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BRIEF REPORT

Cost-Effectiveness of the Early Arthritis Clinic Organizational Model

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Objective. Early diagnosis and tight control improve outcomes of rheumatoid arthritis (RA). However, whether establishing an early arthritis clinic (EAC) is sustainable for national health systems is not known. This analysis aimed to compare effectiveness and costs of an EAC compared to patients followed by the current standard of care.

Methods. A retrospective study on administrative health databases of patients with a new diagnosis of RA was conducted: 430 patients followed in an EAC were enrolled, and 4 non-EAC controls were randomly matched for each. During 2 years of follow-up, the mean health care costs (outpatient, inpatient, pharmaceutical, and global) and 3 effectiveness measures (number and length of hospitalization and quality of care) of the EAC and non-EAC were estimated. The incremental cost-effectiveness ratio was calculated as well as the cost-effectiveness acceptability curve.

Results. The cohorts included patients with a mean age of 55.4 years, and 1,506 patients (70%) were female. The mean pharmaceutical (2,602 versus 1,945 euros) and outpatient (2,447 versus 1,778 euros) costs were higher in the EAC cohort. Conversely, a higher rate of non-EAC patients had a low adherence to quality-of-care indicators. The expected number of hospitalizations and the length of stay were statistically significantly higher in the non-EAC versus EAC.

Conclusion. Despite an expected increase in outpatient costs (visits and diagnostic tests) and pharmaceutical costs, the reduction in terms of number and length of hospitalizations and the higher adherence to international quality-of-care guidelines support the effectiveness of the EAC model.

INTRODUCTION

The diagnosis and treatment of inflammatory arthritis, and of rheumatoid arthritis (RA) in particular, can be delayed by a late disease recognition and by a long waiting period for an appointment with a rheumatologist (1), although improvement of patients' outcomes requires early treatment (2). In fact, early and effective suppression of disease activity is expected to reduce pain, prevent progression of joint damage and disability (3), and increase the patients' quality of life (4). Early access to an accurate diagnosis, prognostic stratification, and early treatment with strict monitoring of clinical response are the fundamental steps for a correct management of patients with early-onset RA. There is, however, wide variation in the provision of early arthritis services in different health care settings of the national health systems (NHS). Although the possibilities and the potential of the health model of an early arthritis clinic (EAC) to deliver the aforementioned aims have been known since the 1980s, such clinics are not widespread (5,6). A reason can be that although evidence exists that dedicated EACs improve referral lag time and reduce delay in establishing disease-modifying therapy (5), whether EACs improve relevant disease outcomes and are economically sustainable remains questionable (7).

Considering that diagnosing and treating RA entail potential high costs (8), health economic studies are mandatory to assess the balance between costs and effects of this health model. Until now, these studies have referred to data coming from pivotal trials using modeling as methodology to evaluate this balance.

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SIGNIFICANCE & INNOVATIONS

- The use of an early identification and referral model for rheumatoid arthritis (RA) may generate cost savings.
- An early arthritis clinic (EAC) service for diagnosing RA patients can reduce the number and length of hospitalizations.
- The health model of an EAC has the potential to be effective and sustainable for the Italian National Health Service.

However, clinical trial data, clinical experience, and mathematical models have their restrictions. To our knowledge, real-world experiences are still scarce in literature for this issue (3,4). Therefore, real-life data are needed to study the economic impact of EACs compared with the current standard of care. The ability to assess whether the quality of care (QoC) provided by an EAC is superior to that of nonspecialized centers, in the face of cost-effectiveness, could open new scenarios in the management of patients with RA and could lead to a widespread adoption of EACs by NHS. The aim of this analysis was to evaluate whether managing patients at RA onset can be considered cost-effective (compared to nonspecialized facilities [non-EACs]), considering the number and length of hospitalizations and the adherence to international QoC guidelines (effectiveness measures) and costs in euros.

PATIENTS AND METHODS

Study design and patient selection. The design of the study involved the ELECTRA cohort (including incident RA patients attending the EAC of the IRCCS Policlinico San Matteo Foundation of Pavia, a district of Lombardy region, Italy) and the RECORD cohort (including all RA patients of Lombardy region) obtained by means of administrative health databases covering the period between 2004 and 2013, applying the RECORD algorithm (9). Patients in the 2 cohorts with a diagnosis of RA between 2006 and 2011 and who could be followed for a 2-year follow-up were eligible for the analyses. To delete RECORD RA cases (already present in ELECTRA) we used a deterministic record-linkage using birth date, sex, information of hospital discharge forms, outpatient services, pharmaceutical prescriptions, and exemptions. From the residual cases, we randomly selected 4 subjects for each patient of the EAC cohort (ratio 4:1). Additional details are in the Supplementary Methods (see Supplementary Appendix A, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24897). The study was approved by the ethical committee of Pavia University Hospital (P-20130002166) and performed in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments.

Covariates. For each member of both cohorts, we considered the following covariates: sex, age at diagnosis, year of diagnosis, Charlson Comorbidity Index (CCI), a polypharmacy indicator (the sum of different classes of drugs), and the number of hospitalizations for all causes before RA diagnosis (9). The last 3 covariates derived from data available in the 2 years before diagnosis from AHD.

Outcomes. To evaluate the medical costs during the 2-year follow-up period, we used the outpatient NHS-refundable drug delivery, the hospital discharge database, and the outpatient services database, which contained the costs of each NHS service for each patient separately by type (pharmaceutical and inpatient and outpatient services [intended as global costs, i.e., for all causes, not only for RA]) and overall. The number of hospitalizations and the length of stay were derived from the hospital discharge database.

In terms of adherence to international guidelines of QoC, the following aspects were taken into consideration: the pharmacologic treatment with disease-modifying antirheumatic drugs (particularly methotrexate, leflunomide, or sulfasalazine) and/or concomitant use of glucocorticoids (for <6 months) and the clinical and laboratory assessments (2). The adherence score was categorized in 2 levels: high/medium versus low (high/medium score value greater than or equal to –1 and low less than –1), as previously reported (9).

Statistical analysis. To model the costs, a quantile regression model (to estimate the difference in the median of the EAC and non-EAC groups) was applied, whereas the number of hospitalizations and the days of hospitalization were modeled by a zero-inflated negative binomial regression model. To estimate the adjusted mean costs, we excluded the use of average values to perform regression models, as the variable is deeply asymmetric, and not even the common transformations (including logarithmic) were able to reduce this problem. For this reason, performing quantile regression models that estimated the median was necessary. A penalized logistic regression model (with lasso penalty) was considered when the outcome was the QoC level (QoC indicators with related weights are reported in Supplementary Table 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24897). All estimates were adjusted for sex, age, year of RA diagnosis, CCI, polypharmacy indicator, and the number of previous hospitalizations (i.e., before RA diagnosis).

The incremental cost-effectiveness ratio (ICER) over 2 years was used. This index represents the additional cost of 1 unit of outcome gained by 1 strategy compared with another. In particular, in our study we calculated the additional cost to gain 1 day free from hospitalization. To take into account the skewness of costs distribution, 2 ICERs using 2 different central tendency measures (mean and median) were calculated to compare the EAC versus non-EAC (10). The 2 ICERs considered the mean

Table 1. Patient characteristics*

Characteristic	EAC (n = 430)	Non EAC (n = 1,720)	*P*
At baseline			
Female, no. (%)	309 (71.9)	1,197 (69.6)	0.309
Age	53.5 ± 14.1	55.9 ± 14.2	0.003
Year of diagnosis, no. (%)			
2006	85 (19.8)	386 (22.4)	<0.001
2007	44 (10.2)	342 (19.9)	<0.001
2008	73 (17)	311 (18.1)	<0.001
2009	86 (20)	233 (13.5)	<0.001
2010	62 (14.4)	228 (13.3)	<0.001
2011	80 (18.6)	220 (12.8)	<0.001
Charlson Comorbidity Index	0.33 ± 0.83	0.25 ± 0.82	<0.001
Polypharmacy indicator	5.3 ± 3.3	4.7 ± 3.1	<0.001
Number of previous hospitalizations	0.63 ± 1.5	0.61 ± 1.2	0.202
During follow-up (all costs in euros)			
Number of hospitalizations	0.73 ± 1.38	0.80 ± 1.44	0.735
Days of hospitalization	5.1 ± 16.1	10.3 ± 33.1	0.096
Low adherence to quality-of-care indicators, no. (%)	12 (2.8)	380 (22.1)	<0.001
Pharmaceutical cost, median (IQR)	1,556.2 (795–2,747)	1,134 (474–2,086)	<0.001
Pharmaceutical cost	2,602 ± 3,839	1,945 ± 3,352	–
Outpatient services cost, median (IQR)	1,537 (1,024–2,845)	1,086 (581–1,966)	<0.001
Outpatient services cost	2,447 ± 5,662	1,778 ± 2,854	–
Inpatient cost, median (IQR)	0 (0–878)	0 (0–3,898)	0.251
Inpatient cost	4,426 ± 15,574	6,666 ± 19,483	–
Overall cost, median (IQR)	4,138 (2,499–8,444)	3,359 (1,645–9,538)	<0.001
Overall cost	9,475 ± 19,651	10,389 ± 20,945	–

* Values are the mean ± SD unless indicated otherwise. EAC = early arthritis clinic; IQR = interquartile range.

(or median) of days free from hospitalization as an effectiveness measure, and the mean (or median) of daily costs as the numerator.

Estimates of the ICER and corresponding 95% confidence interval (95% CI) were obtained via 1,000 bootstrap resamplings. The EAC was considered cost-effective if the ICER was below the willingness-to-pay (WTP) threshold, defined based on the mean daily cost of hospitalization in the 2 centers. Based on the 1,000 bootstrap resampling, we conducted a probabilistic sensitivity analysis to assess the probability of the EAC to be cost effective at a different level of WTP threshold, expressed as euros per day free from hospitalization. The results of the probabilistic sensitivity analysis were represented by the cost-effectiveness acceptability curve (CEAC). Additional details are in the Supplementary Methods (see Supplementary Appendix A, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24897). All hypothesis tests were 2-sided, and *P* values for statistical significance were set at 0.05. All the analyses were performed using R statistical software, 3.6 version.

RESULTS

Patient characteristics. The EAC cohort consisted of 430 patients and the non-EAC of 1,720 patients. Patient characteristics of the EAC and non-EAC cohorts are reported in Table 1. Briefly, both cohorts consisted predominantly of female patients. EAC patients were significantly younger (53.5 versus 55.9 years), with a higher CCI score (0.33 versus 0.25) and polypharmacy indicator (5.3 versus 4.7).

Outcome results. Median costs for pharmaceutical (1,556.2 versus 1,134 euros), outpatient (1,537 versus 1,086 euros), and overall (4,138 versus 3,359 euros) were higher in the EAC cohort than in the non-EAC group (for details see Supplementary Table 2, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24897). Conversely, a lower rate of EAC patients had a low adherence to QoC indicators (2.8% versus 22.1%) (Table 1).

Table 2. Adjusted models comparing cost and effectiveness outcomes between EAC and non-EAC*

	Non-EAC vs. EAC	*P*
Costs, median difference		
Pharmaceutical	−449.1 (−553.4, 310.4)	<0.001
Outpatient	−434.97 (−581.41, 318.71)	<0.001
Inpatient	0 (0, 0)	1
Overall	−420.8 (−647.7, 20.8)	0.002
Quality of care		
Number of hospitalizations, IRR	1.51 (1.24, 1.85)	<0.001
Days of hospitalizations, IRR	2.29 (1.64, 3.20)	<0.001
Low quality of care, OR	8.98 (5.3, 15.2)	<0.001

* Values are the statistical value indicated (95% confidence interval). Adjusted by Charlson Comorbidity Index, sex, age, year of diagnosis, polypharmacy indicator, and number of previous hospitalizations. EAC = early arthritis clinic; IRR = incidence rate ratio; OR = odds ratio.

The difference in median costs (as per quantile regression models) between the EAC and non-EAC, adjusted by CCI, sex, age, year of diagnosis, polypharmacy indicator, and the number of previous hospitalizations, was 420.8 euros in the first 2 years. In other terms, the NHS would spend an additional 420.8 euros to treat a patient with RA for 2 years in the EAC (Table 2).

The incident rate of the number and length of hospitalizations was statistically lower in the EAC versus non-EAC (1.51 [95% CI 1.24, 1.85] and 2.29 [95% CI 1.64, 3.20], respectively). The adjusted risk for a patient to fall into the "low adherence QoC" group is significantly lower in the EAC cohort than for a patient managed in the non-EAC (Table 2).

The estimated mean-based ICER was –147.5 euros (95% CI –841, 527). The estimated median-based ICER was 268.6 euros (IQR 90.4–597.3). Considering the mean-based ICER, to earn a day free from hospitalization in the EAC, the NHS saves 147.5 euros. Instead, considering the ICER with median values, to earn a day free from hospitalization, the additional NHS cost for the EAC will be equal to 268.6 euros.

The 2 plots in Figure 1 show the distribution of mean-based (Figure 1A) and median-based (Figure 1B) ICER obtained through bootstrap resampling. In both panels, the points are especially distributed on the right side of the figures, which implies a greater number of days free from hospitalization in the EAC than in the non-EAC (and therefore greater effectiveness). As regards Figure 1A, most of the points are in the lower right corner, which also implies, in addition to effectiveness, a cost for the EAC that is on average lower than for the non-EAC. Figure 1B indicates that a greater effectiveness is consolidated at the expense of a higher median cost.

Sensitivity analysis: CEAC. Based on the CEAC, the EAC showed a 92% probability to be the cost-effective intervention using a WTP threshold of 200 euros for a day free from hospitalization and a 96% probability using a WTP threshold of 942 euros (see Supplementary Figure 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24897). The EAC is more cost-effective than the non-EAC from 92% to 96%, i.e., the EAC is associated with a 92–96% probability to be the more cost-effective intervention, using a WTP threshold between 200 and 942 euros for a day free from hospitalization.

DISCUSSION

The aims of EACs are early recognition and timely treatment of RA. Nevertheless, EACs are not at all widespread, and core standards of this organizational model are yet to be defined and shared (7). Where EACs are set, the operational model is usually determined by availability of resources and local health care system needs. Effectiveness and cost-effectiveness of EACs, although fundamental for the rationale of setting up the clinic, have not yet been addressed appropriately in the literature, since most evidence supporting the establishment of this health-care service is based on studies comparing aggressive and early treatment versus others (5–7), whereas the best comparison would be between the setting of the EAC as a whole and the standard of care clinical pathway. Our study aimed to compare outcomes and NHS costs of RA patients treated in an established EAC versus outcomes of patients in other areas where referral from primary care was not based on specific procedures, nor were there

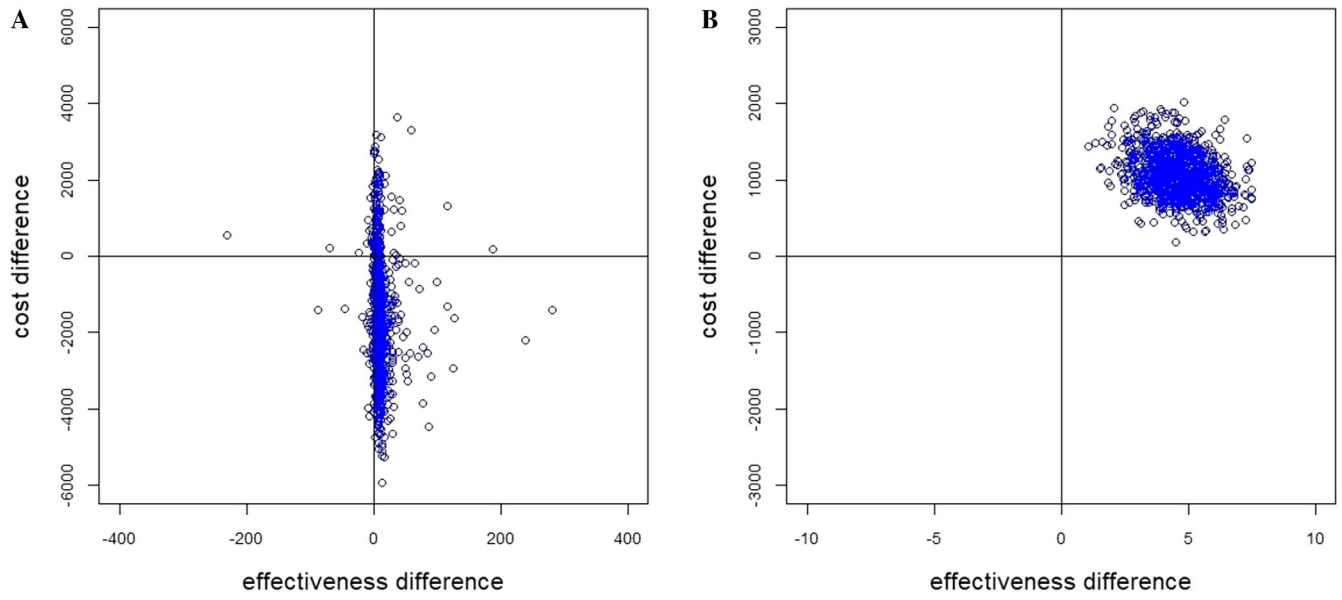

Figure 1. **A**, Mean-based incremental cost-effectiveness ratio (ICER), and **B**, median-based ICER obtained through bootstrap resampling. The points in the figure show the ICER calculated in each bootstrap replication. On the horizontal axis the mean or median difference in costs between the early arthritis clinic (EAC) and non-EAC is shown, while the vertical axis shows the mean or median difference in days free from hospitalization.

any standardized protocols for following or treating early RA patients.

We reported population-based results of an Italian EAC established in 2005. Matching an EAC cohort with a concurrent non-EAC cohort, we assessed the effectiveness of this health care model in 2 comparable populations. The expected number of hospitalizations and the length of stay were statistically lower in an EAC versus a non-EAC, as well as the risk for a patient to fall into the "low adherence QoC" group.

Patients may benefit from attending structured and organized programs for the management of disease, such as an EAC (1,11). What is more, the proposed solution would reduce the requirement for diagnostic investigations in the inpatient setting. Acknowledging this gap between primary and specialized care, many countries (UK, The Netherlands, Austria, Norway, France, Spain, Germany, Finland, and US) have started an EAC (12–14).

Considering the ICER calculated with the mean values, an earned day free from hospitalization for an EAC patient also corresponds to a cost saving of 147.5 euros. Instead, considering the ICER with median values, the additional cost will be 268.6 euros. Although some apparent advantages of other central tendency measures, such as the median for cost data that are often highly skewed, are well understood, the median has rarely been considered in the ICER. As previously reported, mean- and median-based ICERs have to be assessed together as complementary tools for decision making (10). If the mean- and median-based ICER give discordant results, as in these present analyses, researchers' confidence may need to be adjusted accordingly, pending further evidence.

Nevertheless, we can assume that the NHS is implicitly willing to pay the amount of 942 euros, i.e., the average cost of 1 day of hospitalization calculated for our patients. Defining cost-effectiveness as a median ICER below that threshold, our results encourage the EAC model. As reported in Supplementary Figure 1, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.24897, in the case of a threshold of 200 euros as well, the EAC would be cost-effective in 92% of cases, with an estimated median-based ICER of 268.6 euros.

A strength of the ELECTRA study is that to our knowledge it is the first Italian study on a nonselected population evaluating the effectiveness and the NHS sustainability of a dedicated EAC path for RA patients. A further strength of our analysis is that the health area, the variables, and the timing of evaluation overlapped in both cohorts. Furthermore, the study design considered real-life observational data regarding effectiveness and adherence to QoC guidelines of treatment compared with the standard of care (nonstructured clinical pathway).

This approach is in contrast with many health economic evaluations, which often use modeling techniques with many underlying assumptions or which use clinical trial data of highly selected patients. However, our study has some limitations too. Since our patients are unselected, randomization between the comparing cohorts was not performed, with the risk of selection bias present in the comparison. However, participation in either of the cohorts was determined by the area of residence, while patients attended comparable rheumatology clinics, all working within the same health care system. Notably, in the EAC population, we are sure the intervention took place because it is part of a structured path, and to date, we cannot exclude the fact that even in a non-EAC cohort there were patients who followed a structured path, thus possibly leading to an underestimation of the effect. In addition, we cannot discern whether the benefit found in the EAC cohort is due to early diagnosis or to the close monitoring provided by this model.

Another limitation could be the short follow-up (2 years). The extent to which improvement is maintained in the long term needs clarification to evaluate the additional costs of both RA-related adverse events and those attributable to typical late-RA comorbidities, and also to define the optimal duration, in which a more intensive management is of value. Calculating the ICER using clinical outcomes as efficacy measures (for example, disease remission) would have been interesting, but unfortunately, the clinical outcomes are not available in administrative databases. Dedicated EACs help achieve good clinical outcomes in RA patients. Whether effectiveness of this model rises along with cost-effectiveness has to be the subject of further investigation, but this study shows that the establishment of dedicated EACs has advantages for both RA patients and the NHS. Policy makers should evaluate the sustainability of costs for treatment of RA patients in an EAC.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Scirè had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Zanetti, Sakellariou, Scirè.

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Analysis and interpretation of data. Zanetti, Sakellariou, Zambon, Carrara, Argnani, Montecucco, Scirè.

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