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Systematic Review

Cost Estimations of Managing Adverse Drug Reactions in Hospitalized Patients: A Systematic Review of Study Methods and Their Influences

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Abstract: This study aimed to systematically review and explore the impact of study methods on the cost of managing adverse drug reactions (ADRs) among hospitalized patients to guide policymakers and researchers. A literature search was conducted in MEDLINE, EMBASE, CINAHL, Cochrane Library, and Google Scholar. The search was restricted to studies from 2000 to 2017. Two authors independently reviewed the studies, assessed their risk of bias, and extracted information for analysis. Data abstraction was based on the study design, ADR reporting, and costing approaches. Of 677 studies identified, 12 were included for analysis. All studies defined ADR according to WHO classifications. The percentage of admission due to ADR ranged from 0.03% to 17.11%. All studies adopted a healthcare provider perspective, using either a micro-costing (n = 7), case-mix group costing (n = 3), or average-per-diem costing (n = 2) approach. The cost per ADR widely fluctuated from USD 65.00 to USD 12,129.90 based on various factors. The micro-costing approach generally had a lower cost compared to other approaches. The cost per ADR in high-income countries was also 10 times higher than in lower- or middle-income countries. This study evidenced that the methodological heterogeneity across studies has resulted in a wide range of cost estimations for ADR management.

Keywords: cost analysis; adverse drug reaction

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1. Introduction

An adverse drug reaction (ADR) is defined as any response to a drug that is noxious and unintended, and that occurs at normal therapeutic doses [1,2]. These reactions can range from mild and self-limiting to severe reactions that can lead to disability and death. ADRs can occur in both hospital and outpatient settings, albeit varying in terms of the frequency, types, and severity of the reactions. Reactions in outpatient settings are often thought to be underreported and most often self-limiting [3–5]. On the other hand, the ADRs in hospitals are well studied and characterized as patients are closely monitored during the drug administration process. Additionally, hospitalized patients are more susceptible to ADR due to a combination of factors such as more complex and potent treatment regimens, compromised organ functions, and underlying health conditions [6]. Studies have reported that about 10 to 20% of hospitalized patients will experience ADRs during their stay [7]. These high numbers create concern, as ADRs can impair the treatment outcomes and impact the quality of life of patients.

Aside from the health consequences, ADRs cause a substantial economic impact on individuals, the healthcare system, and society as a whole. From the perspective of the patient, the longer hospitalization due to ADR results in a greater loss of productivity and an increase in caregiver burden. Conversely, the healthcare system may face a significant escalation of cost and resource use from ADRs. This is because any reaction would require

close monitoring and additional interventions, on top of prolonging the duration of care. A study by Evans et al., for example, evidenced that ADRs can extend hospitalization by 8 to 12 days, which corresponds to an additional expenditure of USD 16,000 to USD 24,000 per patient [8]. In more life-threatening reactions such as Steven-Johnsons syndrome or toxic epidermal necrolysis, the patient would require admission to the intensive care unit and multidisciplinary team effort. Some studies have demonstrated that these expenditures, collectively, can be as high as 15% to 20% of the hospital budgets [9]. The annual expenditure on drug-related events in the United States for example reaches an exorbitant spending of USD 30.1 to 136.8 billion [10]. A separate study exploring drug-related morbidity and mortality in 2000 demonstrated that the cost of illness of ADR amounted to USD 177.4 billion in that year [11]. Out of this amount, healthcare-related drug costs accounted for the largest portion.

Although the clinical consequences and the corresponding healthcare costs are critical public health concerns, the exact economic impact of ADRs is still poorly characterized [2]. This is primarily due to underreporting, arising from a shortcoming in existing pharmacovigilance systems, which underestimates the true economic burden of ADRs [12]. As experimental clinical trials are not possible in this context, the determination of the actual expenditure incurred remains challenging due to the unpredictable nature of ADRs. Reported studies are also often focused on the simulation and extrapolation of existing data and data from cost-of-illness studies [13]. These studies typically vary in the measures used to identify ADRs, the resource use, and how the total cost was established [14]. The ADR classification, for instance, requires a systematic approach to determine if an event is related to drugs and to assess the causality [15,16]. However, the numerous classification systems and guides pose a challenge to the generalizability and interpretation of findings by the level of causality [17].

Information on the economic burden of ADRs is vital to policymakers as it helps in the planning of resource allocation and management. It is also critical to push forward prioritization and the development of patient safety initiatives. However, the current scarcity of evidence, on top of the heterogeneity of findings, makes the interpretation of findings difficult. For instance, between 1998 and 2013, there were at least 14 systematic reviews on the incidence and risk factors of ADRs [6,17–28]. Out of this, only three of them [17,25,27] looked into ADR costs while only one [29] explored the potential effect of methodological approaches to cost estimations. Furthermore, the lack of consistent cost data and unascertained methodological influences also limit the ability to evaluate cost-effectiveness strategies such as pharmacovigilance programs, medication reviews, and patient education campaigns. Hence, this study aims to systematically review the methodological impacts on assessing the cost of ADRs with a focus on events occurring in a hospital setting. This review will also identify and explore the association of ADR cost-related factors such as patient characteristics, the type of drug involved, causality tools applied in diagnosing, and the incidence of ADRs.

2. Results

The search yielded a total of 677 potentially relevant articles. After removing the duplicates, 450 abstracts were reviewed and screened for eligibility. Based on the inclusion criteria, 94 articles were selected for further evaluation. A total of 12 studies were found to be eligible for the review. The complete process of the literature search and study selection is illustrated in Figure 1.

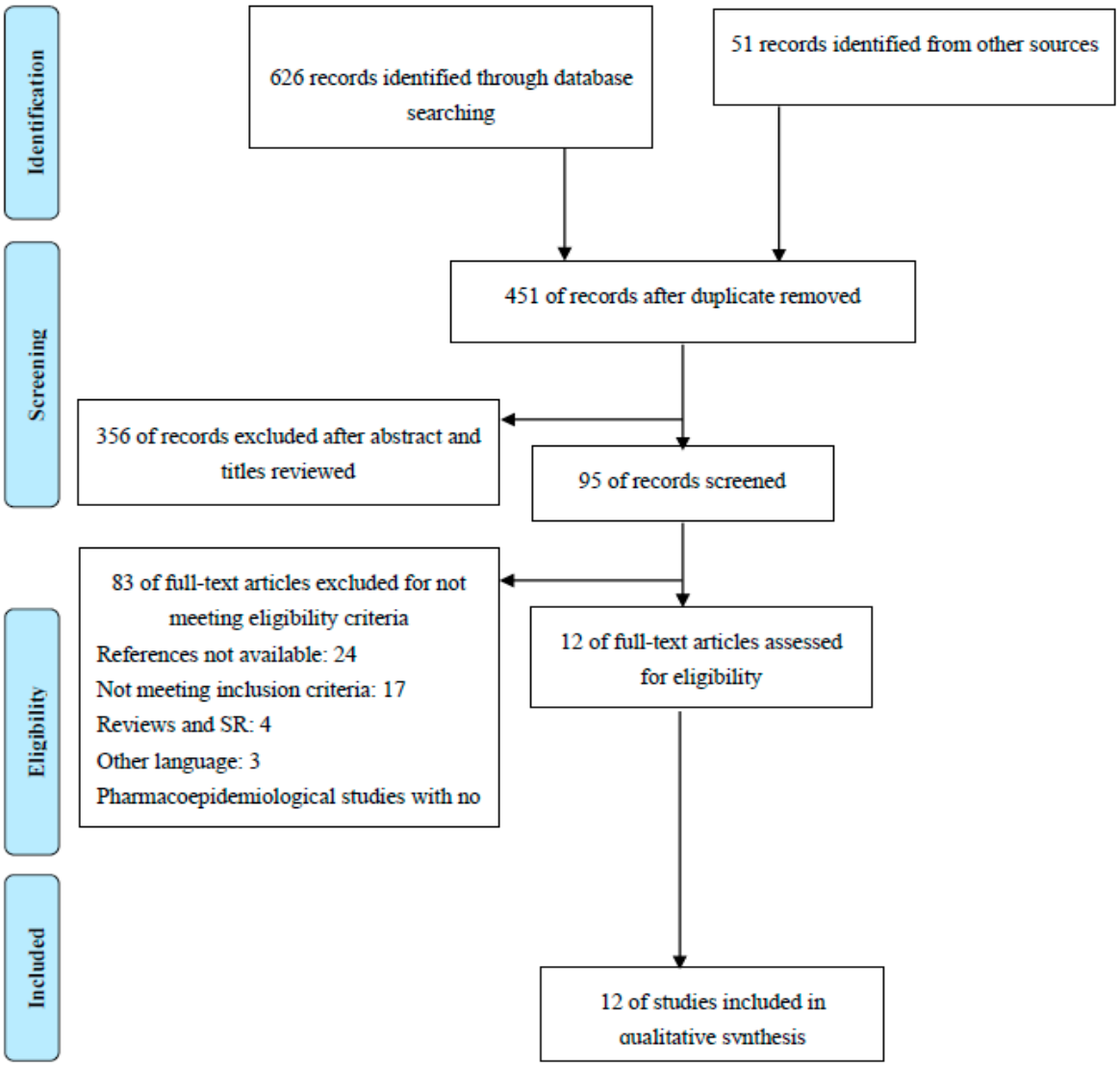

Figure 1. Flow diagram of selection of studies.

2.1. Characteristics of the Included Studies

As shown in Table 1, most of the studies selected for the review were from India (n = 4), followed by one study each from the US, Taiwan, France, Switzerland, Spain, and Germany. Ten of the reports were from single-center studies (n = 10), with five of them conducted at the emergency departments [30–34]. Most studies were based on a prospective study design (n = 7), followed by retrospective data collection [34–37]. The study duration ranged from as short as 1.5 months to 72 months. In terms of patient characteristics, the mean age of patients ranged from 40 to 72 years. Generally, the ADRs were shown to be more common in males than females in six of the studies [10,32,34,35,38,39].

Table 1. Characteristics of included studies.

Author (Publication Date)	Suh et al. (2000) [38]	Bordet et al. (2001) [10]	Wasserfallen et al. (2001) [33]	Wu and Pantaleo (2003) [37]	Yee et al. (2005) [34]	Patel et al. (2007) [31]	Chan et al. (2008) [39]	Pattanaik et al. (2009) [32]	Carrasco-Garrido et al. (2010) [35]	Rottenkolber et al. (2011) [36]	Rajakannan et al. (2012) [40]	Geer et al. (2016) [30]
Country	USA	France	Switzerland	USA	USA	India	Taiwan	India	Spain	Germany	India	India
Type of study design	Prospective	Prospective	Prospective	Retro-spective	Retro-spective	Prospective	Prospective	Prospective	Retro-spective	Retro-spective	Prospective	Prospective
Single/Multi centre	Single centre	Single centre	Single centre	Single centre	Single centre	Single centre	Single centre	Single centre	Multicentre	Multicentre	Single centre	Single centre
Study duration (months)	5	18	5	24	3	1.5	36	4	72	24	6	9
No. Patients included	9311	16,916	3195	191	2225	2046	142,295	1833	20,712,399	57,000	1438	5483
Age range	Mean 56.6 (SD 20.3)	Mean 66.0 (SD 2.0)	Mean 61.4 (Range 16–93)	Mean/median age (NR)	Mean 60.2 (SD 14.2)	Mean 40.0 (NR)	Mean 66.0 (SD 2.0)	Mean or median age (NR)	Mean or median age (NR)	Mean 71.0 (14.7) Median 74 (17–103)	Mean 45.9 (SD 15.8)	Mean 62.0 (SD 2.3)
Gender	Male: 50.4% Female: 49.6%	Male: 55.3% Female: 44.7%	Male: 47.0% Female: 53.0%	Male: 44.0% Female: 56.0%	Male: 92.3% Female: 7.3%	NR	Male: 54.0% Female: 46.0%	Male: 57.7% Female: 42.3%	Male: 50.5% Female: 49.5%	Male: 41.8% Female: 58.2%	Male: 42.3% Female: 57.7%	Male: 38.6% Female: 61.4%
Setting (medical specialty)	General medical	Medical, surgical, paediatrics, and ICU	Emergency	Emergency	Emergency	Emergency	General medical	Medical emergency	General hospital admission	Internal medicine	Medical wards	Internal medicine and emergency

2.2. ADR Identification Methods, Incidence, and Length of Stay (LOS)

Table 2 describes the characteristics of the ADRs reported and the methods applied to detect them. All studies defined ADR according to WHO classifications. Two studies [30,36] further included additional identification methods based on Edward and Aronson's classification [41] and Rawlins and Thomson's classification [42]. All assessments of ADR were conducted by healthcare professionals, including pharmacists, physicians, or nurses. Six studies [9,30,35,37,38,42,43] reported the severity of the ADRs and categorized the events into "mild" (18.5–53.0%) and "moderate" (48.8–74.7%) based on different criteria [1,44]. The Naranjo probability scale was found to be the most widely used tool for the ADR causality assessment (n = 7). Interestingly, a majority of the ADR causalities were reported as being probable (n = 5) [30,31,38–40].

Studies by Wasserfallen et al. and Rajakannan et al. demonstrated the highest incidence of admission due to ADR, at 7.10% and 17.11%, respectively [33,40]. Only three studies reported percentages of ADR preventability from 20.0 to 81.6% [31,33,36]. The major types of ADR can be categorized based on gastrointestinal (n = 6, 3.8–24.4%), dermatologic (n = 5, 12.6–75.6%), cardiovascular (n = 5, 3.1–24.1%), and hematologic (n = 5, 9.9–15.2%) system disorders. The most common drugs causing ADRs were anticoagulants (n = 8, 7.5–22.1%), anti-infectives (n = 7, 6.3–40.9%), cardiovascular drugs (n = 5, 7.0–36.0%), and antidiabetic agents (n = 4, 6.0–27.8%). In addition, the means of the length of ADR-caused hospitalization ranged from 3 to 12.8 days.

Table 2. ADR characteristics and methods used for ADR detection in included studies.

Author (Publication Date)	Suh et al. (2000) [38]	Bordet et al. (2001) [10]	Wasserfallen et al. (2001) [33]	Wu and Pantaleo (2003) [37]
ADR definition and type classification	WHO	WHO	WHO	WHO
Method of ADR detection (ADR defined by WHO)	Assessed by healthcare providers (pharmacists, nurses) from ADR reporting system and medical records.	Assessed by healthcare professionals (physicians and nurses) upon admission at all units and reviewing medical records.	Assessed by healthcare providers (research investigators) from hospital admission book.	Assessed by healthcare providers from ADR-related hospital admissions and patient's medication profiles.
Method of ADR severity	No reference Mild: 30.0% Moderate: 53.0% Severe: 17.0%	WHO Mild: 53% Moderate: 34% Severe: 10%	No reference Evaluated using 5-point scale	NR
Causality assessment of ADR	Naranjo probability scale Definite: 8.0% Probable: 69.0% Possible: 21.0% Doubtful: 2.0%	French method Very likely: 1.0% Likely: 21.0% Possible: 25.0% Doubtful: 53.0%	WHO algorithm for imputability Certain: 18.0% Likely: 26.0% Possible: 56.0%	NR
Admission due to ADR (%)	2.1	2.2	7.1	NR
Preventable ADR (%)	NR	NR	20.0 (10-item Qs, Livio 1998)	NR
Length of hospitalization due to ADR (days)	1–3 ADR: 10.3 (10.7) [mean] >4 ADR: 12.8 (6.8) [mean]	11 (NR) [mean]	9.0 (0.6) [mean]	8.0 (3.0) [mean] 5.0 (NR) [median] (Range 0 to 99 days)
Top five causative agents of ADR (therapeutic group)	Anti-infectives (17.1%) CVS drugs (16.5%) Antineoplastic (14.6%) NSAIDs (14.6%) Psychotropics (5.5%)	CVS Agents (36.0%) Contrast media (20.0%) Anti-infectives (14.0%) Anticoagulant (13.0%) Diuretics (6.0%)	Antineoplastic (22.7%) Anticoagulant (8.4%) NSAIDs (8.1%) Analgesics (8.1%) Antihypertensive (7.3%)	Antidiabetics (27.8%) CVS drugs (26.2%) Anticoagulant (15.2%) Psychotropics (11.5%) Analgesics (10.0%)
Top five ADRs	Gastrointestinal (24.4%) Dermatology (18.6%) Immunology (14.5%) CNS (13.2%) Hematological (9.9%)	Cutaneous (24.0%) CVS condition (21.0%) Metabolic cond. (12.0%) Coagulation (10.0%) CNS (10.0%)	GI bleeding (22.2%) Febrile neutropenia (14.4%) Hypotension (7.9%) Enterocolitis (5.7%) Hypoglycemia (4.6%)	Endocrine (28.3%) CVS condition (24.1%) Hematological (15.2%) Neurologic (14.1%) Renal (14.1%)

Table 2. *Cont.*

Author (Publication Date)	Yee et al. (2005) [34]	Patel et al. (2007) [31]	Chan et al. (2008) [39]	Pattanaik et al. (2009) [32]
ADR definition and type classification	WHO	WHO	WHO	WHO
Method of ADR detection (ADR defined by WHO)	Assessed by healthcare professionals upon admission at ED and reviewing electronic medical record system.	Assessed by healthcare professionals (senior lecturers and authors) upon admission at ED.	Assessed by healthcare providers from hospital admission cases.	Assessed by healthcare professionals (doctors, pharmacists, nurses) upon admission at medical ED.
Method of ADR severity	NR	Modified Hartwig and Siegel Scale. Mild: 18.5% Moderate: 74.7% Severe: 6.8%	WHO Mild: 34.4% Moderate: 58.5% Severe: 7.1%	NR
Causality assessment of ADR	Naranjo probability scale Definite:1.0% Probable: 31.0% Possible: 68.0%	Naranjo probability scale Definite:3.8% Probable: 85.9% Possible: 10.3%	Naranjo probability scale Definite: 4.1% Probable: 73.2% Possible: 22.3% Doubtful: 0.4%	Naranjo probability scale Definite: 86.0% Probable: 6.0% Possible: 8.0%
Admission due to ADR (%)	1.1	6.9	0.03	1.4
Preventability of ADR (%)	NR	59.6 (Hallas 1990)	NR	NR
Length of hospitalization due to ADR (days)	6.3 (NR) [mean]	5 (NR) [median] (95% CI 5.37 to 7.11)	NR	3 (NR) [median]
Top five drugs causing ADR (therapeutic group)	Anticoagulant (22.1%) Anti-infectives (13.2%) Antineoplastic (13.2%) Antidiabetics (10.3%) Diuretics (8.8%)	Anti-TB agents (19.6%) Antiepileptic (13.6% Antimalarials (11.3%) Anticoagulants (9.4%) OHA (6.0%)	Anti-infectives (38.8%) Analgesics (11.0%) CVS drugs (9.9%) NSAIDs (5.7%) Antiepileptic (5.1%)	NR
Top five nature of ADR occurred	Dermatologic allergic reaction (75.6%)	Hepatitis (10.6%) GI bleeding (9.1%) Gastritis (8.3%)	Cutaneous (52.5%) Hematological (10.8%) CVS condition (9.6%) Hepatic (5.9%) GI effects (5.0%)	NR

Table 2. *Cont.*

Author (Publication Date)	Carrasco-Garrido et al. (2010) [35]	Rottenkolber et al. (2011) [36]	Rajakannan et al. (2012) [40]	Geer et al. (2016) [30]
ADR definition and type classification	WHO	WHO Edwards and Aronson (2000) classification	WHO	WHO Rawlins and Thomson classification
Method of ADR detection (ADR defined by WHO)	Assessed by healthcare professionals (physicians) from hospital admission database.	Identified by evaluators from pharmacovigilance database and reviewing medical history.	Identified by investigator based on indicator list developed during manual screening of patients.	Assessed by healthcare professionals (multidisciplinary medical team) through hospital admission cases.
Method of ADR severity	NR	Hartwig severity scale Hosp: 89.3% Intensive: 9.1% Harm: 0.7% Fatal: 0.9%	Hartwig severity scale Mild: 36.6% Moderate: 61.5% Severe: 1.9%	Modified Hartwig and Siegel Scale. Mild: 41.5% Moderate: 48.8% Severe: 9.7%
Causality assessment of ADR	NR	Begaud et al. (1985) algorithm Predictable: 91.1% Unpredictable: 7.8%	Naranjo scale Definite: 1.0% Probable: 61.2% Possible: 37.8%	Naranjo scale Definite: 5.3% Probable: 78.6% Possible: 16.1%
Admission due to ADR (%)	1.69 (1.65, 1.73)	3.25	17.11	1.24
Preventability of ADR (%)	NR	20.1 (Schumock and Thornton 1992)	NR	81.6 (Hallas 1990)
Length of hospitalization due to ADR (days)	8.0 (10) [median]	9.3 (7.1) [mean]	5.0 (Range 5–28) [median]	7 (NR) [median]
Top five drugs causing ADR (therapeutic group)	Antineoplastic (21.5%) Steroids (13.5%) Anticoagulant (7.5%) CVS drugs (7.0%) Anti-infectives (6.3%)	Anticoagulant (18.3%) Antidiabetics (15.9%) Diuretics (10.0%)	Anti-infectives (27.6%)	Anti-infectives (40.9%) Anti-TB agents (13.2%) Steroids (14.0%) Anticoagulant (8.8%) NSAIDs (7.9%)
Top five nature of ADR occurred	Neutropenia (5.0%) Chronic bronchitis (4.9%) CVS condition (3.1%) Neoplastic (3.0%) Pneumonia (2.9%)	GI bleeding (16.5%) Hypoglycemic (13.3%) Bradycardia (5.5%) Colitis (3.9%) Gastric ulcer (3.8%)	GI effects (19.5%) CNS condition (18.6%) Dermatology (15.4%) Metabolic cond. (15.1%) Hepatic (12.0%)	GI effects (23.7%) Dermatology (12.6%) CNS condition (11.7%) Hematological (10.0%) Metabolic cond. (9.6%)

Note: WHO = World Health Organization, NR = not reported, CVS = cardiovascular, NSAIDs = non-steroidal anti-inflammatory agents, CNS = central nervous system, Anti-TB = antituberculosis; OHA = oral hypoglycemic agent, GI = gastrointestinal.

2.3. Study Quality and Risk of Bias

Table 3 and Figure 2 show a summary of the assessment of the risk of bias, level of evidence, and potential hierarchies of data sources for all 12 selected studies. Overall, the studies had moderate to high risk of bias. Five studies were considered to have a moderate risk of bias as they have distinctly defined the outcome measure and variables, in addition to outcomes being measured using reliable statistical methods [30,31,34,35,37].

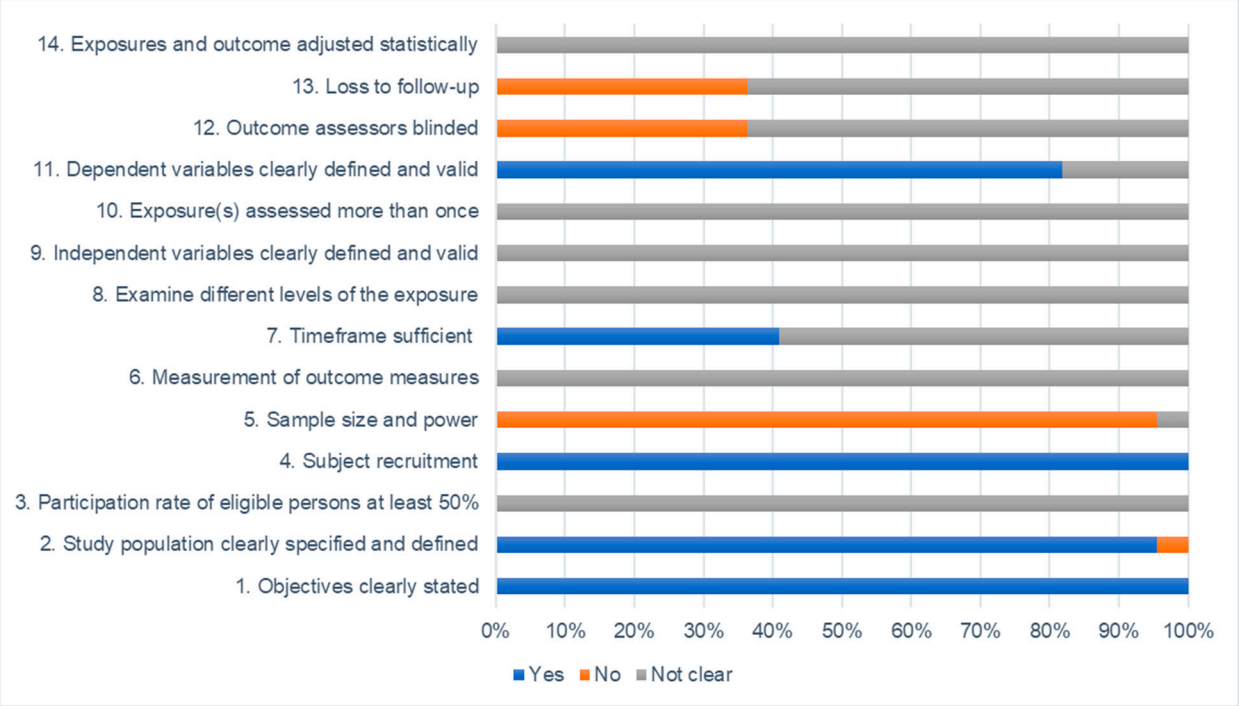

Figure 2. Summary of assessment for methodological quality of the selected studies.

Each method has its own advantages and disadvantages. Reliance on patients, for instance, is the most common approach, but is limited by recall biases, non-response, and evasiveness [45]. As for the use of routinely collected data, this depends on the accurate recording and stability of information technology infrastructure. To estimate costs related to ADR, two key data inputs were needed: the frequency of ADRs over a defined period and the cost per episode of care (associated with the event). Frequently, this information was extracted from the baseline clinical data input.

In terms of baseline clinical input data, four studies [34–37] used reliable administrative medical record databases. Additionally, Wasserfallen et al. (2001) and Rottenkolber et al. (2011) were the only two studies identified to be using previously published resource use results and cost calculations for analysis [33,36]. It was discussed that referring to recently published data and eliciting expert opinions is convenient but is not generally considered a reliable or unbiased method of resource use estimation [46].

2.4. Method of Cost Calculation

Economic analysis frequently combines information from various data sources to estimate cost. Studies in this review collated the cost data from patients' self-reported health (by questionnaire, interview, and diary cards), available secondary data such as medical records, and hospital administrative databases, in addition to expert opinions [46]. The summary of methods used to calculate ADR costs is shown in Table 4. All studies estimated the cost of ADR management from the healthcare provider's perspective, with one study incorporating both the provider's and patient's perspectives.

Table 3. Risk of bias analysis and level of clinical evidence and potential hierarchies of data sources for economic analysis.

Study	Author	Year Published	Quality Assessment (Risk of Bias) [1]	Baseline Clinical Data [2]	Resource Use [2]	Costs [2]
1	Suh et al.	2000	High	1++	1++	1++
2	Bordet et al.	2001	High	1++	1++	1++
3	Wasserfallen et al.	2001	High	1++	1+	1+
4	Wu and Pantaleo	2003	Moderate	1+	1++	1++
5	Yee et al.	2005	Moderate	1+	1++	1++
6	Patel et al.	2007	Moderate	1++	1++	1++
7	Chan et al.	2008	High	1++	1++	1++
8	Pattanaik et al.	2009	Moderate	1++	1++	1++
9	Carrasco-Garrido et al.	2010	High	1+	1++	1++
10	Rottenkolber et al.	2011	High	1+	1+	1+
11	Rajakannan et al.	2012	High	1++	1++	1++
12	Geer et al.	2016	Moderate	1++	1++	1++

[1] National Institutes of Health (2017). Quality assessment tool for observational cohort and cross-sectional studies. National Heart, Lung, and Blood Institute. [2] Coyle D, Lee MK (2002). Evidence-based economic evaluation: how the use of different data sources can impact results.

Seven studies applied a micro-costing approach, where the unit cost of each resource consumed was calculated and multiplied by the length of stay in the hospital to generate the total healthcare cost of managing ADRs [30–34,39,40]. Most of the studies using the micro-costing approach were prospective in design, while three [35,36,38] were found to have used the diagnosis-related groups (DRG) to determine such costs. The remaining two studies calculated the ADR management costs based on daily hospital charges for patients using the hospital-specific cost/charge ratio [9,36]. It is worth highlighting that while sensitivity analysis was generally not possible for micro-costing approaches, the study conducted by Wasserfallen et al. (2001) reported sensitivity analysis for their imputability (or causality) and avoidability figures [33].

Table 4. Method of cost calculation and estimated cost per ADR case.

Authors (Date Published)	Type of Study Design	No. of Pat. (Cost Analysis)	Data Extraction (Database Used)	Cost Analysis Perspective	Cost Calculation	LOS Definition	Sensitivity Analysis	Total Cost ADR (Duration)	Cost/Case (As Reported, Mean (SD))	Cost/Case, USD (Adjusted 2016)
Micro-costing or unit cost (component of resource use estimated and unit cost derived)										
Wasserfallen et al. (2001) [33]	Prospective	229	Admission database and medical records	Provider (health sector)	Hospital marginal costs divided by no. of patients in ward and computed according to no. of stays	Number of days spent in different wards	Imputability and avoidability figures (10–100%)	NR	CHF 3586.00 (342.00)	2908.77
Yee et al. (2005) [34]	Retrospective	274	Admission database (ED) and medical records (electronic) and VAD system	Provider (health sector)	Costs from activity-based costing system implemented	NA	NR	USD 333,433.00 (12 wk)	USD 3704.00 (NR)	4463.59
Patel et al. (2007) [31]	Prospective	141	Hospital admissions reports and patients' profiles	Provider (health sector)	Products of total admission days for all patients admitted with ADR	Number of days admitted to hospital due to ADR	NR	INR 1.12 million (6 wk)	INR 6197.00 (NR)	581.74
Chan et al. (2008 [39])	Prospective	564	ADR reporting system and patients' profiles	Provider (health sector)	Hospital cost for services related to ADR treatment based on hospital's claim data system	NA	NR	USD 150,027.14 (36 mo)	USD 3489.00 (NR)	3896.97
Pattanaik et al. (2009) [32]	Prospective	92	Admissions reports (ED) and patients' profiles	Provider and patients (health and societal)	Cost for healthcare (direct) and non-healthcare (indirect) in ADR treatment	NA	For variability in components of the indirect cost	EUR 5556.00 (4 mo)	EUR 214.00 (NR)	346.25
Rajakannan et al. (2012) [40]	Prospective	246	Patients' medical records in wards (patient notes)	Payer (health sector)	Hospital cost for services related to ADR treatment based on hosp patient admin system	Number of days in ward due to ADR	NR	USD 36,451.00 (6 mo)	USD 115.00 (NR)	327.38

Table 4. *Cont.*

Authors (Date Published)	Type of Study Design	No. of Pat. (Cost Analysis)	Data Extraction (Database Used)	Cost Analysis Perspective	Cost Calculation	LOS Definition	Sensitivity Analysis	Total Cost ADR (Duration)	Cost/Case (As Reported, Mean (SD))	Cost/Case, USD (Adjusted 2016)
Geer et al. (2016) [30]	Prospective	342	Hospital admissions reports and patients' profiles	Provider (health sector)	Products of total admission days for all patients admitted with ADR	Measured by excess days: difference duration of hosp stays of ADR patient and mean duration of hosp stays for non-ADR patients	NR	USD 22,469.00 (9 mo)	USD 65.00 (NR)	65
Case-mix group costing (gives cost by case or patient category, e.g., DRG)										
Suh et al. (2000) [38]	Prospective	131	Institutional database	Provider and payer (health sector)	DRG-based estimates (using hospital-specific cost/charge ratio)	NA	NR	USD 22,775 (SD 21,088.00) (5 mo)	USD 20,745.00 (20,040.00) (1–3 ADR) USD 34,445.00 (24,025.00) (>4 ADR) *(Values were based on ADR cost per patient)*	28,082.65 (1–3 ADR) 46,628.44 (>4 ADR) *(Values were based on ADR cost per patient*)
Carrasco-Garrido et al. (2010) [35]	Retrospective	350,835	Admission database (minimum basic data set, MBDS) and patients' profiles	Payer (health sector)	DRG-based estimates (reimbursement)	NA	NR	EUR 272 million (12 mo)	EUR 4382.00 (NR)	6668.84
Rottenkolber et al. (2011) [36]	Retrospective	1834	Regional regulatory database and admissions reports	Payer (health sector)	DRG-based estimates (reimbursement)	NA	NR	EUR 434 million (12 mo)	EUR 2250.00 (1321.00)	3102.71

Table 4. *Cont.*

Authors (Date Published)	Type of Study Design	No. of Pat. (Cost Analysis)	Data Extraction (Database Used)	Cost Analysis Perspective	Cost Calculation	LOS Definition	Sensitivity Analysis	Total Cost ADR (Duration)	Cost/Case (As Reported, Mean (SD))	Cost/Case, USD (Adjusted 2016)
Average per diem (or daily cost)										
Bordet et al. (2001) [10]	Prospective	371	Admission database and medical records	Provider (health sector)	Hospital charges converted using hospital-specific cost/charge ratio	NA	NR	EUR 1815 million (18 mo)	EUR 4150.00 (NR)	6222.52
Wu and Pantaleo (2003) [37]	Retrospective	191	Pharmacy depart. reports and medication profiles	Provider (health sector)	Hospital charges converted using hospital-specific cost/charge ratio	NA	NR	NR	USD 9491.00 (12,843.00)	12,129.90

2.5. Cost of ADR

The adjusted hospitalization costs per ADR in each country ranged between USD 65 and 12,129 (n = 11). These costs, however, were not standardized as they varied in terms of their reporting. Suh et al., for example, reported the ADR cost by the number of ADRs occurring per patient case, USD 28,082.65 for one to three ADRs (n = 119) and USD 46,628.44 for more than four ADRs (n = 12) [37]. On the other hand, a study conducted by Geer et al. reported that the cost of ADR per patient per day was USD 65 [30]. Nevertheless, most studies opted to report the cost of ADR in terms of expenditures required per case. Aside from the four studies conducted in India [30–32,40], all other studies were from high-income countries. The average costs per case of ADR in high-income countries were demonstrated to be more than 10 times higher than in low-income countries. For instance, the average cost per case of ADR ranged from USD 2908.77 to 12,129.90 in high-income countries, and from USD 65.00 to 581.71 in India.

The average cost was also found to be lower in two studies with a mean length of hospital stay of fewer than five days (USD 346.25 [32] and USD 581.74 [31]). Among the three studies which computed ADR cost based on length of stay (LOS), only the study by Geer et al. defined LOS as "excess days". This was defined as the difference between the individual duration of the hospital stays of a patient having an ADR and the mean duration of hospital stays for patients without ADRs. This form of reporting was shown to also generate the lowest cost of ADR per case. It was also discovered that the ranges of ADR cost per case were smaller among studies conducting unit cost analysis [31–33,39,40].

3. Discussion

Our review found a wide range of values for total ADR costs. Factors such as the study location, ADR characteristics, and methodological differences primarily contributed to this. The lowest reported ADR costs per case were from Indian studies, ranging from USD 65 to USD 581.74 [30–32,40]. Meanwhile, those studies from high-income countries reported higher ADR costs [10,35,37,38]. This is due to factors such as the lower currency exchange rates and lower labor costs in India, relative to the high medical inflation rates in developed nations. Despite GDP and health spending growing fastest in low- and middle-income countries, a large gap persists between rich and poor countries. In 2016, the median per capita health spending was over USD 2000 in high-income countries but just a fifth of that (USD 400) in upper-middle-income countries and one-twentieth of that (USD 100) in low- and lower-middle-income countries [47]. A study conducted by Chevat et al. [48] further reported that healthcare costs are country-specific, and the main contributing differences are interventions such as cost per day in hospitals or specific laboratory tests. Therefore, to extrapolate costs from different healthcare settings, policymakers may consider using appropriate conversion methods such as purchase power parities.

It is also postulated that, generally, the cost estimations reported are an underestimation of the true economic impact of ADRs. This is because most studies provide the resource use from a healthcare provider perspective. The inclusion of patient and household expenses for travel, food, and stay during the hospitalization may further increase the actual financial burden of ADRs [32,49]. Furthermore, both hospitalization- and ADR-associated temporary or permanent disabilities can lead to a significant loss of productivity for patients and their households [50]. Thus, the exploration of costs from a wider societal perspective is warranted to push for higher investments in preventive and pharmacovigilance activities.

Streamlining ADR Costing Methods

Almost all studies applying the micro-costing methods had a lower ADR cost (USD 65.00 to USD 4463.59) compared to case-mix group and average-per-diem costing at USD 3102.71 to USD 46,628.44 [34,35,37] and USD 6222.52 to USD 12,129.90, respectively [10,37]. This might be, however, partly attributed to the inadequate identification of contributing cost components. A comprehensive micro-costing study conducted by Gyllensten and colleagues evidenced that if all components are taken into consideration, the cost estimates

tend to be higher than those based on registered diagnoses [29]. This was achieved by combining data registers with information from medical records. Furthermore, methods such as micro-costing or using reimbursement records can provide a more accurate picture of the healthcare resources used. However, it is also crucial for both researchers and policymakers to consider the inclusion of factors such as overheads and personnel time to quantify the additional burden caused by ADRs arising during the inpatient stay.

Evaluating the ADR-related length of stay has the advantage of capturing the burden of ADR in terms of prolonging inpatient care [51]. The cost per hospital day provides a crude estimation that can be adapted to different regions and hospitals. However, such reporting also requires two critical factors to be considered for the interpretation of the values: Firstly, whether the mechanism or analysis used could discriminate between the length of stay contributed by the ADR and the primary admission reason. Estimation of the length of stay which includes disease management can underestimate the actual burden of ADR [30,31,33]. Secondly, the most acute interventions and managements often occur in the first few days of the ADRs, especially in mild to moderate conditions. This is then followed by monitoring and maybe symptomatic support. Thus, the process of averaging the expenditures in these cases may discount the initial high resource use during the acute phase of ADRs. Therefore, it is advisable that aside from the total ADR management costs, the researcher can consider reporting the costs based on the acute phase and the monitoring or stabilized phase.

From a clinical and drug safety evaluation point of view, the definition, identification, and causality of ADRs were also found to affect the cost of the ADR [51]. For instance, choosing a threshold causality level of at least "possible" as opposed to at least "probable" could likewise lead to false-positive ADRs [52]. Such an approach often leads to an overestimation of ADR-related costs [53]. To the best of our knowledge, no adjustment methods have been suggested for assessing the level of the causal relationship between drug and symptom for ADR cost estimation [17]. Therefore, current ADR detection systems and tools must be chosen carefully when calculating ADR costs.

From earlier reviews [17,23–25,27,28], findings have reported the presence of methodological heterogeneity between studies measuring ADR costs in terms of assessing causal relationships between the drug and the resulting morbidity, and how to define ADR. This is similar to our review, where there is also a large heterogeneity between the methods and cost sources used for cost analysis within these studies. Cost estimation approaches should be viewed as an equally important part of the methods section. It has been argued that there is a need for closer relationships between researchers and research within the fields of pharmacoeconomics and pharmacoepidemiology [54]. It would be useful for researchers if there was an evaluation tool developed based on published checklists aimed at measuring the quality or guiding research within the field of observational descriptive studies and economic evaluation [14,55]. However, still, it depends on the research question, and adapting to international guidelines and terminology within economic cost analyses is required [56].

It is worth highlighting that there were limitations in this review. First, the search process only included articles published in English and reports from the last 18 years. The exclusion of non-English articles could have resulted in a selection bias, especially from lower-income nations. This consequently limits the ability to explore or visualize other methods of costing or ADR classification systems. On the other hand, the more recent time horizon may have excluded past classification and assessment methods. This, conversely, reduces the understanding of how such approaches can be interpreted in our current time. Lastly, this review was only able to explore methodological impacts qualitatively. This was because multiple factors which impacted on the estimated costs made further statistical analysis difficult.

4. Methods

4.1. Search Strategy

This systematic review was conducted in line with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines [57]. Literature search was performed on MEDLINE, EMBASE, CINAHL, Cochrane Library, and Google Scholar. The search was restricted to only observational studies published from 1 January 2000 to 31 December 2017. A more recent time period was selected based on the emergence of standardized new approaches to identify adverse events [18,19,55,58]. Papers were confined to the English language only or if a full copy in English was available for abstraction. Appropriate Medical Subject Headings (MeSH), thesauruses, and specific keywords were combined using Boolean operators in search terms and guided by the criteria in Table 5.

Table 5. Search concepts and examples of phrases used.

Concept	Examples of Similar Phrases
Population	"adult", "children", or "pediatric"
ADR	"adverse drug reactions", "drug toxicity", "hospitalized adverse drug reactions", "hospitalized side effect", "hospitalized adverse effect", "hospital acquired ADRs (MeSH)", "hospital induced ADRs (MeSH)", "ADRs occurred during hospitalization (MeSH)"
Surveillance	"drug monitoring (MeSH)", "drug surveillance program", "pharmacovigilance"
Cost	"ADR economic burden", "direct cost", "cost of illness", "cost", and "economic"

4.2. Study Selection Criteria

The study title and abstracts were first scrutinized by two reviewers (SFA and HC) based on set criteria. The inclusion criteria were (1) direct or indirect cost of ADRs based on observational studies of clinical data from general patient groups; (2) contains sufficient information to calculate ADR incidence; and (3) prospective or retrospective monitoring to identify ADRs. Studies were only excluded if (1) responses were due to therapeutic failures, intentional poisoning, overdosing, drug abuse, and non-adherence to treatment; (2) patients studied were selected for particular conditions or specific drug exposures; and (3) they contained the cost of specific types of ADRs or specific medications or drug categories only.

4.3. Data Extraction

The information required for the review was independently extracted by two reviewers (SFA and HC) and cross validated by AAS. Data were extracted into three major sections to aid the discussion of findings: (1) study design, (2) ADR reporting, and (3) costing approaches [15]. Study design consists of the adopted methodologies, including the study duration, setting, and population age range and size. For ADR reporting, we abstracted the guidelines used for the definition, classification, severity, causality assessment, and detection methods. The costing approaches were focused on the cost perspectives, method of cost calculation, data sources, the total estimated cost, and adjustment mechanisms. All extracted articles were then scrutinized to determine the relationship between the data collected with the aforementioned hospitalized ADR parameters.

4.4. Quality Assessments

The quality of the studies was subsequently evaluated based on the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies of NIH (National Institute of Health—USA) [59]. The checklist consists of 14 questions which are rated as Yes, No, or Cannot Determine. The list is intended to focus on the key concepts for evaluating the internal validity of the studies. These questions were taken into consideration when a summary judgment on the quality of the study was made. Studies were also appraised

according to the methods of measuring the cost of drug-related morbidity, which were based on items used for assessing economic evaluation studies, mainly study viewpoint and costing methods.

4.5. Data Analysis

A qualitative review approach was taken in interpreting the methodological influences on the ADR cost estimates. The study perspective was categorized as provider, payer, or patient. Studies were judged to measure societal costs if they included direct and indirect costs to the hospital, any third-party payer, and patients. In this review, the terms used for direct and indirect cost follow the categorization in Drummond, 2015 [14]. The methods used to measure the cost of ADR in each study were divided into micro-costing, case-mix group, or average per diem [14]. Micro-costing involves studies which identify and estimate the cost for each component of the resource used (e.g., laboratory tests, days of stay by ward, drugs). Case-mix or disease-related groups, on the other hand, involve the cost estimation by case category using the length of stay. Disease-specific or average per diem involves estimating the average daily cost for treatments in each disease category.

To facilitate the comparison across different settings and years, the cost per case was presented in USD by inflating the cost to its 2016 value using country-specific GDP inflators [43]. The data analysis was performed using Microsoft Excel 2010 (Microsoft Corporation, Redmond, WA, USA).

5. Conclusions

Despite the high incidences and significant impact of ADRs among hospitalized patients, there is still a paucity of evidence in terms of their cost implications. Furthermore, a lack of guidance and standardization in reporting makes it difficult for future researchers to adopt a comprehensive and established methodology. This review well evidenced that these limitations lead to the large heterogeneity in study designs, which consequently causes large variations in ADR cost estimations. The three main recommendations from this review are (1) to adopt a societal perspective in costing, (2) to identify and include all related cost components, and (3) to apply well-acknowledged classification and causal relationships when identifying ADRs. It is hoped that the findings from this study can encourage a more robust exploration of the economic burden of managing ADRs to fill the current knowledge gaps.

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