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A cohort study following up on a randomised controlled trial of a telemedicine application in COPD patients

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Abstract

Introduction: The studies that constitute the knowledge base of evidence based medicine represent only 5%–50% of patients seen in routine clinical practice. Therefore, whether the available evidence applies to the implementation of a particular service often remains unclear. Chronic obstructive pulmonary disease (COPD) is no exception.

Methods: In this article, the effects of implementing a telemedicine intervention for COPD patients were analysed using data collected before, during, and after a randomised controlled trial (RCT).

More specifically, regression techniques using robust variance estimators were used to analyse whether the use of telemedicine, patient age, and gender could explain the risk of readmission, length of hospital admission, and death during a five-year observation period.

Results: Increased risk of readmission was significantly related to both use of telemedicine and increased age in three sub-periods of the study, whereas women showed a more pronounced risk of readmission than men only during and after the RCT period. The number of days admitted to hospital was higher for patients using telemedicine and being of older age. Risk of death during the observation period was decreased for patients using telemedicine and for female patients and increased for elderly patients. No interaction between intervention and time period was observed.

Statistically significant relationships were identified between use of telemedicine and risk of readmission, days admitted to hospital, and death.

Discussion: Research on effect modification in telemedicine is essential in designing future implementation of interventions as it cannot be taken for granted that effectiveness follows from efficacy.

Keywords

External validity, telemedicine, evidence based practice, efficacy, effectiveness

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Background

In principle, evidence based medicine should be provided to all patients. However, most guidelines on translating evidence into practice are largely based on randomised controlled trials (RCTs) that may include only between 5 and 50% of patients seen in routine practice.[1–3]

In other words, due to strict inclusion criteria, the external validity of many trials may be low. Formally, external validity has been defined as 'whether the results [of randomised controlled trials] can be reasonably applied to a definable group of patients in a particular clinical setting in routine practice'.[4] This definition highlights the potential efficacy of an intervention (therapeutic benefit under ideal circumstances) versus effectiveness (therapeutic benefit under everyday life circumstances[5]).

Few studies have been carried out to investigate the differences between outcomes in patients in trials compared to real-life, non-enrolled patients.[2,6–10] However, it is acknowledged that efficacy studies are more likely to obtain favourable results than effectiveness studies, and that the difference can be attributed to contextual

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circumstances,[5] for example socio-demographic status and gender.

A systematic literature review on external validity, which was conducted for this article, resulted in 12 articles (details on the search and selection strategy are provided in the supplementary material). These articles presented empirical data on external validity without restrictions on any particular clinical field. Eight of the articles presented data on the proportion of patients seen in routine practice who were considered eligible for randomised trials. In the field of asthma and *chronic obstructive pulmonary disease* (COPD), 4%–6% of patients were included;[1,11] of patients with myocardial infarction, 50% were included;[12] and with stroke/ischaemic attack, 25%–67% were included.[7] Among patients reported as eligible for medication for lowering blood pressure, 60% were actually included,[13] 50% were included in a nicotine dependency trial,[3] and less than 20% of enrolees were part of a trial on anxiety.[14] Finally, in the only article describing the external validity of a telemedicine trial, Riper et al.[9] found that their intervention on alcohol dependency was externally valid, with no difference in the results of their trial compared to the real-life effectiveness.

With these differences in test results versus implementation in practice, it is clear that further understanding of the modifications of effects that cause implementation response to differ from that of RCTs will improve real-life interventions.[15]

In Denmark, hospitals are obliged to develop internal but publicly available guidelines for treatment.[16] From local guidelines it appears that a telemedicine intervention is recommended for patients admitted with COPD.[17] (The telemedicine intervention is described in detail in Rasmussen et al.[17] and Sorknaes et al.[18] It consisted of real-time video-consultations with hospital nurses for approximately 30 mins each day during the first week after discharge. The consultation included measurements of blood oxygen level and airflow.) In the guideline, it is mentioned that an RCT has been conducted, that patients are positive towards the technology, and that no statistically significant differences were identified for the risk of readmission or risk of death.[17] The guideline does not recommend restrictions on the use of telemedicine based on the RCT criteria for inclusion.[18] Thus, in the periods before and after the RCT there were no descriptions of the characteristics of patients to consider for the telemedicine intervention, and the decision was then left to clinical judgement. The impact of this potential difference in selection criteria on the overall effectiveness of the intervention constituted the main focus of this cohort study.

In the present study, the effectiveness of the telemedicine intervention provided to patients admitted to hospital due to exacerbation of their COPD was measured during three different periods of time. The effectiveness was measured in terms of the risk of readmission, number of days spent in hospital, and the risk of dying from any cause. Risk of readmission and risk of death are commonly used as outcome measures throughout the literature on COPD.[19] The number of days spent in hospital was used as it was hypothesised that the intervention could lead to earlier discharge. This hypothesis could not be tested in the RCT because of ethical considerations,[18] so it was reported within this study instead. The aim of the study was to investigate the effectiveness of a telemedicine intervention in COPD patients during, before, and after an RCT while adjusting for age and gender.

Methods

The study was a cohort study covering the time span from 1 January 2009 to 31 December 2013, comprising three periods:

- Pre-RCT: observations registered before introduction of the RCT (1 January 2009–31 April 2010).
- During RCT: observations registered during the period of the RCT (1 May 2010–31 October 2011).
- Post-RCT: the group of observations registered after the RCT ended (1 November 2011–31 December 2013).

Included patients were admitted to hospital because of an acute exacerbation of their COPD. COPD was diagnosed according to the GOLD guidelines (global initiative for chronic obstructive lung disease).[20] In the guideline, COPD is defined as:

> Chronic Obstructive Pulmonary Disease (COPD), a common preventable and treatable disease, is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Exacerbations and comorbidities contribute to the overall severity in individual patients.

Thus, the condition is complex and multifactorial, and the diagnostic guidelines are revised on a five-year basis.[21] While airflow as measured by spirometry is a prerequisite for the diagnostic procedure, it is further qualified by the assessed risk and number of symptoms.[20,21]

Population and assignment to intervention

The population studied was composed of all patients admitted to Odense University Hospital (OUH), Denmark, during the years 2009 to 2013 with acute exacerbation of COPD registered as primary diagnosis on the basis of ICD-10-codes (international classification of diseases).[22,23] Patients were classified within each period into those who received telemedicine intervention subsequent to their admission to hospital (cases) and those who did not (controls), where the telemedicine intervention was registered in the hospital administrative system. During the RCT phase, a group of patients selected on the basis of criteria for inclusion was asked to participate in the study. Half of the patients included were randomly assigned to the intervention versus control group.

In comparison, in the periods before and after the RCT, the patients were selected for intervention on the basis of clinical judgement (incorporating the knowledge generated from the RCT regarding the latter). So there were, theoretically, different ways of selecting patients for telemedicine intervention in the different periods of time. The control group included all patients not receiving the intervention throughout the study period and was, therefore, not restricted to selected patients.

Outcomes

Outcomes were:

- Readmissions (defined as admission to hospital subsequent to a previous admission within a period of 42 days);
- Number of days being admitted to hospital;
- Death during period of observation.

Data were extracted from a hospital administrative system, so that selection of variables was based on (a) availability of data, (b) data previously used in telemedicine studies on COPD,[19] and (c) outcomes of the previous efficacy study (RCT).[18] These also comprised the demographic covariates age and gender.

Data management

The dataset was composed of observations representing either an admission to hospital or an ambulatory visit. Ineligible observations were excluded prior to the statistical analysis as follows. Observations in patients under the age of 30 years were excluded from the dataset ($N = 51$) because COPD usually develops over a period of 20 years, thus indicating an age older than 30 is necessary for patients to suffer from COPD. In addition, a number of observations had registrations of admission and discharge from hospital, but lacked registrations such as age or treatment codes ($N = 26$) and, therefore, had to be excluded.

One observation was deleted due to an inconsistency (the patient had been registered as admitted to hospital later than her date of death).

Finally, 17 observations were excluded from the data set due to abnormally long hospital admissions (duration over 90 days) because, according to the professor of the department, admissions longer than this were not caused by the COPD diagnosis.[24]

Statistical analyses

Demographics were described for all groups by means and standard deviations for continuous variables (or medians and ranges in case of skewed data) and proportions with respective percentages for categorical variables. Differences on demographic aspects between intervention and control groups were assessed by Student's t-test and by the χ^2 test where appropriate. Risk of readmission (yes/no) was analysed by means of logistic regression and days of admittance to hospital by negative binomial regression (both using robust variance estimators when appropriate). In case of interaction between telemedicine intervention and time period, stratified analyses by time periods were done. Survival analyses were performed using Cox proportional hazards regression, which took into account the difference in time (measured in days) that each individual contributed to the analyses. The time measurement was started when a person entered the cohort by admittance to hospital and ended at discharge or when the person died (all-cause mortality). In a sensitivity analysis, missing inclusion dates, due to outpatient visits, were imputed by taking the start date of the respective period as replacement. This was done in 1438, 1218, and 1293 cases in the respective three periods (pre-RCT, during RCT and post-RCT).

Explanatory variables in all regression models were telemedicine intervention (yes/no), age, gender, and period (pre-RCT, during RCT and post-RCT).

Significance level was 5% (two-sided testing). All analyses were carried out using STATA/IC 13 (StataCorp Lp, College Station, Texas 77845 USA).

Ethics

This project was approved by the Danish Data Protection Agency and needed no approval from the ethics committee.

Results

The patient administrative system provided data on 11,303 patients admitted to hospital during the five-year period covering 2009 to 2013. While one observation represented either an admission to hospital or an outpatient visit, each person could account for several observations. While 8257 (73.05%) patients contributed only to one period, the remaining patients contributed to two periods ($N = 2130$ (18.85%)) or to all three periods ($N = 916$ (8.10%)), see Table 1. In total, the patients contributed

Table 1. Distribution of how 11,303 patients contributed to either single time periods alone or to multiple time periods (N=15,265 occurrences).

Pre-RCT	During RCT	Post-RCT	Frequency	Percentage	Cumulative
X			3403	30.11	30.11
	X		1628	14.40	44.51
		X	3226	28.54	73.05
X	X		839	7.42	80.47
X		X	533	4.72	85.19
	X	X	758	6.71	91.90
X	X	X	916	8.10	100.00

RCT: randomised controlled trial.

Table 2. Demographic and clinical characteristics of patients.

Age	Telemedicine mean (SD)	Control mean (SD)	*p*-value	Number of observations	
				Telemedicine	Control
Pre-RCT	72.85 (9.31)	71.68 (11.72)	0.16	206	5485
During RCT	71.99 (9.60)	71.97 (11.75)	0.98	210	3931
Post-RCT	71.80 (9.83)	72.87 (12.16)	0.03	689	4744
Gender (f)	*N* (%)	*N* (%)			
Pre-RCT	113 (54.85)	2804 (51.12)	0.29	206	5485
During RCT	127 (60.48)	2027 (51.56)	0.01	210	3931
Post-RCT	394 (57.18)	2425 (51.12)	0.003	689	4744
Fatalities	*N* (%)	*N* (%)			
Pre-RCT	41 (19.90)	1463 (26.67)	0.03	206	5485
During RCT	35 (16.67)	823 (20.94)	0.14	210	3931
Post-RCT	153 (22.21)	1278 (26.94)	0.008	689	4744
Readmission	*N* (%)	*N* (%)			
Pre-RCT	102 (49.51)	1281 (23.35)	<0.0001	206	5485
During RCT	103 (49.05)	868 (22.08)	<0.0001	210	3931
Post-RCT	406 (58.93)	943 (19.88)	<0.0001	689	4744
Number of readmissions	Mean (SD)	Mean (SD)			
Pre-RCT	1.51 (2.58)	0.51 (1.75)	<0.0001	206	5485
During RCT	1.54 (2.69)	0.45 (1.83)	<0.0001	210	3931
Post-RCT	1.79 (3.09)	0.34 (0.96)	<0.0001	689	4744
Days admitted	Mean (SD)	Mean (SD)			
Pre-RCT	16.67 (17.75)	8.01 (13.38)	<0.0001	206	5485
During RCT	11.87 (13.69)	6.45 (11.71)	<0.0001	210	3931
Post-RCT	12.97 (16.01)	6.82 (11.80)	<0.0001	689	4744
Average days admitted	Mean (SD)	Mean (SD)			
Pre-RCT	4.43 (4.23)	4.14 (6.72)	0.53	206	5485
During RCT	3.42 (2.75)	3.58 (6.40)	0.72	210	3931
Post-RCT	3.11 (2.89)	4.02 (6.59)	0.0004	689	4744

Note: Individual patients could be represented only once within each period, but were allowed to contribute to different periods over time.
RCT: randomised controlled trial

with 89,050 observations in terms of hospital admissions and outpatient visits.

Table 2 summarises the distribution of demographic variables (age and gender) and outcome variables (fatalities, readmission, number of readmissions, days admitted, and average number of days admitted) separately for patients receiving the telemedicine intervention and for those who did not. Data are presented for each of the three periods of time (pre-RCT, during RCT and post-RCT).

Age differed between the intervention and the control group only in the last period of measurement (post-RCT, 71.80 years vs. 72.87 years, $p = 0.03$). There were significantly more females in the intervention group in the during RCT period (60.48% vs. 51.56%, $p = 0.01$) and in the post-RCT period (57.18% vs. 51.12%, $p = 0.003$). Smaller proportions of fatalities were observed in the telemedicine group throughout all periods of time, but to a statistically significant degree only in the pre-RCT phase (19.90% vs. 26.67%, $p = 0.03$) and the post-RCT phase (22.21% vs. 26.94%, $p = 0.008$). Every second patient in the intervention group was readmitted to hospital, whereas this was the case for only every fourth to fifth patient of the control group ($p < 0.0001$ in all three periods). Patients of the intervention group were, on average, 1–1.45 times more often readmitted to hospital than patients of the control group ($p < 0.0001$ in all three periods). Moreover, patients receiving telemedicine were admitted to hospital longer than those who did not receive telemedicine (between 5.42 and 8.66 days, $p < 0.0001$ in all three periods), but the average stay at hospital was significantly shorter in patients using telemedicine in the post-RCT period (3.11 vs. 4.02 days, $p = 0.0004$).

Readmission

In the pre-RCT group, the odds ratio (OR) for a readmission in patients with telemedicine intervention was 3.18 (95% CI 2.40–4.22, $p < 0.0001$; see Table 3). During the

Table 3. Odds ratio of readmission for patients.

	Telemedicine			Age			Gender (female)			
Period	OR	95% CI	*p*-value	OR	95% CI	*p*-value	OR	95% CI	*p*-value	Number of observations
Pre-RCT	3.18	2.40–4.22	<0.0001	1.023	1.018–1.029	<0.0001	1.11	0.99–1.26	0.09	5691
During RCT	3.44	2.59–4.57	<0.0001	1.03	1.02–1.04	<0.0001	1.25	1.08–1.45	0.003	4141
Post-RCT	6.04	5.09–7.16	<0.0001	1.022	1.017–1.028	<0.0001	1.15	1.01–1.31	0.04	5433

Each patient could contribute only once per period, but could contribute in different periods of time. Due to stratification by period, no adjustment for the correlation structure was done.
OR: odds ratio; RCT: randomised controlled trial.

Table 4. Negative binomial regression on days admitted to hospital.

	IRR	95% CI	*p*-value
Telemedicine	1.97	1.82–2.15	<0.0001
Age	1.017	1.014–1.021	<0.0001
Gender (female)	1.01	0.95–1.08	0.70
Pre-RCT	–	–	–
During RCT	0.80	0.74–0.85	<0.0001
Post-RCT	0.84	0.79–0.90	<0.0001

Observations: 15,265, adjusted for 11,303 clusters.
IRR: incidence rate ratio; RCT: randomised controlled trial.

Table 5. Cox proportional hazard regression on death during the study period.

	HR	95% CI	*p*-value
Telemedicine	0.50	0.37–0.68	<0.0001
Age	1.035	1.032–1.039	<0.0001
Gender (female)	0.84	0.78–0.89	<0.0001
Pre-RCT	–	–	–
During RCT	0.95	0.87–1.04	0.25
Post-RCT	1.0	0.93–1.08	0.98
Interaction	–	–	–
Telemedicine × RCT	1.05	0.66–1.66	0.83
Telemedicine × post-RCT	1.14	0.80–1.63	0.46

Observations: 11,316 in 8040 patients; deaths: 3729; time at risk: 9561.29 person-days.
HR: hazard ratio; RCT: randomised controlled trial.

RCT, patients receiving telemedicine were more likely to experience a readmission compared to patients not receiving telemedicine (OR 3.44, 95% CI 2.59–4.57, $p < 0.0001$). In the post-RCT group, patients receiving telemedicine were more likely to be readmitted to hospital (OR 6.04, 95% CI 5.09–7.16, $p < 0.0001$).

In all three periods, higher age was significantly associated with the risk of experiencing a readmission (OR between 1.022 and 1.03, $p < 0.0001$). Females were more likely to be readmitted to hospital than males during all three periods of time. In the pre-RCT period, the difference was not statistically significant (OR 1.11, 95% CI 0.99–1.26, $p = 0.09$), during the RCT period (OR 1.25, 95% CI 1.08–1.45, $p = 0.003$) and in the post-RCT period (OR 1.15, 95% CI 1.01–1.31, $p = 0.04$) it was statistically significant.

Days spent admitted to hospital

Patients receiving the telemedicine intervention, compared to patients who did not receive the telemedicine intervention, had a rate 1.97 times greater for days of admission (incidence rate ratio (IRR) 1.97, 95% CI 1.82–2.15, $p < 0.0001$; see Table 4). Age was positively related to days spent in hospital, indicating that an increase in age by one year was associated with an increase of 1.7% in the rate of days spent at hospital (IRR 1.017, 95% CI 1.014–1.021, $p < 0.0001$). Female gender was not significantly related to days spent in hospital (IRR 1.01, 95% CI 0.95–1.08, $p = 0.70$). The group of patients admitted during the RCT experienced a decreased rate for days admitted to hospital in comparison to the pre-RCT group (IRR 0.80, 95% CI 0.74–0.85, $p < 0.0001$). The same applied for the post-RCT group when compared to the pre-RCT group (IRR 0.84, 95% CI 0.79–0.90, $p < 0.0001$).

Death

Patients receiving telemedicine had half the risk of dying during the five-year observation period of those who did not (hazard ratio (HR) 0.50, 95% CI 0.37–0.68, $p < 0.0001$; see Table 5). Increased age increased the risk of death by approximately 3.5% per year (HR 1.035, 95% CI 1.032–1.039, $p < 0.0001$), and females were less likely to die during the study period than males (HR 0.84, 95% CI 0.78–0.89, $p < 0.0001$). No statistically significant differences were observed between the pre-RCT and the during RCT and post-RCT periods. No significant interaction between intervention and period of time was observed.

When imputing missing start dates for outpatient visits with the purpose of conducting a sensitivity analysis, patients receiving telemedicine still had a lower risk of

Table 6. Sensitivity analysis of Cox proportional hazard regression on death during the study period, imputing missing start dates for outpatient visits.

	HR	95% CI	*p*-value
Telemedicine	0.65	0.47–0.88	0.006
Age	1.051	1.047–1.054	<0.0001
Gender (female)	0.90	0.84–0.96	0.001
Pre-RCT	–	–	–
During RCT	0.82	0.76–0.90	<0.0001
Post-RCT	0.91	0.84–0.98	0.01
Interaction	–	–	–
Telemedicine × RCT	1.22	0.77–1.93	0.40
Telemedicine × post-RCT	1.27	0.89–1.81	0.18

Observations: 15,265 in 11,303 patients; deaths: 3793; time at risk: 16,033.35 person-days.
HR: hazard ratio; RCT: randomised controlled trial.

dying during the five-year observation period than those who did not (HR 0.65, 95% CI 0.47–0.88, $p = 0.006$), see Table 6. Increased age increased the risk of death by approximately 5% per year (HR 1.051, 95% CI 1.047–1.054, $p < 0.0001$), and females were less likely to die during the study period than males (HR 0.90, 95% CI 0.84–0.96, $p = 0.001$). During the RCT and in the post-RCT period, lower risk of death was observed than in the pre-RCT period (HR 0.82, 95% CI 0.76–0.90, $p < 0.0001$ and HR 0.91, 95% CI 0.84–0.98, $p = 0.01$, respectively), but no significant interaction between intervention and period of time was observed.

Discussion

To our knowledge, this is the first study on the routine practice effectiveness of telemedicine used in COPD patients. It was based on a large dataset including hospital admissions over a five-year period, corresponding to 11,303 patients contributing with a total of 15,265 occurrences during the three time periods.

Our results showed that patients who received telemedicine were (a) more likely to be readmitted to hospital during the study period, (b) more likely to be admitted for a longer time, and (c) less likely to die during the study period than patients not receiving telemedicine. All analyses were adjusted for patients' age and gender. In our sensitivity analysis, the risk of death from any cause was lower for people admitted during the two latter periods of the study, i.e. during RCT and post-RCT, as compared to those admitted prior to the RCT. This may, however, simply be due to the reduced follow-up time in the latter phases of the study as compared to the pre-RCT phase.

Due to limitations in the availability of data, the selection criteria for the telemedicine intervention in the during RCT period compared to periods of non-restricted implementation was determined for age and gender, but not other relevant covariates such as severity of COPD, history of disease or socio-economic status. Further analyses including these variables would be highly relevant contributions to the knowledge of external validity of telemedicine for COPD patients.

Another important limitation in the data extraction procedure could be the request for data. In the case of this article, the criterion for entry into the cohort was COPD as primary diagnosis. Different registration procedures imply that not all usage of the telemedicine equipment was included in the used data set. This is quite likely in that only 1105 observations of usage were registered over the period. Whether the possibly missed registrations would affect the outcomes positively or negatively remains unknown.

Previously, only one published article has reported differences between efficacy and effectiveness of a telemedicine intervention.[9] A web-based self-help intervention was tested in an RCT, and subsequently the intervention was made available to the general public. Demographic differences between the RCT population and the implementation population were identified. Nevertheless, outcomes within the two populations were similar, and the authors concluded that the external validity of the RCT was high. However, this article did not have sufficient data from which to draw conclusions on the effectiveness in routine practice, and the results were thus not comparable to those presented by Riper et al.[9]

Methods of excluding observations within our cohort are debatable. All excluded observations were, however, thoroughly considered before the decision to exclude them was made. Fifty-one observations with an age below 30 years were excluded on the basis of their age. The 26 observations that did not provide data supplementary to the days of admission and discharge were disregarded, since the lack of additional information would have excluded them from the analyses in any case. The 17 admissions with duration of more than 90 days were regarded as typing or registration errors. In the department treating COPD patients at OUH, admissions of this length do not occur.[24] Finally, one observation was removed due to a register error since the date of admission was registered as occurring after the date of death.

All-cause mortality was used in the survival analyses. In the data, only the date of death was provided, not the cause. There were two reasons for including mortality from any cause in the analysis. First, a number of causes of death can be difficult to distinguish from the COPD diagnosis, e.g. breathlessness, which is caused by the COPD, may imply concomitant heart failure or ventricular arrhythmia causing sudden cardiac death. Second, there was no reason to believe that deaths from causes unrelated to COPD would be distributed differently between the intervention group and the control group.

Although it might have further enlightened the findings with more information on death causality, we do not expect that the distribution of cause of death differed between the groups in a way that would affect the results.

The decision to assign a patient to the intervention group whenever he/she had received telemedicine at least

once at any time point during the respective time periods is likely to have had an impact on analyses, since we therefore analysed the data according to the intention-to-treat principle. This is a very conservative approach in this setting, and readmissions as well as days admitted to hospital are, therefore, likely to be overestimated in the intervention group. However, a favourable effect on survival in patients having received telemedicine at some point could still be observed. When patients were – during a specific time period – sometimes admitted while receiving telemedicine and sometimes not, differentiation of effects was challenging. Therefore, we did not see an alternative to our conservative approach of applying the intention-to-treat principle, which in turn is likely to be the method of choice in similar, other investigations.

This paper constitutes, to the best of our knowledge, the third quantitative, scientific contribution on one intervention for COPD patients. The first publication was a cohort study of 100 consecutively selected patients that were assigned to intervention or control in a 1:1 ratio on the basis of geographic location of their residence.[25] The first study identified a statistically significant protective effect of the telemedicine intervention (HR: 0.25, CI: 0.09–0.69). The results were, however, discussed to be subject to selection bias. The second publication was an RCT of 266 patients, which identified no statistically significant differences in risk of readmission between intervention and control groups.[18] Finally, this third publication – a cohort study of the effectiveness – found a statistically significant increased risk of readmission among the recipients of telemedicine compared to non-recipients.

This discrepancy among findings is highly interesting and highlights both the divergence among results of different methodological approaches and the need for follow-up data collections on interventions implemented on the basis of scientific studies.

A number of further analyses are necessary for any final conclusions on the effectiveness of telemedicine for COPD patients. The most important data that would further clarify the issue include severity or history of the COPD, comorbidities, experience with the intervention, number of days until first readmission, residential area, and socio-demographic status. It was not possible to include these variables in the current research project, but further knowledge about these indicators could help clarify the relationship between the intervention and patient outcomes.

Conclusion/perspectives

Knowledge of routine practice effectiveness is relevant for many current and future patients treated in healthcare systems throughout the world. Along with Riper et al.,[9] this article suggests that the external validity of telemedicine applications for COPD patients may differ from telemedicine applications in other clinical fields. Riper et al.[9] found external validity to be high. The current article shows diverging results in that patients receiving the intervention had a higher risk of readmission and simultaneously a lower risk of death when the intervention was applied in routine practice. This is in contrast to findings in other fields in which a clearer pattern emerges: everyday effectiveness has been shown to be less beneficial than suggested by efficacy studies. At this point, it is not clear why this discrepancy was observed. It may be due to chance or caused by unknown differences between telemedicine and other clinical fields. To elucidate this possibility requires further research. Relevant analyses should include additional explanatory variables and/or the matching of patients on the basis of criteria for inclusion. Follow-up of cohorts is a relatively low-cost procedure of potential advantage to many patients falling outside the eligibility criteria for RCTs and of major importance for the interpretation of studies like the present one. For this reason, relevant follow-up should be included in the design phase of future RCTs.

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Authors' contributions

AKD suggested the research strategy, collected data, carried out all analyses and drafted the text. OG supported strategy for and conduct of analyses and reviewed the text. KK reviewed the strategy for analyses and the text. HV was the main supervisor of all aspects of preparing and writing the manuscript.

All authors have read and approved the final version of this manuscript.

Declaration of Conflicting Interests

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