick blood sampling, mail-in samples, or self-administered point-of-care tests like lateral flow tests used during the SARS-CoV-2 pandemic. Inflammatory cytokines in sputum and Volatile Organic Compounds (VOC) in exhaled breath are also targets for at-home monitoring, contingent on the development of suitable devices [85, 86].

Despite the potential benefits, implementing remote biological monitoring encounters challenges in cost and scalability. Substantial expenses for developing and deploying home-based detection equipment, ensuring data accuracy, and managing sensor development, deployment, data transmission, and storage impede practical execution. Achieving scalability for costly digital biological monitoring technology demands significant investment.

## Discussion

We have undertaken a systematic literature review and narrative synthesis of RPM and machine learning for COPD exacerbations to address the problem of identifying better ways to intervene early or prevent exacerbations to improve outcomes in AECOPD.

The narrative synthesis of available evidence reveals that RCTs using RPM to monitor patients at risk of AECOPD tends to exhibit non-significant outcomes. This can be attributed to the heterogeneity in study design and the use of traditional symptom counting algorithms. In addition, there is limited insight into the accuracy or timeliness of AECOPD detection and intervention. Orchard *et al.* points to limitations relating to the basic algorithms which seem to generate alerts from RPM that may perform no better than chance [60] and highlights the potential of machine learning to significantly enhance the predictive capabilities of RPM.

We chose not to exclusively limit our second search to RCTs due to the lack of available RCTs in the relevant literature. The comparison of these two bodies of literature presents a challenge, and instead of considering them as comparators, it is more apt to view them as conjugates. While similarities exist in the methodologies of the two bodies of literature, particularly in the RPM indices, there are significant divergences in their outcomes. The first search primarily focuses on patient outcomes, whereas the second centers on the performance of machine learning models. This contrast underscores the importance of a shift in trajectory of research, RCTS of RPM in AECOPD should introduce machine learning models to identify their efficacy and draw a conclusion to the question if early detection of AECOPD can improve patient outcomes. Whilst early research for machine learning in the prediction of AECOPD is promising, there is much need for further development in the field. Much of the literature evaluates the ability of machine learning models to predict AECOPD yet fails to provide evidence on how these models translate into improving patient outcomes. Notable exceptions include Patel *et al.* whose COPDPredict™ may reduce hospitalisation [66] but required frequent blood testing and the use of expensive home-based detection equipment. Due to the lack of research in this field, it is too early to determine if exacerbation prediction and intervention can be deployed with machine learning to improve AECOPD outcomes, especially without the incorporation of biological indices.

Some adjustments can be made in future studies that may lead to more robust conclusions. For example, exacerbation definition and labelling are heterogeneous and would benefit from standardisation, it is critical to ensure that there is sufficient data capture by increasing the number of participants and keeping the study length to a minimum of 1 year should result in better generalisation of predictive models. In addition, integrating data augmentation, resampling, and feature selection techniques can further enhance training data for machine learning. Furthermore, incorporating neural networks into a modelling approach may greatly enhance the predictive power of AECOPD models. Clinically validated PRO like that of CAT, should be considered as an alternative to study-specific questionnaires. SpO2, RR, HR, weight, FEV1, and PEF appear frequently in remotely monitored indices and may have potential for

exacerbation prediction if combined with machine learning. Additionally, further research could demonstrate the predictive capabilities of physical activity. PPI research needs to be conducted with these sensors to explore the feasibility and likelihood of long-term adherence. The incorporation of sensing technologies that monitor in the background and are seemingly burdenless (wrist-worn wearables/smartwatches) should be considered. The use of biological measures is a rarely used method in RPM but research, as seen from the study by Patel *et al.,* is needed to develop cost-effective tools for predicting AECOPD.

## Limitations

This review has some limitations. The number of studies initially identified in searches is relatively small and limited to those full and freely available in English. This is due to a combination of stringent search terms to identify RCT and machine learning papers and the strict inclusion and exclusion criteria. This may influence our confidence in drawing conclusions regarding the efficacy or accuracy of RPM and machine learning in COPD or, international variations or those not freely available can't be reported. However, clearly defined criteria are necessary to minimise bias and subjectivity in the search and enable reproducibility and rigour that add validity to a systematic review. This study did not include a formal risk of bias assessment. However, the evaluation of the studies using CASP checklists and according ranking should highlight the quality of studies included in this dual systematic review.

## Recommendations

1. The methodologies for exacerbation intervention using RPM exhibit inconsistency, potentially contributing to the variability in the success of outcomes. The current landscape is hindered by inadequate evidence and the substantial resource burden associated with clinical oversight of remotely monitored indices. Therefore, it becomes apparent that a shift away from conventional intervention methods is warranted, with a compelling case for exploring the integration of machine learning approaches as a more pragmatic and potentially effective alternative.

2. While the literature emphasises the accuracy of machine learning in AECOPD prediction, demonstrating the clinical utility of these approaches requires evidence from RCT and real-world studies, both of which are currently lacking.

3. Physiological and functional indices, such as SpO2, RR, HR, weight, FEV1, and PEF, are commonly found in the literature and have the potential to serve as robust predictors of AECOPD when integrated with machine learning. Exploring the inclusion of PA as a predictive index is justified, and the incorporation of PRO, particularly through clinically validated questionnaires, is strongly recommended.

4. There is a lack of research into patient factors, there is a need to study the adoption of RPM in the long term and to develop an understanding of the burden of daily/weekly RPM and potential solutions to overcome this burden. Active engagement with patient communities is required to understand their needs, ensuring optimal responses and the best possible outcomes.

## Conclusion

RPM has yet to consistently prove a successful intervention in AECOPD, facing significant challenges with accuracy in predicting and identifying exacerbations, resource-intensive processes, and scalability limitations. Although machine learning

demonstrates the potential for high accuracy for AECOPD, its clinical utility is still to be validated through RCTs. Considering the heterogeneity of COPD, a one-size-fits-all approach may not be suitable. Leveraging machine learning, an individualised approach tailored to each patient's unique data holds the potential to enhance patient outcomes in AECOPD.

# References


[1] Soriano JB, Kendrick PJ, Paulson KR, Gupta V, Abrams EM, Adedoyin RA, et al. Prevalence and attributable health burden of chronic respiratory diseases, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. The Lancet Respiratory Medicine. 2020;8(6):585–596.

[2] Ko FW, Chan KP, Hui DS, Goddard JR, Shaw JG, Reid DW, et al. Acute exacerbation of COPD. Respirology. 2016;21(7):1152–1165.

[3] Suissa S, Dell'Aniello S, Ernst P. Long-term natural history of chronic obstructive pulmonary disease: severe exacerbations and mortality. Thorax. 2012;67(11):957–963.

[4] Hoogendoorn M, Hoogenveen RT, Rutten-van Mölken MP, Vestbo J, Feenstra TL. Case fatality of COPD exacerbations: a meta-analysis and statistical modelling approach. Eur Respir J. 2011 Mar;37(3):508-15.

[5] Halpin DM, Miravitlles M, Metzdorf N, Celli B. Impact and prevention of severe exacerbations of COPD: a review of the evidence. International journal of chronic obstructive pulmonary disease. 2017 Oct 5:2891-908.

[6] Day K, Ostridge K, Conway J, Cellura D, Watson A, Spalluto CM, Staples KJ, Thompson B, Wilkinson T. Interrelationships among small airways dysfunction, neutrophilic inflammation, and exacerbation frequency in COPD. Chest. 2021 Apr 1;159(4):1391-9.

[7] Perera WR, Hurst JR, Wilkinson TM, Sapsford RJ, Mu¨llerova H, Donaldson GC, et al. Inflammatory changes, recovery and recurrence at COPD exacerbation. European Respiratory Journal. 2007;29(3):527–534.

[8] Anzueto A. Impact of exacerbations on COPD. European Respiratory Review. 2010;19(116):113–118.

[9] Kerkhof M, Voorham J, Dorinsky P, Cabrera C, Darken P, Kocks JW, Sadatsafavi M, Sin DD, Carter V, Price DB. Association between COPD exacerbations and lung function decline during maintenance therapy. Thorax. 2020 Jun 10.

[10] Hurst JR, Skolnik N, Hansen GJ, Anzueto A, Donaldson GC, Dransfield MT, Varghese P. Understanding the impact of chronic obstructive pulmonary disease exacerbations on patient health and quality of life. European journal of internal medicine. 2020 Mar 1;73:1-6.

[11] Whittaker H, Rubino A, Müllerová H, Morris T, Varghese P, Xu Y, De Nigris E, Quint JK. Frequency and severity of exacerbations of COPD associated with future risk of exacerbations and mortality: a UK routine health care data study. International Journal of Chronic Obstructive Pulmonary Disease. 2022 Mar 3:427-37.

[12] de Nigris E, McEwan P, Marshall J, Holmgren U, Foos V. POSB65 Economic Burden of COPD in the United Kingdom (2021–2040) Estimated with the COPD Health Outcome Policy and Intervention (CHOPIN) Model. Value in Health. 2022 Jan 1;25(1):S72-3.

[13] Iheanacho I, Zhang S, King D, Rizzo M, Ismaila AS. Economic Burden of Chronic Obstructive Pulmonary Disease (COPD): A Systematic Literature Review. International Journal of Chronic Obstructive Pulmonary Disease. 2020;15:439.

[14] Alqahtani JS, Aquilina J, Bafadhel M, Bolton CE, Burgoyne T, Holmes S, et al. Research priorities for exacerbations of COPD. The Lancet Respiratory Medicine. 2021;9(8):824–826.

[15] Wilkinson TM, Donaldson GC, Hurst JR, Seemungal TA, Wedzicha JA. Early therapy improves outcomes of exacerbations of chronic obstructive pulmonary disease. American

journal of respiratory and critical care medicine. 2004;169(12):1298–1303.

[16] Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group* t. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Annals of internal medicine. 2009;151(4):264–269.

[17] de Toledo P, Jim´enez S, del Pozo F, Roca J, Alonso A, Hernandez C. Telemedicine experience for chronic care in COPD. IEEE transactions on information technology in biomedicine. 2006;10(3):567–573.

[18] Koff P, Jones RH, Cashman JM, Voelkel NF, Vandivier R. Proactive integrated care improves quality of life in patients with COPD. European Respiratory Journal. 2009;33(5):1031–1038.

[19] Vitacca M, Bianchi L, Guerra A, Fracchia C, Spanevello A, Balbi B, et al. Tele-assistance in chronic respiratory failure patients: a randomised clinical trial. European Respiratory Journal. 2009;33(2):411–418.

[20] MG Halpin D, Laing-Morton T, Spedding S, L Levy M, Coyle P, Lewis J, et al. A randomised controlled trial of the effect of automated interactive calling combined with a health risk forecast on frequency and severity of exacerbations of COPD assessed clinically and using EXACT PRO. Primary Care Respiratory Journal. 2011;20(3):324–331.

[21] Dinesen B, Haesum LK, Soerensen N, Nielsen C, Grann O, Hejlesen O, et al. Using preventive home monitoring to reduce hospital admission rates and reduce costs: a case study of telehealth among chronic obstructive pulmonary disease patients. Journal of telemedicine and telecare. 2012;18(4):221–225.

[22] De San Miguel K, Smith J, Lewin G. Telehealth remote monitoring for community-dwelling older adults with chronic obstructive pulmonary disease. Telemedicine and e-Health. 2013;19(9):652–657.

[23] Jehn M, Donaldson G, Kiran B, Liebers U, Mueller K, Scherer D, et al. Tele-monitoring reduces exacerbation of COPD in the context of climate change–a randomized controlled trial. Environmental Health. 2013;12:1–8.

[24] Pedone C, Chiurco D, Scarlata S, Incalzi RA. Efficacy of multiparametric telemonitoring on respiratory outcomes in elderly people with COPD: a randomized controlled trial. BMC health services research. 2013;13:1–7.

[25] Pinnock H, Hanley J, McCloughan L, Todd A, Krishan A, Lewis S, et al. Effectiveness of telemonitoring integrated into existing clinical services on hospital admission for exacerbation of chronic obstructive pulmonary disease: researcher blind, multicentre, randomised controlled trial. Bmj. 2013;347.

[26] Sorknaes AD, Bech M, Madsen H, Titlestad IL, Hounsgaard L, Hansen-Nord M, et al. The effect of real-time teleconsultations between hospital-based nurses and patients with severe COPD discharged after an exacerbation. Journal of telemedicine and telecare. 2013;19(8):466–474.

[27] McDowell JE, McClean S, FitzGibbon F, Tate S. A randomised clinical trial of the effectiveness of home-based health care with telemonitoring in patients with COPD. Journal of telemedicine and telecare. 2015;21(2):80–87.

[28] Ringbæk T, Green A, Laursen LC, Frausing E, Brøndum E, Ulrik CS. Effect of tele health care on exacerbations and hospital admissions in patients with chronic obstructive pulmonary disease: a randomized clinical trial. International journal of chronic obstructive pulmonary disease. 2015:1801–1808.

[29] Cordova FC, Ciccolella D, Grabianowski C, Gaughan J, Brennan K, Goldstein F, et al. A telemedicine-based intervention reduces the frequency and severity of COPD exacerbation symptoms: a randomized, controlled trial. Telemedicine and e-Health. 2016;22(2):114–122.

[30] Ho TW, Huang CT, Chiu HC, Ruan SY, Tsai YJ, Yu CJ, et al. Effectiveness of telemonitoring in patients with chronic obstructive pulmonary disease in Taiwan-a randomized controlled trial. Scientific reports. 2016;6(1):23797.

[31] Vianello A, Fusello M, Gubian L, Rinaldo C, Dario C, Concas A, et al. Home telemonitoring

for patients with acute exacerbation of chronic obstructive pulmonary disease: a randomized controlled trial. BMC pulmonary medicine. 2016;16(1):1–12.

[32] Farmer A, Williams V, Velardo C, Shah SA, Yu LM, Rutter H, et al. Self-management support using a digital health system compared with usual care for chronic obstructive pulmonary disease: randomized controlled trial. Journal of medical Internet research. 2017;19(5):e144.

[33] Lilholt PH, Udsen FW, Ehlers L, Hejlesen OK. Telehealthcare for patients suffering from chronic obstructive pulmonary disease: effects on health-related quality of life: results from the Danish 'TeleCare North'cluster-randomised trial. BMJ open. 2017;7(5):e014587.

[34] Rixon L, Hirani SP, Cartwright M, Beynon M, Doll H, Steventon A, et al. A RCT of telehealth for COPD patient's quality of life: the whole system demonstrator evaluation. The Clinical Respiratory Journal. 2017;11(4):459–469.

[35] Kessler R, Casan-Clara P, Koehler D, Tognella S, Viejo JL, Dal Negro RW, et al. COMET: a multicomponent home-based disease-management programme versus routine care in severe COPD. European Respiratory Journal. 2018;51(1).

[36] Soriano JB, Garc´ıa-R´ıo F, V´azquez-Espinosa E, Conforto JI, Hernando-Sanz A, L´opez-Yepes L, et al. A multicentre, randomized controlled trial of telehealth for the management of COPD. Respiratory medicine. 2018;144:74–81.

[37] Tupper OD, Gregersen TL, Ringbaek T, Brøndum E, Frausing E, Green A, et al. Effect of tele–health care on quality of life in patients with severe COPD: a randomized clinical trial. International journal of chronic obstructive pulmonary disease. 2018:2657–2662.

[38] Walker PP, Pompilio PP, Zanaboni P, Bergmo TS, Prikk K, Malinovschi A, et al. Telemonitoring in chronic obstructive pulmonary disease (CHROMED). A randomized clinical trial. American journal of respiratory and critical care medicine. 2018;198(5):620–628.

[39] M´ınguez Clemente P, Pascual-Carrasco M, Mata Hern´andez C, Malo de Molina R, Arvelo L, Cadavid B, et al. Follow-up with telemedicine in early discharge for COPD exacerbations: randomized clinical trial (TELEMEDCOPD-trial). COPD: Journal of Chronic Obstructive Pulmonary Disease. 2020;18(1):62–69.

[40] Sink E, Patel K, Groenendyk J, Peters R, Som A, Kim E, et al. Effectiveness of a novel, automated telephone intervention on time to hospitalisation in patients with COPD: a randomised controlled trial. Journal of Telemedicine and Telecare. 2020;26(3):132–139.

[41] Koff PB, Min Sj, Freitag TJ, Diaz DL, James SS, Voelkel NF, et al. Impact of proactive integrated care on chronic obstructive pulmonary disease. Chronic Obstructive Pulmonary Diseases: Journal of the COPD Foundation. 2021;8(1):100.

[42] Rassouli F, Germann A, Baty F, Kohler M, Stolz D, Thurnheer R, et al. Telehealth mitigates COPD disease progression compared to standard of care: a randomized controlled crossover trial. Journal of Internal Medicine. 2021;289(3):404–410.

[43] Andersen FD, Trolle C, Pedersen AR, Køpfli ML, Børgesen S, Jensen MS, et al. Effect of telemonitoring on readmissions for acute exacerbation of chronic obstructive pulmonary disease: A randomized clinical trial. Journal of Telemedicine and Telecare. 2023:1357633X221150279.

[44] Køpfli ML, Børgesen S, Jensen MS, Hyldgaard C, Bell C, Andersen FD. Effect of telemonitoring on quality of life for patients with chronic obstructive pulmonary disease-A randomized controlled trial. Chronic Respiratory Disease. 2023;20:14799731231157771.

[45] Jensen MH, Cichosz SL, Dinesen B, Hejlesen OK. Moving prediction of exacerbation in chronic obstructive pulmonary disease for patients in telecare. Journal of telemedicine and telecare. 2012;18(2):99–103.

[46] van der Heijden M, Lucas PJ, Lijnse B, Heijdra YF, Schermer TR. An autonomous mobile system for the management of COPD. Journal of biomedical informatics. 2013;46(3):458–469.

[47] Bellos CC, Papadopoulos A, Rosso R, Fotiadis DI. Identification of COPD patients' health

status using an intelligent system in the CHRONIOUS wearable platform. IEEE journal of biomedical and health informatics. 2013;18(3):731–738.

[48] Fern´andez-Granero M, S´anchez-Morillo D, Le´on-Jim´enez A, Crespo L. Automatic prediction of chronic obstructive pulmonary disease exacerbations through home telemonitoring of symptoms. Bio-medical materials and engineering. 2014;24(6):3825–3832.

[49] Shah SA, Velardo C, Gibson OJ, Rutter H, Farmer A, Tarassenko L. Personalized alerts for patients with COPD using pulse oximetry and symptom scores. In: 2014 36th Annual International Conference of the IEEE Engineering in Medicine and Biology Society. IEEE; 2014. p. 3164–3167.

[50] Fernandez-Granero MA, Sanchez-Morillo D, Lopez-Gordo MA, Leon A. A machine learning approach to prediction of exacerbations of chronic obstructive pulmonary disease. In: International Work-Conference on the Interplay Between Natural and Artificial Computation. Springer; 2015. p. 305–311.

[51] Fernandez-Granero MA, Sanchez-Morillo D, Leon-Jimenez A. Computerised analysis of telemonitored respiratory sounds for predicting acute exacerbations of COPD. Sensors. 2015;15(10):26978–26996.

[52] Mohktar MS, Redmond SJ, Antoniades NC, Rochford PD, Pretto JJ, Basilakis J, et al. Predicting the risk of exacerbation in patients with chronic obstructive pulmonary disease using home telehealth measurement data. Artificial intelligence in medicine. 2015;63(1):51–59.

[53] Sanchez-Morillo D, Fernandez-Granero MA, Jim´enez AL. Detecting COPD exacerbations early using daily telemonitoring of symptoms and k-means clustering: a pilot study. Medical & biological engineering & computing. 2015;53:441–451.

[54] Christian Riis H, Jensen MH, Cichosz SL, Hejlesen OK. Prediction of exacerbation onset in chronic obstructive pulmonary disease patients. Journal of Medical Engineering & Technology. 2016;40(1):1–7.

[55] Shah SA, Velardo C, Farmer A, Tarassenko L. Exacerbations in chronic obstructive pulmonary disease: identification and prediction using a digital health system. Journal of medical Internet research. 2017;19(3):e7207.

[56] Fernandez-Granero MA, Sanchez-Morillo D, Leon-Jimenez A. An artificial intelligence approach to early predict symptom-based exacerbations of COPD. Biotechnology & Biotechnological Equipment. 2018;32(3):778–784.

[57] Kronborg T, Mark L, Cichosz SL, Secher PH, Hejlesen O. Population exacerbation incidence contains predictive information of acute exacerbations in patients with chronic obstructive pulmonary disease in telecare. International Journal of Medical Informatics. 2018;111:72–76.

[58] Nunavath V, Goodwin M, Fidje JT, Moe CE. Deep neural networks for prediction of exacerbations of patients with chronic obstructive pulmonary disease. In: Engineering Applications of Neural Networks: 19th International Conference, EANN 2018, Bristol, UK, September 3-5, 2018, Proceedings 19. Springer;
2018. p. 217–228.

[59] Orchard P, Agakova A, Pinnock H, Burton CD, Sarran C, Agakov F, et al. Improving prediction of risk of hospital admission in chronic obstructive pulmonary disease: application of machine learning to telemonitoring data. Journal of medical Internet research. 2018;20(9):e263.

[60] Boer LM, van der Heijden M, van Kuijk NM, Lucas PJ, Vercoulen JH, Assendelft WJ, et al. Validation of ACCESS: an automated tool to support self-management of COPD exacerbations. International journal of chronic obstructive pulmonary disease. 2018;13:3255.

[61] Boer L, Bischoff E, van der Heijden M, Lucas P, Akkermans R, Vercoulen J, et al. A smart mobile health tool versus a paper action plan to support self-management of chronic

obstructive pulmonary disease exacerbations: randomized controlled trial. JMIR mHealth and uHealth. 2019;7(10):e14408.

[62] Jin Y, Zhang T, Cao Z, Zhao N, Chen C, Wang D, et al. Prediction Indicators for Acute Exacerbations of Chronic Obstructive Pulmonary Disease by Combining Non-linear analyses and Machine. In: 2018 IEEE International Conference on Bioinformatics and Biomedicine (BIBM). IEEE; 2018. p. 2515–2521.

[63] Iadanza E, Mudura V, Melillo P, Gherardelli M. An automatic system supporting clinical decision for chronic obstructive pulmonary disease. Health and Technology. 2020;10:487–498.

[64] Kronborg T, Hangaard S, Cichosz SL, Hejlesen O. A two-layer probabilistic model to predict COPD exacerbations for patients in telehealth. Computers in Biology and Medicine. 2021;128:104108.

[65] Patel N, Kinmond K, Jones P, Birks P, Spiteri MA. Validation of COPDPredict™: unique combination of remote monitoring and exacerbation prediction to support preventative management of COPD exacerbations. International journal of chronic obstructive pulmonary disease. 2021:1887–1899.

[66] Wu CT, Li GH, Huang CT, Cheng YC, Chen CH, Chien JY, et al. Acute exacerbation of a chronic obstructive pulmonary disease prediction system using wearable device data, machine learning, and deep learning: development and cohort study. JMIR mHealth and uHealth. 2021;9(5):e22591.

[67] Chmiel FP, Burns DK, Pickering JB, Blythin A, Wilkinson TM, Boniface MJ. Prediction of chronic obstructive pulmonary disease exacerbation events by using patient self-reported data in a digital health app: statistical evaluation and machine learning approach. JMIR medical informatics. 2022;10(3):e26499.

[68] Wu CT, Wang SM, Su YE, Hsieh TT, Chen PC, Cheng YC, et al. A Precision Health Service for Chronic Diseases: Development and Cohort Study Using Wearable Device, Machine Learning, and Deep Learning. IEEE Journal of Translational Engineering in Health and Medicine. 2022;10:1–14.

[69] Jang S, Kim Y, Cho WK. A systematic review and meta-analysis of telemonitoring interventions on severe COPD exacerbations. International Journal of Environmental Research and Public Health. 2021;18(13):6757.

[70] Kruse C, Pesek B, Anderson M, Brennan K, Comfort H, et al. Telemonitoring to manage chronic obstructive pulmonary disease: systematic literature review. JMIR medical informatics. 2019;7(1):e11496.

[71] Buekers J, De Boever P, Vaes AW, Aerts JM, Wouters EF, Spruit MA, et al. Oxygen saturation measurements in telemonitoring of patients with COPD: a systematic review. Expert review of respiratory medicine. 2018;12(2):113–123.

[72] Milkowska-Dymanowska J, Bia-las AJ, Obrebski W, G´orski P, Piotrowski WJ. A pilot study of daily telemonitoring to predict acute exacerbation in chronic obstructive pulmonary disease. International Journal of Medical Informatics. 2018;116:46–51.

[73] Van der Heijden M, Velikova M, Lucas PJ. Learning Bayesian networks for clinical time series analysis. Journal of biomedical informatics. 2014;48:94–105.

[74] Chau JPC, Lee DTF, Yu DSF, Chow AYM, Yu WC, Chair SY, et al. A feasibility study to investigate the acceptability and potential effectiveness of a telecare service for older people with chronic obstructive pulmonary disease. International journal of medical informatics. 2012;81(10):674–682.

[75] Burton C, Pinnock H, McKinstry B. Changes in telemonitored physiological variables and symptoms prior to exacerbations of chronic obstructive pulmonary disease. Journal of telemedicine and telecare. 2015;21(1):29–36.

[76] Watz H, Tetzlaff K, Magnussen H, Mueller A, Rodriguez-Roisin R, Wouters EF, et al. Spirometric changes during exacerbations of COPD: a post hoc analysis of the WISDOM

trial. Respiratory research. 2018;19(1):1–7.

[77] Chawla H, Bulathsinghala C, Tejada JP, Wakefield D, ZuWallack R. Physical activity as a predictor of thirty-day hospital readmission after a discharge for a clinical exacerbation of chronic obstructive pulmonary disease. Annals of the American Thoracic Society. 2014;11(8):1203–1209.

[78] Jones P, Harding G, Berry P, Wiklund I, Chen W, Leidy NK. Development and first validation of the COPD Assessment Test. European Respiratory Journal. 2009;34(3):648–654.

[79] Min SJ, Lee YS, Park YB, Yum HK, Park MJ, Yoo JH. COPD Assessment Test (CAT) has a positive relationship with exacerbations in COPD patients. Eur Respiratory Soc; 2019.

[80] Rassouli F, Baty F, Stolz D, Albrich WC, Tamm M, Widmer S, et al. Longitudinal change of COPD assessment test (CAT) in a telehealthcare cohort is associated with exacerbation risk. International Journal of Chronic Obstructive Pulmonary Disease. 2017;12:3103.

[81] Lacoma A, Prat C, Andreo F, Dominguez J. Biomarkers in the management of COPD. European Respiratory Review. 2009;18(112):96–104.

[82] Hurst JR, Donaldson GC, Perera WR, Wilkinson TM, Bilello JA, Hagan GW, et al. Use of plasma biomarkers at exacerbation of chronic obstructive pulmonary disease. American journal of respiratory and critical care medicine. 2006;174(8):867–874.

[83] Butler CC, Gillespie D, White P, Bates J, Lowe R, Thomas-Jones E, et al. C-reactive protein testing to guide antibiotic prescribing for COPD exacerbations. New England Journal of Medicine. 2019;381(2):111–120.

[84] Koutsokera A, Kostikas K, Nicod LP, Fitting JW. Pulmonary biomarkers in COPD exacerbations: a systematic review. Respiratory research. 2013;14(1):1–12.

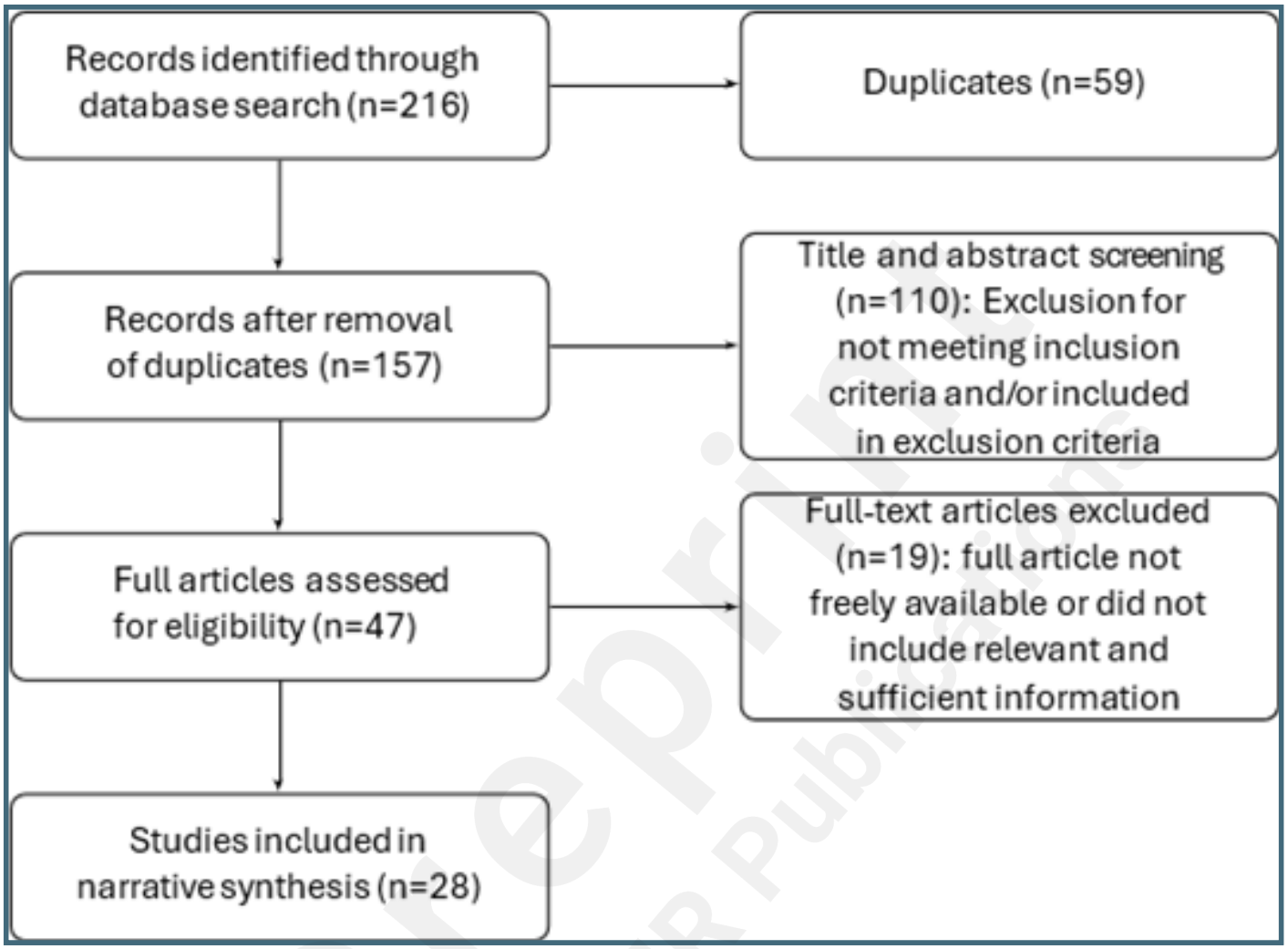
[85] Lawal O, Ahmed WM, Nijsen TM, Goodacre R, Fowler SJ. Exhaled breath analysis: a review of ‘breath-taking’methods for off-line analysis. Metabolomics. 2017;13:1–16.

[86] Kamal F, Kumar S, Edwards MR, Veselkov K, Belluomo I, Kebadze T, Romano A, Trujillo-Torralbo MB, Shahridan Faiez T, Walton R, Ritchie AI. Virus-induced volatile organic compounds are detectable in exhaled breath during pulmonary infection. American Journal of Respiratory and Critical Care Medicine. 2021 Nov 1;204(9):1075-85.

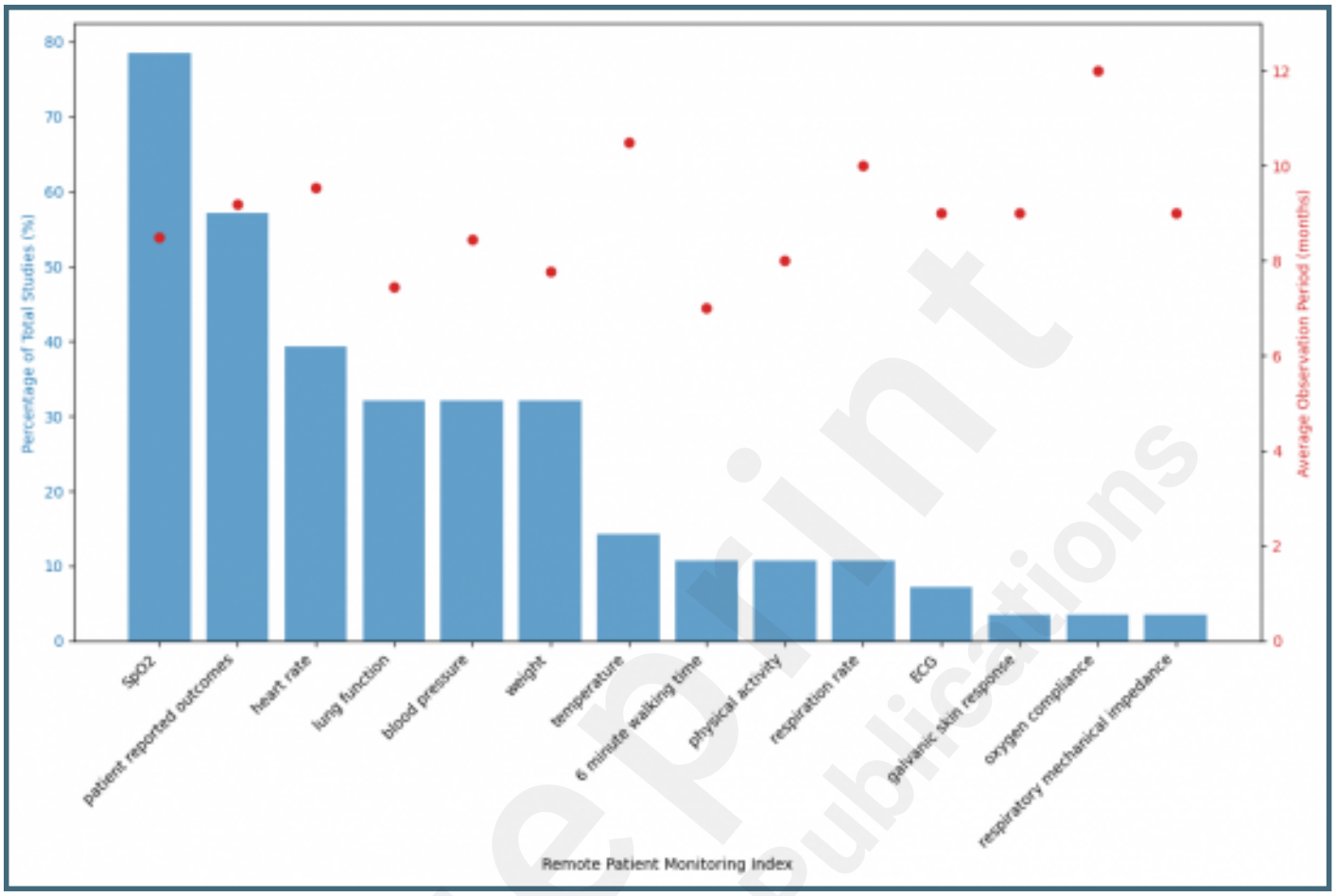
# Supplementary Files

# Figures

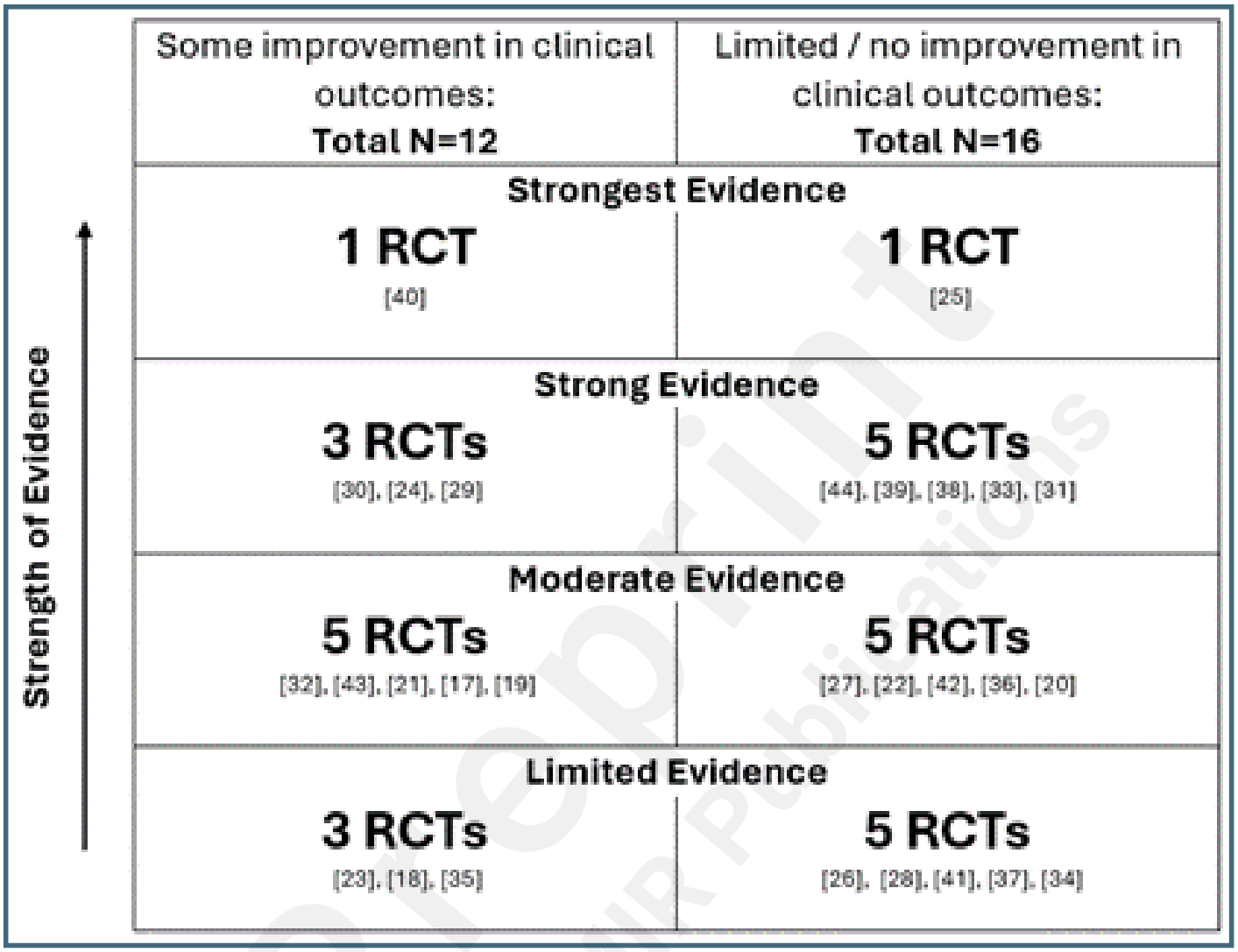
Search procedure for randomised controlled trials where remote patient monitoring was used as an intervention to treat or improve AECOPD.



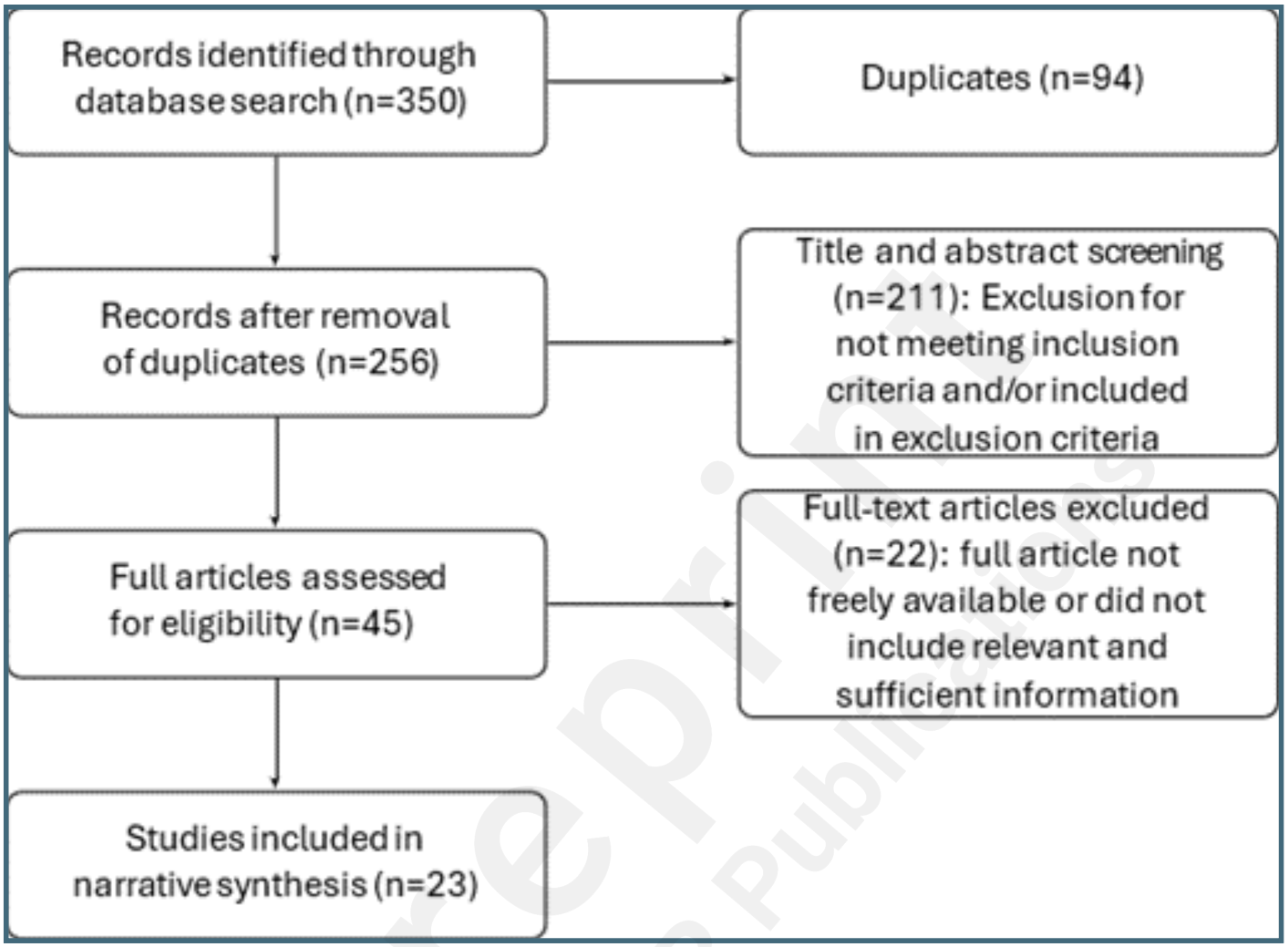
Distribution of RPM Indexes and Average Study Duration for the first search. The figure illustrates the percentage of total studies each RPM index appears in, alongside the average duration of these studies.



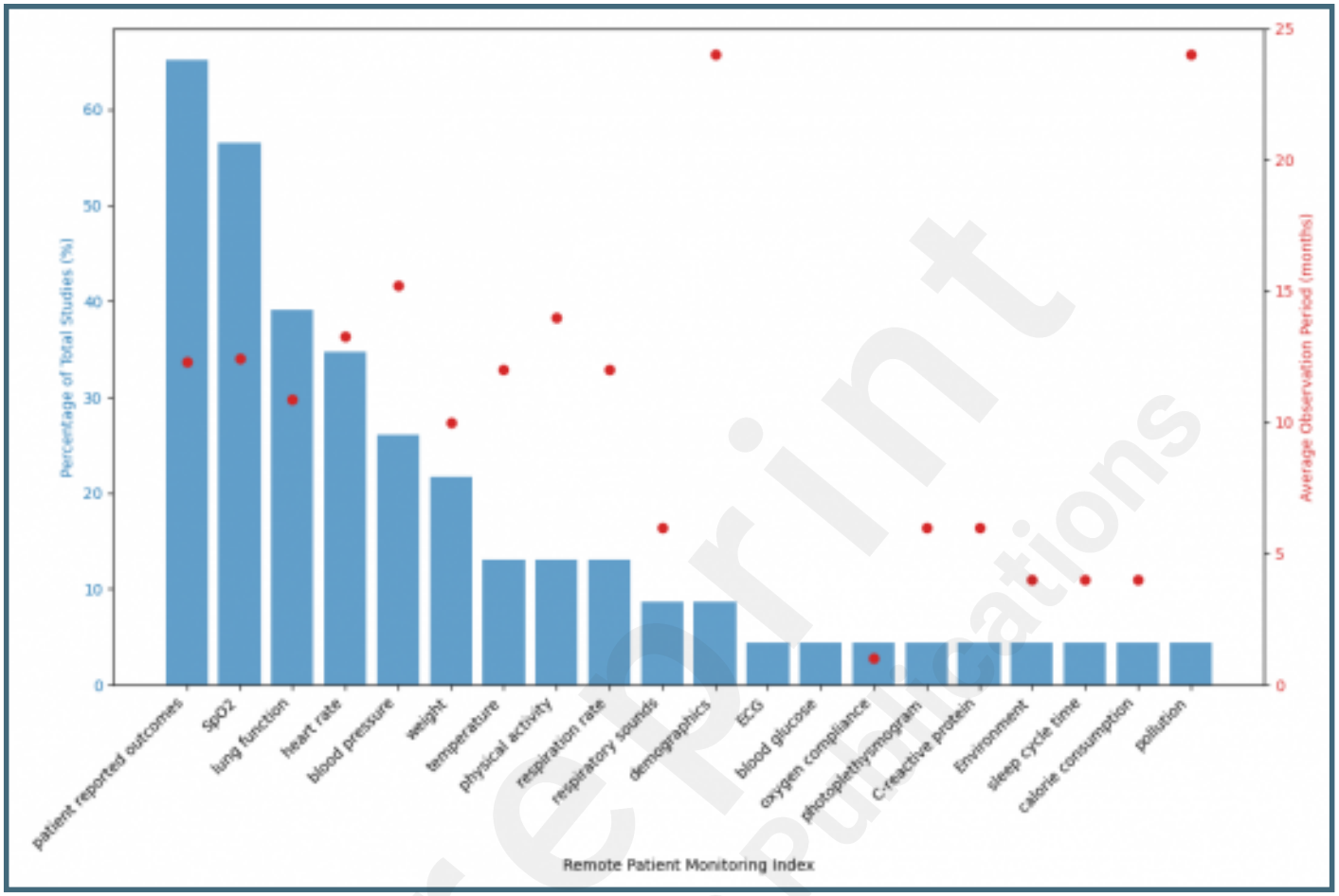
CASP RCT Checklist Rankings of RCTs on RPM in COPD. This figure presents the rankings of RCTs on RPM in COPD according to the CASP RCT checklist.



Search procedure for empirical studies on RPM and machine learning to predict AECOPD.



Distribution of RPM Indexes and Average Study Duration for the second search. The figure illustrates the percentage of total studies each RPM index appears in, alongside the average duration of these studies.



# Multimedia Appendixes

Search methods and strategy.
URL: http://asset.jmir.pub/assets/a435d0b646eaa1ce9ce440cc2c256341.docx

A detailed breakdown of the study characteristics, method of intervention delivery, and outcomes.
URL: http://asset.jmir.pub/assets/aadfa99a8433c2f01994e005404e7c39.docx