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The Economic Burden of Rheumatoid Arthritis: a Systematic Review of Literature in Biologic Era

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Abstract

Background The past decades have seen rapid advances in the treatment of rheumatoid arthritis (RA). In particular, the introduction of biologic and targeted synthetic disease modifying anti-rheumatic drugs have improved clinical outcomes and reconfigured traditional RA cost compositions.

Objectives To map the existing evidence concerning cost-of-illness of RA as the treatment pathway evolves in the biologic era and examine how costs have been measured and estimated, so to assemble and appropriately interpret available data.

Methods Systematic review of studies that estimated the costs of patients with RA. Multiple electronic databases were searched to identify studies published between 2000 and 2019. The reported total costs and cost components were evaluated according to study and population characteristics. The Cochran-Armitage test was used to determine statistically significant trends in increasing or decreasing proportions over time.

Results Overall, 72 studies were included. Drug costs compromised the main component (up to 87%) of direct costs with an increasing trajectory over time, albeit not statistically significant. The proportion of costs for hospitalisation showed a statistically significant decrease chronologically ($p = 0.044$). Indirect costs, primarily associated with absenteeism and work disability accounted for 39% to 86% of total costs. The reported indirect costs are highly sensitive to the approach to estimation.

Conclusions A decreasing trend in inpatient costs chronologically suggested a cost shift in other components of direct costs. Indirect costs still contributed a considerable proportion of total costs, with work disability being the main cost component. Economic analyses that do not incorporate or appropriately measure indirect costs will underestimate the full economic impact of RA.

Introduction

Over the past decades, there have been major advances in the management of rheumatoid arthritis (RA). The identification of cytokines that promote synovial inflammation (e.g. TNF, GM-CSF and IL-6) led to therapeutics that target the disease process itself.[1] The introduction of biologic (b) disease-modifying antirheumatic drugs (DMARDs) in the late 1990s offered potent options for patients with inadequate response to conventional synthetic DMARDs. This situation has advanced further with the advent of Janus Kinase inhibitors (targeted synthetic DMARDs) in the last three years. However, these targeted therapies are significantly more expensive than the previous conventional DMARDs. A recent meta-analysis estimated an annual direct medical costs in the US for RA of $12,509 for all patients using any treatment regimen and $36,053 for biologics users.[2]

Cost-of-illness (COI) is an estimate of the total burden of disease in monetary terms, and is highly relevant to policy decision making.[3] Decisions on reimbursement of healthcare intervention require not only evidence on potential health gains from interventions, but also evidence on relevant cost components. A clear understanding on where the costs are incurred and what cost savings are occurring as a consequence is essential to resource allocation.

Although many COI studies in RA exist, these studies have different definitions for COI. Further, varying methodological approaches have been used, and costs have been estimated from different settings and perspectives. The aim of this systematic review was to map the existing evidence on COI of RA. In particular, this review examined how costs have been measured and estimated, as well as assembled and interpreted based on available data.

Methods

The systematic review was carried out according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement[4] and registered on PROSPERO (registered number: CRD42018085227).

Studies were included if they met the following criteria: (1) population included adult patients diagnosed with RA; (2) cost associated with RA were measured or estimated, such as direct costs, indirect costs or both. Because COI studies are descriptive analyses the economic burden of health problems on a population, trials were not included in this systematic review. Common cost components and terminologies in COI studies are presented in Box 1.

Box 1. Common Cost Components and Terminology in Cost-of-illness Studies

Direct costs: The cost of resources used for treating a particular illness, including:

Direct medical costs: medical care expenditures, such as drugs, hospitalisation, surgery, outpatient, emergency room visit, healthcare workers, diagnostic test.

Direct non-medical costs: the consumption of non-healthcare resources, such as device and adaptation to home/car, transportation and informal care.

Indirect costs: Indirect costs refers to productivity losses due to morbidity and mortality, borne by the individual, family, society, or the employer.[5] Morbidity costs represent the monetary value of lost production due to sick leave, early retirement and reduced work performance, whereas the monetary value of lost production due to the premature death of the patient is defined as a mortality cost.[6]

Absenteeism: Time off to work, such as sick leaves, lost wages

Presenteeism: Work performance impacted by health problems, such as productivity impairment

Work disability: The permanent partial or complete disablement for work purposes,[7] which can be measured by unemployment, disability pension, and early retirement.

Human capital vs. friction cost approach:

There are two approaches commonly used to value indirect costs. The friction cost approach only values the estimated actual production that is lost during the time it takes to replace the sick worker, known as the 'friction period', while the human capital approach is generally taken to reflect lost productive potential.[8]

Perspective*:*

The COI studies may be carried out from a variety of perspectives, each of which then includes different cost components leading to different results for the same illness. These perspectives may measure costs to a society, healthcare system, third-party payers, patients and their families, and business sectors.

The societal perspective is the most comprehensive because it includes all direct and indirect costs for all members in a given society where they are involved, and it is often

preferred because it allows a complete analysis of all of the opportunity costs attributable to an illness.[5] The cost components in each perspective is presented in the table below.

Costs included in COI studies by perspectives

Perspective	Medical cost	Non-medical cost	Indirect costs
Societal	All costs*	All costs*	All costs*
Payer	Covered costs	Covered costs	
Patient	Our-of-pocket costs	Transportation/ Informal care	Wage losses
Employer			Absenteeism / Presenteeism

* This refers to all costs attributable to an illness, subject to data availability of each study.

Prevalence- vs. incidence-based approach

There are two key approaches to estimating COI – namely prevalence- and incidence-based approaches. The prevalence-based approach estimates the total cost of a disease incurred in a given year, while the incidence-based approach involves calculating the lifetime costs of cases first diagnosed in a particular year, providing a baseline against which new interventions can be evaluated.[9]

A search was carried out on Ovid MEDLINE and EMBASE (last searched, February 2019). Due to the introduction of first biologics in the late 90s and the subsequent evolution of the treatment pathway, only studies from 2000 onwards were included. In addition to search terms relating to RA, a search filter[10] for economic studies was also used to capture potentially relevant studies (Supplementary Table S1). The search was restricted to English language studies only. The titles and abstracts of all retrieved studies were screened, and full-text of all potentially eligible articles were reviewed in detail.

All relevant data, including patient characteristics, costs (and its breakdown when reported), setting, methodologies, main findings and limitations, were extracted by one reviewer, using a pre-piloted data extraction form. A random sample of 50% of studies was validated independently by a second reviewer. In the absence of a quality assessment tool for COI studies, we modified the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist[11] (Supplementary Table S2) to evaluate the quality of included studies. A narrative synthesis approach was adopted to summarise the evidence. The estimated total COI was evaluated according to study characteristics and expressed in their cost compositions of direct or indirect costs if

reported. All absolute costs were converted to US dollars, inflated to 2017 levels and adjusted for buying power using purchasing power parities to facilitate comparison. For studies, where the cost year was not reported, the last year of the enrolment period was used. In order to determine if there was an increasing or decreasing trend in the proportion of drug costs and inpatient costs of overall direct costs, the Cochran-Armitage test for linear trend in proportions was used. [12] Data were entered into a Microsoft Excel spreadsheet and analysed using R V3.5.2.

Results

The search identified 2981 potentially relevant studies, of which 72 met the inclusion criteria (Supplementary Figure S1).

Study characteristics

Overall, these studies estimated the COI of RA in 28 countries (Supplementary Table S3). The majority were conducted in Europe (n=34; 47.2%), followed by North America (n=19; 26.4%), Asia (n=15; 20.8%), Latin America (n=3; 4.2%), and Australasia (n=1; 1.4%). Among the studies, females accounted for the main composition of population ranging from 57.5% to 95.6% among studies. The mean age of participants ranged from 46 to 63 years old. The mean duration of disease among participants ranged from the onset of disease to 25.9 years.

Methodological approaches

In the majority of the studies, the data sources were retrospective databases (n=61; 84.7%), including health insurance databases, disease registries, and hospital administrative records, followed by self-reported questionnaire surveys (n=10; 13.8%). One study estimated costs by simulation modelling approach.[13] Cost of illness estimates were estimated from different perspectives – that of the society (n=32; 44.4%), payers (n=14; 19.4%), patients (n=2; 2.8%), and employers (n=3; 4.2%); 21 studies (29.2%) did not report perspective.

Overall, the majority of included studies (n=58; 80.5%) were carried out using a prevalence-based approach (Box 1). The studies that adopted the incidence-based approach, focused on recent-onset patients and were primarily conducted in a European setting.[14-21] Cost components and measurement of direct or indirect costs also varied markedly due to the aims and data availability among studies. Twenty-seven studies reported both direct and indirect costs, while 36 studies and 9 studies reported direct and indirect costs only, respectively. The following sections are presented based on this arrangement to avoid cross-reporting of studies that reported both direct and indirect costs.

Direct costs of RA

In estimating direct costs, multiple cost components were included in the estimates. Most commonly, these consisted of drug costs, inpatient costs, outpatient costs (including costs of visiting different healthcare professionals), and various other healthcare-related costs (including costs of diagnosis, devices and adaptation to homes/cars, transportation and informal care). The annual estimates of direct costs of patients with RA ranged from $401 to $67,306 in the 36 studies that reported direct costs. Of these, 22 studies included these common cost components (Figure 1), i.e. drug costs, inpatient and outpatient costs. Except for two studies with different patient characteristics (newly-diagnosed patients[14] and elderly population[22]), drug costs contributed to between 9.8% and 87.2% of direct costs. Although drug costs comprised the main component of direct costs, no statistically significant increasing trend was found ($p = 0.647$, Table 1). However, the proportion of costs for hospitalisation showed a statistically significant decrease over time ($p = 0.044$).

Table 1. The Cochran-Armitage test for linear trend analysis in proportions of drug costs and hospitalisation costs.

Cost component	Proportion of direct costs (correlation structure) (ρ_1, ρ_2, ρ_3, ρ_4, ρ_5 ... ρ_{20})	One sided test	Test statistic	
			Z	*P* value
Drug	(0.122, 0.098, 0.130, 0.234, 0.237) (0.482, 0.588, 0.599, 0.838, 0.417)	Increasing	0.376	0.647
	(0.485, 0.364, 0.732, 0.661, 0.735) (0.872, 0.832, 0.762, 0.846, 0.865)	Decreasing		0.353
Hospitalisation	(0.106, 0.438, 0.203, 0.342, 0.058) (0.099, 0.032, 0.313, 0.033, 0.380)	Increasing	1.706	0.956
	(0.254, 0.344, 0.106, 0.183, 0.140) (0.044, 0.080, 0.049, 0.116, 0.052)	Decreasing		0.044*

Indirect costs of RA

Indirect costs in COI studies refers to productivity losses due to morbidity and mortality, borne by the individual, family, society, or the employer.[5] Morbidity costs represent the monetary value of lost production due to sick leave, reduced work performance and early retirement. These are also known as absenteeism (time off work), presenteeism (work performance impacted by health problems), and work disability.

Absenteeism and work disability were the major cost components of indirect costs although the definitions varied among studies. The measurements of sick leave, work hour loss, and short-term work disability were the most commonly reported items in terms of absenteeism; receiving disability pension and early retirement were categorized as work disability. Others included presenteeism, unemployment due to RA, unpaid work or non-marketplace activities, and third-party help. Only 4 of the 9 studies that reported only indirect costs provided a breakdown of cost components (Table 2).

With heterogeneous definitions in the limited number of studies, it is challenging to compare cost compositions. Presenteeism, while rarely estimated in studies, accounted for 8.8% and 92.9% of indirect costs in the Danish and Japanese studies, respectively.[23,24] Overall, annual estimates of indirect costs ranged from $595 to $22,444 in the 9 reported studies.

Table 2. Measurements of cost components in indirect cost of RA

Reference	Absenteeism	Work disability	Others
Malinowski[25]	short-term/long-term/ permanent work disability	NA	NA
Sogaard[24]	work hour loss/sick leave	NA	presenteeism
Sruamsiri[23]	work hour loss	NA	presenteeism
Merkesdal[26]	sick leave	disability payment from cessation of work	NA

Direct and indirect costs of RA

Overall, 27 studies estimated both direct and indirect costs (Figure 2). The annual estimates of combined direct and indirect costs ranged from $2,408 to $83,845; the majority of the estimates were in the range of $10,000 to $30,000. One outlier was

observed – a study conducted in Norway;[27] in which the high monetary value was due to the subgroup on biologic treatments as well as a high proportion of indirect costs accounting for 67.7%.

The human capital approach (HCA, Box 1) was used in 10 studies to estimate indirect costs, whereas one study used the friction cost approach (FCA). Five studies used both approaches.[16,27-30] The remaining 11 studies did not report their approach. Estimates using the HCA were 1.5 to 4.4 times higher than those using FCA in those studies that adopted both approaches.

In terms of the composition of direct and indirect costs, the approach to estimating indirect costs had an important impact. For studies where indirect costs dominated, the approach to estimating indirect costs had an important impact. It was observed that work disability measured by disability pension was taken into account in these studies[16-18,30,31], except for two studies from Mexico and Hong Kong[32,33], where indirect costs were driven by unemployment due to RA. On the other hand, for those studies where direct costs dominated, work disability was generally not included as an indirect cost component [28,34-38]. Indirect costs mainly consisted of sickness absence, resulting in a lower percentage of indirect costs. In addition, these studies have relatively lower annual estimates of absolute costs (<$10,000) in common. With the exception of studies in which indirect costs mainly consisted of sickness absence, indirect costs accounted from 39.4% to 85.5% total costs in the biologic era.

Modified CHEERS scores

Overall studies scored well against the 21 criteria of the modified CHEERS checklist (Supplementary Figure S2 and Supplementary Table S4). Four items relating to study perspective, characterising uncertainty, characterising heterogeneity, and conflicts of interests scored less with over a quarter of studies failing to report the details.

Discussion

The aim of this systematic review was to examine how cost components have been measured and estimated in COI studies of RA in the biologic era, so as to assemble and appropriately interpret available data. Results included 72 studies that were conducted in 28 countries, with differences in populations, healthcare systems, cost estimates, and methodologies across and within countries. The variety in methodologies might be due to different study purposes as well as data availability. The prevalence-based approach provides a snapshot on the economic burden of RA to the society, while the incidence-based approach aims to estimate from the onset of disease, and therefore, requires longitudinal data. Also, most studies conducted retrospective analyses from claim database or disease registries rather than developing a dedicated primary data collection. The majority of included studies estimated costs directly and entirely attributed to RA, whereas few studies measured all expenditures incurred to the patients with RA or incremental costs by using matched-control or regression-based approaches. For indirect costs, although HCA was more commonly used, this approach has been criticised as possibly over-estimating actual indirect costs, while the FCA is relatively difficult to implement as it requires detailed information or assumptions.[5]

On visual inspection, the proportion of drug costs, as the main component contributing to direct costs, was increasing over time. Although no statistically significant increase in this trend could be established. However, the statistically significant decrease in the proportion of costs for hospitalisation suggests that costs have shifted to other components of direct costs. These results need to be interpreted with caution though due to the small sample size. The cost of informal care was only available in a limited number of studies, which indicated it could contribute to a significant proportion in direct costs.[20,21,39] For indirect costs, absenteeism and work disability were the most commonly reported components. Work disability, which mainly included pay-outs for disability pensions, was identified as the key cost driver of indirect costs. Although presenteeism was rarely addressed, it varied substantially in our findings (8.8%, 92.9%).[23,24] While absenteeism and work disability are relatively straightforward to measure, presenteeism still lacks a clear measurement methodology.[40,41] Where indirect costs dominated in those studies that reported both direct and indirect costs, the approach to estimating indirect costs had an important impact. In the studies measuring work disability rather than considering sickness absence only, indirect costs contributed a much larger proportion than direct costs, and also resulted in relatively higher monetary values.

Since the introduction of first biologic (etanercept) in 1998 in the US and subsequent wide adoption of early and intensive treatment strategies, the composition of total costs of RA has been transformed. In an earlier systematic review conducted by Rat et al,[42] direct costs accounted for 25% to over 50% of the total cost among the included studies between 1978-2002. In addition, costs associated with inpatient care contributed up to 75% of direct costs. Our findings from included studies from 2000 onwards indicated

that drug costs comprised the main cost component of direct costs although disease progression of RA has been postponed and slowed with biologics. Higher direct costs were consistently observed when the entire or a high proportion of the population were on biologic treatments ($9,618-$26,964 versus $401-$9,493). Indirect costs continue to contribute a considerable proportion to total costs in the biologic era, with work disability accounting for the majority of costs. However, the strength of the current evidence is not sufficient to conclude that biologics live up to their promise that expensive drug costs could easily be recovered. Thus, economic analyses that exclude or only partially include indirect costs will underestimate the full economic impact of RA.

In the value-based pricing system, criteria such as those for severe diseases, addressing unmet needs, innovative technologies, and having wider societal benefits are well supported by general public.[43] A COI study provides a clear understanding on where the costs are incurred and what cost savings are occurring as a consequence. However, owing to disparities in costing methodologies, perspectives, and healthcare settings across studies, even if they were undertaken in the same country, it is difficult to draw a meaningful chronological trajectory to examine the change in landscape. Ideally, future COI studies of RA ought to include both direct costs (including drug costs, inpatient and outpatient costs) and indirect costs (including costs associated with absenteeism, presenteeism and work disability). Furthermore, the inclusion and reporting of sensitivity analyses is vital for readers to understand the uncertainty around the COI estimates and the robustness of the conclusions that studies reach.[44] Sensitivity analyses can also be used to explore alternative methodological approaches may lead to differences in results, for example FCA and HCA.

Our results have potential limitations. First, we refrained from excluding studies based on certain quality criteria, such as study design, costing approaches, or sample size, resulting in a high degree of uncertainty and large variation in cost estimates. There are additional methodological challenges which, together with the countries where the studies were performed, lead to variation in findings across studies. However, our objective was to ensure a truly comprehensive overview of the literature on the economic burden of RA. Second, because total costs included various components that were not homogenous in all studies, and a breakdown of total costs into individual components was not reported in all studies, it is not appropriate to pool estimates from different countries or to perform formal quantitative analyses (meta-analysis). Therefore, we assembled and analysed available data narratively and explored the heterogeneity between studies. Third, we searched for published English-language studies; therefore, some non-English studies will have been omitted.

Although not reported in any of the included studies, the advent of cheaper biosimilars provides potential for reducing pressure on healthcare budgets. To the best of our knowledge, there has been no COI study exploring the economic impact of biosimilars in RA since the first biosimilars for infliximab and etanercept were approved in the US and Europe in 2016. It has been suggested that highly equivalent and lower cost biosimilars could reduce the pressure on healthcare budgets and compensate for inequalities in

access to therapy potentially caused by economic differences between countries[45]. However, challenges remain regarding price, biologics switching in clinical practice, and post-marketing pharmacovigilance.[46] Hence, future studies should focus on the economic impact of informal care from patients' perspective, presenteeism, and the entry of biosimilars.

Conclusion

Our research findings suggest that in the biologic era, drug costs comprised the main cost component of direct costs while the proportion of inpatient costs was decreasing over time. Indirect costs still contribute a considerable proportion of total costs, with work disability being the main cost component. Economic analyses without taking indirect costs into account or measuring properly will underestimate the full economic impact of RA.

Figure 1. Distribution of cost components in direct costs of RA chronologically.

Costs incurred from visits to other healthcare professionals, such as nurse, physical therapist, and occupational therapist, that were measured separately in some studies,[15,17,18,20,21,27,29,31,37,47-55] were summarized as "Outpatient". Costs for diagnostic tests, devices and adaptation, transportation and informal care were categorised as "Others".
**Drug costs were not the largest contributor to direct costs.*

Figure 2. Distribution between direct and indirect costs in total costs of RA

(No legend)

Key messages

What is already known about this subject?

- The introduction of biologic disease-modifying antirheumatic drugs (DMARDs) and more recently, targeted synthetic DMARDs has transformed the treatment pathway of rheumatoid arthritis. However, new therapies are significantly more expensive than previous treatments.
- A recent meta-analysis estimated the annual direct medical costs in the US, for biologic users to be approximately three times greater than those using any treatment regimen according.

What does this study add?

- The decreasing trend in costs for hospital expenditure and surgery suggested a cost shift in other components of direct costs.
- In the context of RA, indirect costs constitute a considerable proportion of total cost of illness. The evidence is not strong enough to support the argument that biologics live up to their promise that expensive drug costs could easily be recovered.
- Current cost of illness studies may have under-estimated the true economic burden of RA due to indirect costs is not routinely taken into consideration.
- There needs to be more consistency in the approaches being adopted to estimate the cost of illness of RA.

How might this impact on clinical practice or future developments?

- In the face of ageing populations, rising healthcare expenditure and evolving treatment pathways, it is important to understand not only the health gains, but also where costs are being incurred and what cost savings are occurring as a consequence, when making health policy decisions.
- When estimating the cost-of-illness of RA, we need to consider the impact of absenteeism and presenteeism, and informal care from patients' and carers' perspectives.

Contributors

Concept and design: PHH, OW, CG, EMcI. Validation of data extraction: OW, CG, EMcI. First draft of the manuscript: PHH. Critical revisions of the manuscript for important intellectual content: OW, CG, EMcI, SS, IMcI. All authors have full access to all of the data in the study, take responsibility for the integrity of the data, and the accuracy of the data analysis.

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Competing interests

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Ethical approval information

Not applicable

Data sharing statement

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Patient and Public Involvement

Not applicable

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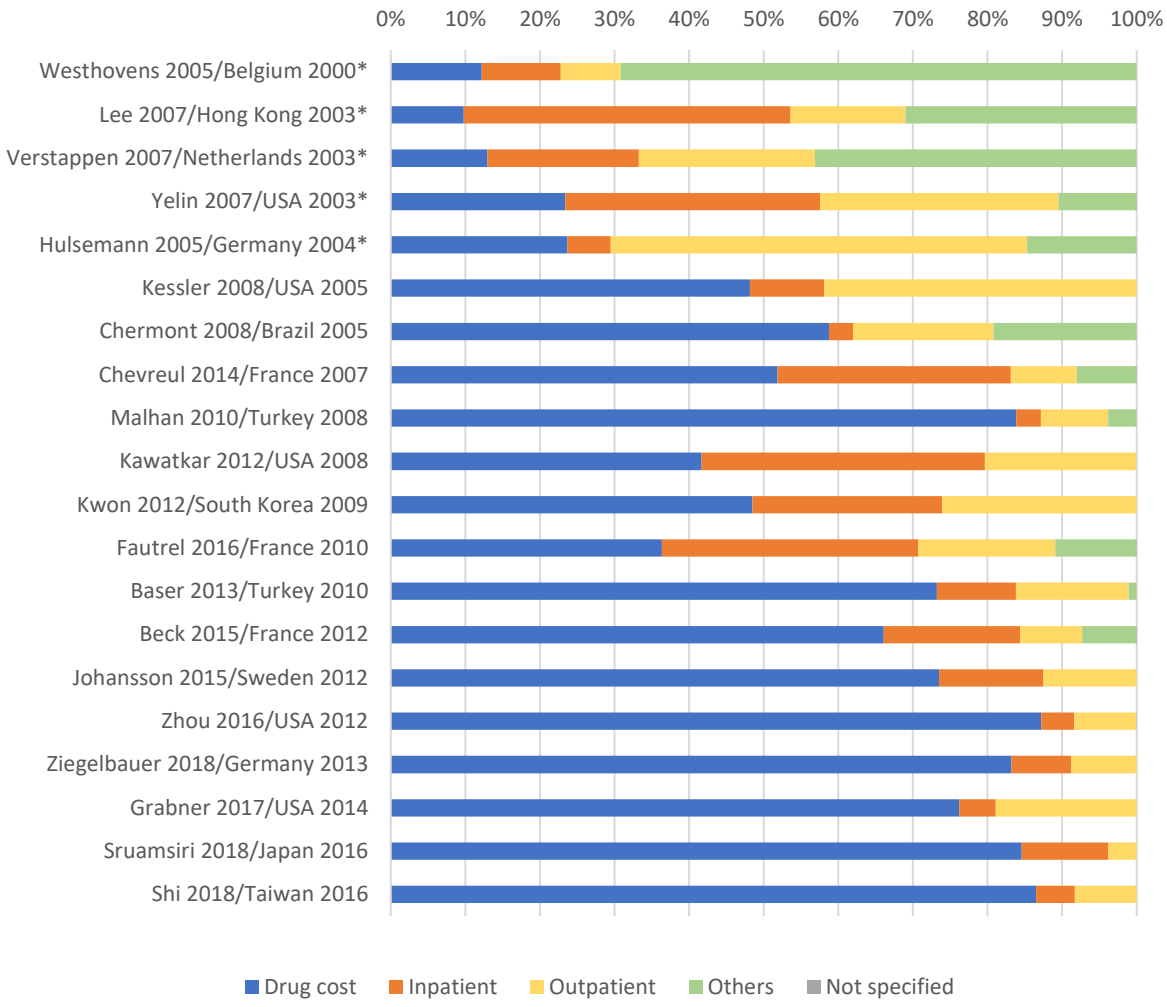
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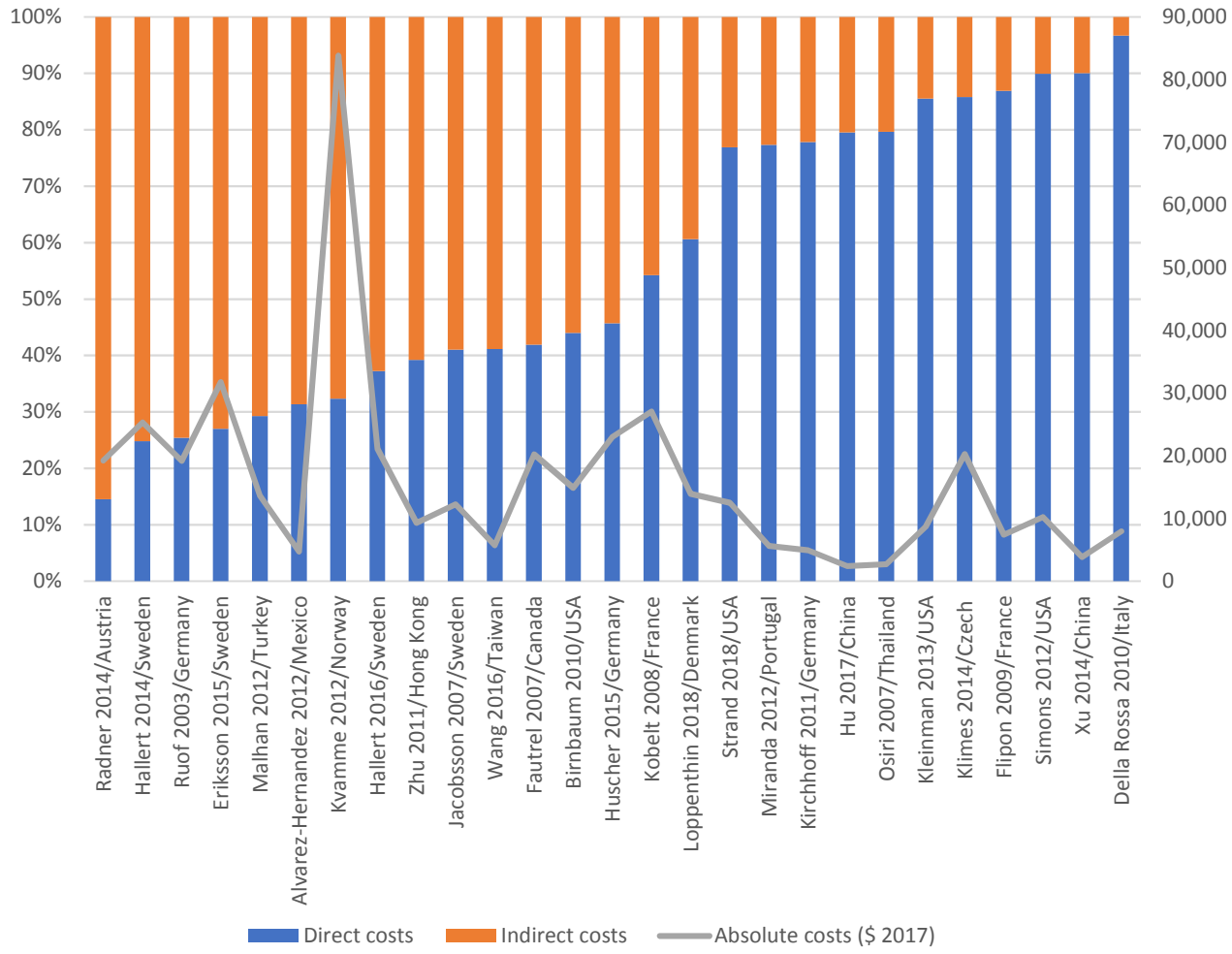
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Della Rossa 2010/Italy
Direct costs
Indirect costs
Absolute costs ($ 2017)