Pharmacoepidemiology and Drug Safety

WILEY

ORIGINAL ARTICLE

Uncovering Medication Errors Leading to Hospital Admissions in the Emergency Department: An External, Prospective Validation of Clinical Decision Rules

Nadjia Amini[1] | Sabrina De Winter[2] | Sanne Nijs[3] | Ann-Sophie Jacob[4] | Sandra Verelst[5] | Peter Vanbrabant[6] | Lorenz Van der Linden[2,7] | Isabel Spriet[2,7]

[1]Geriatrics & Gerontology, Department of Public Health and Primary Care, KU Leuven, Leuven, Belgium | [2]Pharmacy Department, University Hospitals Leuven, Leuven, Belgium | [3]Faculty of Pharmaceutical Sciences, Unit of Student Counseling and Ombuds Service, Leuven, Belgium | [4]Department of Laboratory Medicine, University Hospitals Leuven, Leuven, Belgium | [5]Management Committee, Regional Hospital Heilig Hart Leuven, Leuven, Belgium | [6]Department of General Internal Medicine, University Hospitals Leuven, Leuven, Belgium | [7]Department of Pharmaceutical and Pharmacological Sciences, KU Leuven, Leuven, Belgium

Correspondence: Sabrina De Winter (sabrina.dewinter@uzleuven.be)

Received: 15 October 2024 | **Revised:** 19 June 2025 | **Accepted:** 28 October 2025

Funding: The authors received no specific funding for this work.

Keywords: clinical decision rules | clinical pharmacy | drug safety | drug-related admissions | medication errors

ABSTRACT

Purpose: Drug-related admissions (DRAs) remain highly prevalent and are linked with increased morbidity and mortality. Rapid and accurate identification is key to both their acute management and secondary prevention. To this end, two clinical decision rules (CDRs) were recently developed to identify the causal adverse drug event (ADE-CDR) or the underlying adverse drug reaction (ADR-CDR). The aim of this study was to assess the diagnostic accuracy of both CDRs in a new patient cohort.

Methods: A prospective, cross-sectional study was conducted at the emergency department (ED) of the University Hospitals Leuven in Belgium. Adult patients were included if admitted to the hospital via the ED. DRA was adjudicated by team consensus and compared to both ADE-CDR and ADR-CDR. Diagnostic accuracy was determined, and multivariable logistic regression was used to explore risk factors for DRAs.

Results: From 1 October 2018 to 26 September 2019, 438 patients were included, 58 (13.2%) of whom incurred a DRA. ADE-CDR had a sensitivity of 89.7% and a specificity of 22.4%. The sensitivity and specificity of ADR-CDR were 46.6% and 60.8%, respectively. Two risk factors were found for DRA: the presence of ≥1 comorbidity (odds ratio (OR) 4.71, 95% confidence interval (CI): 1.42–15.49) and ambulance transport (OR 2.16, 95% CI: 1.21–3.82).

Conclusion: ADE-CDR showed a high sensitivity. In terms of specificity, both CDRs were unable to rule in DRAs in our setting. Conversely, the ADE-CDR showcased the potential to rule out DRAs.

Nadjia Amini and Sabrina De Winter shared first author.

Lorenz Van der Linden and Isabel Spriet shared last author.

Summary

- Drug-related admissions are common in emergency departments.
- Traditional methods to identify drug-related admissions often rely on time-consuming assessments.
- Clinical decision rules have been developed to more efficiently identify potential drug-related hospital admissions developed by Hohl et al. in Canada.
- The first external validation of Hohl's clinical decision rules in a European healthcare setting (Belgium) showed similar results.
- The research highlights the need for developing more refined clinical decision rules, potentially by using a two-step approach (rule-out and rule-in) for further implementation.

1 | Introduction

Drug-related harm is persistently common at the emergency department. Approximately more than one out of nine emergency department admissions among adult inpatients concerns a drug-related admission (DRA) [1–4]. DRAs are linked with higher in- and outpatient health service utilization and are associated with increased mortality [5]. Consequently, it is essential to identify DRAs in ED patients to manage actual drug-related harm and/or to prevent recurrent DRAs [6, 7].

Methods to identify DRAs often rely on an assessment by experienced clinicians or by involving an expert panel. Such methods require information on the patient's history and medication use, rendering them time-consuming and overall inefficient [7, 8]. Accordingly, such traditional methods are not readily applicable to the demanding ED setting. As a result, a more efficient approach is required to identify DRAs in ED patients. To this end, there has been a growing interest in risk prediction tools, such as the application of the clinical decision rule (CDR) methodology [9]. CDR methodology is defined as software-supported patient selection based on patient, drug, and disease-related characteristics, structurally available upon emergency department (ED) admission. In this regard, it is important to differentiate between adverse drug events (ADE) and adverse drug reactions (ADR). An ADE pertains to any harm caused by inappropriate medication use, e.g., non-compliance, prescribing errors, discontinuation of medication or a drug–drug interaction. An ADR is regarded as a component of ADE and is defined as an involuntary response to medication [10].

Hohl et al. from Canada derived two CDRs by recursive partitioning analysis, one targeting ADE (ADE-CDR; sensitivity: 96.7% and specificity: 40.3%) and the other ADR (ADR-CDR; sensitivity: 90.8% and specificity: 59.1%) to identify patients in the ED setting who potentially experienced a DRA [9]. Subsequently, Hohl et al. conducted an external validation study in Canada ($n = 1529$) in which both CDRs demonstrated satisfactory sensitivity (ADE-CDR: 95.7%; ADR-CDR: 91.3%), but limited specificity (ADE-CDR: 22.8%; ADR-CDR: 37.9%) A priori, the authors aimed for acceptable specificity while maintaining sensitivity above 90%, prioritizing the identification of true positive cases to avoid missing critical diagnoses [11].

No study has externally validated these CDRs outside Canada. Therefore, the aim of this study was to evaluate the diagnostic accuracy of both CDRs in identifying DRA among adult ED patients in Belgium. Although both countries offer universal healthcare, structural differences in healthcare delivery and data integration underscore the importance of contextual validation of the CDRs. In addition to assessing the diagnostic performance of the CDRs, it is important to examine patient-related factors that may contribute to DRAs. Identifying these risk factors may help refine clinical decision tools and enhance the early recognition of DRA in emergency settings. Previous studies have linked characteristics such as advanced age, polypharmacy and comorbidities to an increased risk of DRA [2, 9, 12]. However, risk factors for DRA specifically relevant to the ED context remain understudied.

2 | Methods

2.1 | Study Design and Setting

The design concerned a prospective, observational study conducted at the ED of a 1900-bed, tertiary care teaching hospital (University Hospitals Leuven, Leuven, Belgium). This study was approved by the hospital's Ethics Committee (S60638). Written informed consent was required and obtained from each participant.

2.2 | Selection of Participants

From 1 October 2018 to 26 September 2019, ED patients were screened for eligibility during 10 weekdays, from Monday to Friday and from 8:30 a.m. to 5:00 p.m. Patients were recruited by pharmacy graduates. Eligible study participants were adults aged 18 years or older, admitted to the ED and subsequently hospitalized. Consecutive patients were included if they were admitted during weekdays to the ED between 5 p.m. (previous day) and 1 p.m. (day of inclusion). All patients were included only once in this study. Patients were excluded if they (1) received end-of-life care, (2) were transferred to the ED from another ward or hospital, (3) were already admitted to a ward prior to being screened by the pharmacy graduate at the ED, (4) did not understand Dutch, French or English, (5) admitted because of intentional intoxication, or (6) if there were insufficient sources available to verify the medication list. Medication lists were compiled through structured medication reconciliation interviews with patients or legal representatives. This was supported by medication packages, medical records, referral notes, national shared electronic medication records, and, when necessary, direct contact with community pharmacists and general practitioners. As community pharmacy records are not electronically accessible from within hospitals in Belgium, personal communication was often required to ensure accuracy. Additional details on the medication reconciliation process are provided in the Supporting Information (Methods_Supplement 1).

2.3 | Evaluation of DRAs: Assessment, Causality, Preventability, Severity and Typology

DRA assessment was performed by achieving consensus between at least a pharmacy graduate and the emergency physician. First, the pharmacy graduate conducted a standardized medication reconciliation and independently evaluated whether the admission was drug-related, using the tool developed by Thevelin et al. [13]. Second, the pharmacy graduate asked the emergency physician whether they believed the admission was drug-related, based on their clinical judgment. The gold standard was then defined if consensus was reached. Causality of the DRA was determined with the Naranjo algorithm [14]. Preventability was ascertained by applying the algorithm of Schumock et al. [15]. Typology of the DRA was defined according to the Pharmaceutical Care Network Europe Foundation classification [16]. Additional information is available as Supporting Information (see Methods_Supplement 1).

2.4 | Clinical Decision Rules of Hohl

The ADE-CDR and ADR-CDR were applied to each patient as proxies for identifying DRAs. A case was considered an ADE or ADR when a specific (i.e., predefined) combination of criteria was met, rather than all criteria simultaneously. ADE-CDR included the following: (1) presence of at least one comorbidity, or (2) use of antibiotics in the past 7 days, and at least one of the following: a change of medication in the past 28 days, or arrival by ambulance combined with a triage acuity level of 1, 2, or 3 (considered as one combined criterium), or hospital admission in the past month, or history of renal failure or creatinine ≥ 150 mmol/L, or use of three or more medications on prescription. The simpler CDR (ADR-CDR) relied on: (1) presence of one or more comorbidities, or (2) use of antibiotics in the past 7 days, and one of the following: a change of medication in the past 28 days, or 80 years of age or older [9]. Having experienced a DRA according to these CDRs was defined as a dichotomous outcome (yes or no DRA).

2.5 | Outcome Measures

The primary outcome in this study was the following performance measurements for both tested CDRs: sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio (LR+), negative likelihood ratio (LR−) along with a 95% confidence interval (CI) and the alert rate for ADE-CDR and ADR-CDR. Additional outcomes concerned the prevalence of DRA in the ED setting and risk factors associated with experiencing a DRA.

2.6 | Data Collection

Data were collected during patient interviews and extracted from the electronic health records. Patient-related factors included age, gender, language, origin, type of arrival, triage acuity score [17], type and number of comorbidities, Charlson Comorbidity Index [18], chief complaint-related DRA versus drug-related problem incidentally found at the ED, treatment plan, length of hospital stay, and hospital admission in the past month. Medication-related factors were the number of medications, use of antibiotics in the past 7 days, any change in chronic medication use in the past 28 days, and availability of a nationwide shared electronic medication list from the community pharmacist or general practitioner.

2.7 | Sample Size Estimation

The sample size calculation was based on the clinical decision rule having a desired sensitivity of at least 80% with a precision of ±10%. Given a conservative prevalence of 14% for ADEs in prior studies [1, 9], the required sample size was estimated at 440 study subjects.

2.8 | Statistical Analysis

Data were presented as counts (percentage), mean ± standard deviation (SD) or median [interquartile range (IQR)], along with their range as appropriate. To explore risk factors associated with DRA, a logistic regression analysis was used. Patient- and medication-related factors were selected as predictors, based on prior literature. Detailed information is available as Supporting Information (Methods_Supplement 2). Univariable logistic regression analysis was performed, and significant factors ($p < 0.05$) were included in a multivariable logistic regression analysis.

Subsequently, the model was adapted using backward selection with a p-value < 0.05 as the selection criterion, resulting in a final parsimonious regression model. Odds ratios (OR) and adjusted odds ratios (ORa) were presented along with 95% CI. All statistical analyses were performed using Stata, Version 17.0 (StataCorp LLC, TX, USA).

3 | Results

3.1 | Characteristics of the Study Population

In total, 438 unique patients were included in this study (Figure 1). The median age of the participants was 69 years (IQR: 55–79) with almost a quarter (22.8%) older than 80 years. The median number of comorbidities was 2 (IQR: 1–3) and the median number of drugs after medication reconciliation was 7 (IQR: 4–11). The baseline characteristics of the study population are shown in Table 1.

3.2 | Assessment and Characteristics of the DRAs

An immediate consensus on the DRA assessment was reached between the pharmacy graduate and the treating physician in 403/438 (92.0%) patients (Table 2). After reaching consensus on DRA assignment in the full cohort, 58 patients (13.2%, 95% CI: 10.1%–16.4%) were considered to have experienced a DRA, which was decided to be related to the chief complaint of ED admission in 54 patients (12.3%). Of all DRAs, 44.8% were identified as preventable DRAs.

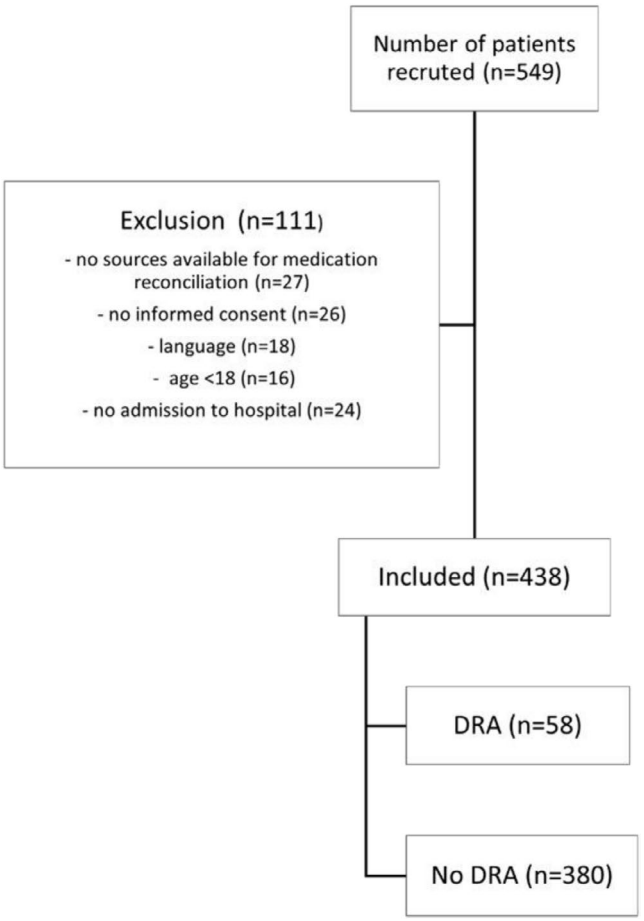

FIGURE 1 | Flowchart of the study population.

One DRA concerned an ADR due to chemotherapy and was classified as having a *definite* causal relationship with the ED admission, whereas 39 DRAs were considered to have a *probable* causal relationship. There was a *possible* causal relationship in 17 cases between the DRA and ED admission. In one case, the causality of the DRA could not be determined since the exact culprit medication was not known.

The median age of patients was 72 years (IQR: 57–81), of whom 25.8% were older than 80 years, and 50% of patients were male. The median number of medications was 8 (IQR: 5–11), and the median length of hospital stay was 6 days (IQR: 3–10). The most common main reasons for admission were fall incidents/fractures (19.0%), dyspnea or orthopnea (15.5%), bleeding (13.8%), and pain (12.0%). The type of DRAs were: (1) ADR (56.9%), (2) non-compliance to the treatment regimen (22.4%), wrong drug/drug–drug interactions (17.2%) or inappropriate dosage (3.4%). The most common medications associated with DRAs were antithrombotic agents (27.6%), antitumor drugs (13.8%), antipsychotics (13.8%), analgesics (8.6%), and diuretics (6.9%). Detailed information of the identified DRAs is shown in Table S1–S3.

3.3 | Diagnostic Accuracy of the CDRs

The ADE-CDR yielded a sensitivity of 89.7% and a specificity of 22.4% to identify a DRA with an alert rate of 79.2%. The

TABLE 1 | Baseline characteristics of the study population.

Characteristic ($n = 438$)	
Age (years), median (IQR)	69 (55–79)
Age > 80 years, number (%)	100 (22.8%)
Gender, number (%)	
Male	240 (54.8%)
Language, number (%)	
Dutch	430 (98.2%)
French	6 (1.4%)
English	2 (0.5%)
Origin, number (%)	
Community-dwelling	422 (96.3%)
Nursing home resident	15 (3.4%)
Other institution	1 (0.2%)
Arrival by, number (%)	
Private transportation	320 (73.1%)
Ambulance	97 (22.0%)
Mobile urgence team	21 (4.8%)
Triage acuity, number (%)	
1	2 (0.5%)
2	137 (31.3%)
3	197 (45.0%)
4	9 (2.1%)
5	1 (0.2%)
Unknown[a]	92 (21.0%)
Allocation referral reason, number (%)	
Emergency medicine	55 (12.6%)
Internal medicine	341 (77.6%)
Surgery	42 (9.6%)
Availability of nationwide shared electronic medication list from the community pharmacist or general practitioner (yes), number (%)	85 (19.4%)
Number of medications (recorded by ED physician), median (IQR)	6 (2–10)
Number of medications (after medication reconciliation), median (IQR)	7 (4–11)
Number of comorbidities, median (IQR)	2 (1–3)
Comorbid conditions, number (%)	
Cardiovascular disorders	200 (45.7%)
Endocrine disorders	102 (28.7%)
Oncology	89 (20.3%)
Gastro-intestinal disorders	72 (16.4%)
Kidney diseases	60 (13.7%)

(Continues)

TABLE 1 | (Continued)

Gynecology	23 (5.2%)
Psychiatry	28 (6.4%)
Neurological disease	41 (9.4%)
Respiratory disease	60 (13.7%)
Musculoskeletal disease	9 (2.0%)
Osteo-articular disease	39 (8.9%)
Urological disease	23 (5.2%)
Hepatological disease	25 (5.7%)
Hematological disease	16 (3.6%)
Dermatological disease	8 (1.7%)
Ear-Nose-Throat disease	4 (0.91%)
Lymphatic system disorders	1 (0.2%)
Hereditary disorders	4 (0.9%)
Microbiological diseases	51 (11.6%)
Eye disorders	21 (4.8%)
Autoimmune diseases	20 (4.6%)
Pain syndrome	14 (3.2%)
Charlson Comorbidity Index, median (IQR)	1 (0–3)

Note: Continuous variables are presented as median (interquartile range); categorical variables are presented as number (percentage).
Abbreviations: ED, emergency department; IQR, interquartile range.
[a]Missing data since no ED nurses were available to code the triage acuity during night time.

TABLE 2 | Assessment of DRAs by physician and pharmacy graduate.

		Physician rating			
		DRA	No DRA	Uncertain	Total
Pharmacist rating	DRA	35	1	6	42
	No DRA	0	368	5	373
	Uncertain	0	2	21	23
	Total	35	371	32	438

Note: Cases with agreement in ratings (DRA/DRA or no DRA/no DRA) were considered final. All cases without consensus between physician and pharmacy graduate ratings were adjudicated during a multidisciplinary session.

ADR-CDR showed a sensitivity of 46.6% and a specificity of 60.8%, with an alert rate of 40.2%. Detailed information and additional evaluation measurements are displayed in Tables 3 and 4.

3.4 | Factors Associated With DRAs

In the univariable analysis, the following variables were significantly associated with DRA: (a) having at least one comorbidity, (b) number of medications, and (c) type of arrival at ED admission. More details are presented in Table S4. The following variables remained statistically significant in the multivariable analysis: (a) having at least one comorbidity (ORa = 4.71, 95% CI: 1.42–15.49) and (b) ambulance transport (ORa = 2.16, 95% CI: 1.21–3.82).

TABLE 3 | The clinical decision rules of Hohl in comparison with the "golden standard".

		Golden standard[a]		
		ADE	No ADE	Total
CDR-ADE	ADE	52	295	347
	No ADE	6	85	91
	Total	58	380	438
CDR-ADR	ADR	27	149	176
	No ADR	31	231	262
	Total	58	380	438

Abbreviations: ADE, adverse drug event; ADR, adverse drug reaction; CDR, clinical decision rule.
[a]Golden standard: consensus between physician and pharmacist in the assessment of drug-related admissions (DRA).

4 | Discussion

4.1 | Prevalence, Typology, and Risk Factors

In this prospective study, a DRA at the ED followed by a subsequent hospitalization was identified in 13.2% of the patients, and in 12.3% this was related to the chief complaint upon admission. Similar findings have been observed previously [1, 3, 4, 8, 9]. In our study, patients with a DRA were typically older and usually complained of dyspnea, bleeding, pain and falls and were mostly taking antithrombotics, antitumor drugs, antipsychotics, analgesics or diuretics. Similar characteristics have been described in the literature, but reported prevalence rates vary, albeit limited [2, 8, 9, 12]. Moreover, we found that almost half of the DRAs were considered preventable, with non-adherence being the largest amenable culprit. Similar results were retrieved from the Hospital Admissions Related to Medication (HARM) study in the Netherlands, where nearly an exact proportion, i.e., 46.6%, was deemed to be preventable [2]. On the other hand, a much higher number of 73.9% of the DRAs in the study by Hohl et al. was determined to be preventable due to non-compliance with the medications or drug–drug interactions.

In our study, risk factors for having a DRA are the presence of at least one comorbidity and ambulance transport. These risk factors are in concordance with previous studies including Hohl's study [2, 9, 12]. Other risk factors associated with DRAs from the literature were higher age, a high number of medications, non-adherence to the medication regimen, impaired cognition, multimorbidity, care dependency, and impaired renal function [2, 9, 12]. In addition, in a recent Norwegian analysis, medical referral and "hemorrhage or anemia" and "dizziness, syncope, or tendency to fall" as reasons for referral were other risk factors for DRA [8].

4.2 | Evaluation of the CDRs

To our knowledge, this study was the first to externally validate both CDRs in a new cohort outside Canada. ADE-CDR correctly identified 52 of the 58 DRAs (sensitivity 89.7%) and ADR-CDR correctly identified 27 of the 58 DRAs (sensitivity 46.6%). The sensitivity was largely comparable to Hohl's validation study

TABLE 4 | Evaluation measurements of the clinical decision rules along with 95% confidence interval.

Evaluation measurements	ADE-CDR (present study)	ADE-CDR (Hohl et al.)[a]	ADR-CDR (present study)	ADR-CDR (Hohl et al.)[a]
Sensitivity	89.7% (86.8%–92.5%)	95.7% (91.6%–98.1%)	46.6% (41.9%–51.2%)	91.3% (86.3%–95.0%)
Specificity	22.4% (18.5%–26.3%)	22.8% (20.6%–25.2%)	60.8% (56.2%–65.4%)	37.9% (35.3%–40.6%)
PPV	15.0% (11.6%–18.3%)	14.5% (14.0%–15.0%)	15.3% (12.0%–18.7%)	16.8% (15.9%–17.6%)
NPV	93.4% (91.1%–95.7%)	97.5% (95.1%–98.9%)	88.2% (85.1%–91.2%)	97.0% (95.2%–98.1%)
LR+	1.16 (1.04–1.28)	1.24 (1.19–1.29)	1.19 (0.88–1.61)	1.47 (1.38–1.56)
LR−	0.46 (0.21–1.01)	0.19 (0.10–0.38)	0.88 (0.68–1.13)	0.23 (0.14–0.37)

Abbreviations: LR−, negative likelihood ratio; LR+, positive likelihood ratio; NPV, negative predictive value; PPV, positive predictive value.
[a]Results from the prospective validation study by Hohl et al. [11].

(95.7%) [11]. In contrast, the specificity and LR+ of the ADE-CDR were low, indicating a large number of false positive cases. A possible reason for the many false positives is that the ADE-CDR already considered an event to be a DRA if the patient had at least one co-morbidity or took at least three medications. Importantly, in our study, the population was older (median age of 69 years) and the median number of medications was 7. Additionally, 75.9% of our whole study population took more than three medications. Therefore, we believe that the current cutoff of "the use of at least three medications" is much too low to reliably identify patients with a DRA. The use of five or more medications (polypharmacy) and the use of 10 or more medications (excessive polypharmacy) has been associated with an increased risk of unplanned and drug-related hospitalizations [19, 20]. A higher threshold may therefore be more appropriate for identifying at-risk patients in our population. Moreover, the mean number of co-morbidities in patients with a drug-related problem was two. These two factors were both common in our sample (80.04% of the total cohort). One key difference between our study and the studies by Hohl et al. is the hospitalization rate of the study population. In our study, all patients were hospitalized, whereas in Hohl's studies, only 15%–18% of ED patients were admitted [9, 11]. This difference likely reflects a sicker population in our study, with a greater comorbidity burden and medication complexity. While hospitalized patients may have a higher incidence of DRAs, the complexity of their clinical presentations may make it harder for simple CDRs to accurately distinguish DRAs. In contrast, in a younger and lower-risk ED population, with fewer confounding factors (e.g., multimorbidity, frailty), CDRs might perform more accurately and efficiently in identifying DRAs. Our older patients might have influenced the generalizability of the results. This is a limitation that should be acknowledged. Nevertheless, it is important to note that the LR+ as reported by Hohl's validation study was also low, which indicates that these CDRs are not helpful aids to rule in patients with a potential DRA in a resource-strained environment such as the ED. On the other hand, the LR− of the ADE-CDR was 0.46 (95% CI 0.21–1.01) in our study and was even 0.19 (95% CI 0.10–0.38) in Hohl's validation study. In literature, a LR− of 0.1 is generally accepted as a level for ruling out a diagnosis and a LR− of 0.5 is acknowledged as the upper limit of a clinically meaningful level for ruling out [21, 22].

To summarize, the low diagnostic accuracy of both CDRs would cause and/or worsen alert fatigue, therefore rendering them unsuitable for implementation in a demanding ED environment. Nevertheless, we do suggest that ADE-CDR might be used as a first step to *rule out* admissions that are unlikely to be drug-related. In a second step, the selected admissions from step 1 can then be assessed more thoroughly by experienced clinicians and clinical pharmacists, preferably collaborating as a dyad as is currently the case at our ED. A two-step approach may be more efficient to adjudicate potential DRAs. Concerning ADR-CDR, both sensitivity and specificity are too low to be useful in our setting.

4.3 | Strengths

One of the major strengths of our study was that we formally trained pharmacy graduates for comprehensive medication reconciliation and standardized screening of DRAs using a validated instrument. Furthermore, the assessment of the DRA was performed prospectively by a multidisciplinary team comprising an ED physician and a clinical pharmacist. Moreover, immediate consensus was reached in 92% of the cases, suggesting that expert consensus might be already sufficient without the need for an explicit prediction tool. However, the assessment of a DRA by experts is time-consuming and frequently not feasible in a busy ED setting, which therefore supports the need for a prediction tool. Lastly, our sample size was in line with the a priori sample size calculation and similar to the prevalence rate of previous studies focusing on DRAs.

5 | Limitations

There are some limitations in the study that need to be taken into account. First, increased awareness of the subject of DRAs may have raised the attention of the physicians in the ED to DRAs and may have caused a potential Hawthorne effect. In addition, pharmacy graduates could also be influenced by ED physicians who were always the first to take the anamnesis and who already added notes about a possible DRA to the patient's file.

Second, this was a study evaluating DRAs for only 47 days and we were unable to enroll patients on weekends and nighttime, which might have led to a possible selection bias. In addition, we did not recruit patients in the winter or spring, which means

that certain side effects, for example associated with antibiotics for respiratory infections or antihistamines for hay fever, could have remained underreported. However, we prospectively included a population with a broad range of medication use and/or medical conditions which increased the generalization to a broader population. Lastly, since our sample size calculation was based on determining the prevalence rate of DRAs and calculating the diagnostic accuracy of the CDRs of Hohl et al. (i.e., our primary outcome measurement), this study might have been underpowered to detect certain risk factors associated with DRA, such as age, polypharmacy or the referral allocation.

5.1 | Further Perspectives

Results from our study indicate that the CDRs of Hohl are not ready to be implemented in daily clinical practice. Future research is now needed to evaluate whether ADE-CDR is appropriate to rule out DRAs and whether we should then build a more specific CDR with additional risk factors, such as excessive polypharmacy, cognitive dysfunction, reason for referral or non-compliance, as a rule-in. The applicability of artificial intelligence to develop high-performance tools in real time needs to be further explored as well [23].

6 | Conclusion

The two CDRs of Hohl et al. are not yet ready to be implemented in our center. Based on the low negative likelihood ratio, the ADE-CDR has the potential to rule out potential DRAs, while the rest of the cases still should be evaluated in an interdisciplinary collaboration with clinicians and clinical pharmacists. Future research should focus on testing this method while also developing a more specific CDR to operate as a rule-in in order to adjudicate potential DRAs more efficiently.

6.1 | Plain Language Summary

Many people are admitted to the hospital because of problems related to the medicines they are taking. These problems can be serious and even life-threatening, so it is important to spot them quickly. In this study, we tested two tools that help doctors decide whether a hospital admission was caused by a harmful effect of a drug. The study was carried out in the emergency department of a hospital in Belgium and included 438 adult patients who were admitted between October 2018 and September 2019. Doctors and clinical pharmacists carefully reviewed each case and compared their findings with the results from the two tools. One tool (ADE-CDR) correctly identified nearly 90% of drug-related cases but also flagged many cases that were not drug-related. The other tool (ADR-CDR) missed more drug-related cases but was better at avoiding false alarms. We also found that people with other existing health conditions and those who arrived by ambulance were more likely to be admitted due to drug-related problems. These findings suggest that the ADE-CDR tool may help doctors quickly rule out drug-related causes and focus on other possible reasons for illness, although improvements are needed to reduce unnecessary alerts.

Acknowledgments

The authors wish to thank all the master students of Pharmaceutical Care (Lies Braeken, Charlotte Lauweryns, Heleen Reumers, Fien Loosveldt, Julie Veys, Ali Zeyrek, Hannah De Baere, and Tess Horemans) for their data collection and data entry.

Ethics Statement

This study was approved by the hospital's Ethics Committee (S60638).

Consent

Written informed consent was required and obtained from each participant.

Conflicts of Interest

The authors declare no conflicts of interest.

References

1. P. J. Zed, R. B. Abu-Laban, R. M. Balen, et al., "Incidence, Severity and Preventability of Medication-Related Visits to the Emergency Department: A Prospective Study," *CMAJ* 178 (2008): 1563–1569.

2. A. J. Leendertse, A. C. Egberts, L. J. Stoker, P. M. van den Bemt, and HARM Study Group, "Frequency of and Risk Factors for Preventable Medication-Related Hospital Admissions in The Netherlands," *Archives of Internal Medicine* 168 (2008): 1890–1896.

3. D. S. Budnitz, N. Shehab, M. C. Lovegrove, A. I. Geller, J. N. Lind, and D. A. Pollock, "US Emergency Department Visits Attributed to Medication Harms, 2017-2019," *JAMA* 326 (2021): 1299–1309.

4. N. El Morabet, E. B. Uitvlugt, B. J. F. van den Bemt, P. Bemt, M. J. A. Janssen, and F. Karapinar-Carkit, "Prevalence and Preventability of Drug-Related Hospital Readmissions: A Systematic Review," *Journal of the American Geriatrics Society* 66 (2018): 602–608.

5. C. M. Hohl, B. Nosyk, L. Kuramoto, et al., "Outcomes of Emergency Department Patients Presenting With Adverse Drug Events," *Annals of Emergency Medicine* 58 (2011): 270–9.e4.

6. T. G. H. Kempen, A. N. Hedman, N. Hadziosmanovic, et al., "Risk Factors for and Preventability of Drug-Related Hospital Revisits in Older Patients: A Post-Hoc Analysis of a Randomized Clinical Trial," *British Journal of Clinical Pharmacology* 89 (2023): 1575–1587.

7. C. M. Hohl, P. J. Zed, J. R. Brubacher, R. B. Abu-Laban, P. S. Loewen, and R. A. Purssell, "Do Emergency Physicians Attribute Drug-Related Emergency Department Visits to Medication-Related Problems?," *Annals of Emergency Medicine* 55 (2010): 493–502.e4.

8. L. D. Nymoen, M. Bjork, T. E. Flatebo, et al., "Drug-Related Emergency Department Visits: Prevalence and Risk Factors," *Internal and Emergency Medicine* 17 (2022): 1453–1462.

9. C. M. Hohl, E. Yu, G. S. Hunte, et al., "Clinical Decision Rules to Improve the Detection of Adverse Drug Events in Emergency Department Patients," *Academic Emergency Medicine* 19 (2012): 640–649.

10. J. R. Nebeker, P. Barach, and M. H. Samore, "Clarifying Adverse Drug Events: A Clinician's Guide to Terminology, Documentation, and Reporting," *Annals of Internal Medicine* 140 (2004): 795–801.

11. C. M. Hohl, K. Badke, A. Zhao, et al., "Prospective Validation of Clinical Criteria to Identify Emergency Department Patients at High Risk for Adverse Drug Events," *Academic Emergency Medicine* 25 (2018): 1015–1026.

12. K. Boockvar, E. Fishman, C. K. Kyriacou, A. Monias, S. Gavi, and T. Cortes, "Adverse Events due to Discontinuations in Drug Use and Dose

Changes in Patients Transferred Between Acute and Long-Term Care Facilities," *Archives of Internal Medicine* 164 (2004): 545–550.

13. S. Thevelin, A. Spinewine, J. B. Beuscart, et al., "Development of a Standardized Chart Review Method to Identify Drug-Related Hospital Admissions in Older People," *British Journal of Clinical Pharmacology* 84 (2018): 2600–2614.

14. C. A. Naranjo, U. Busto, E. M. Sellers, et al., "A Method for Estimating the Probability of Adverse Drug Reactions," *Clinical Pharmacology and Therapeutics* 30 (1981): 239–245.

15. G. T. Schumock and J. P. Thornton, "Focusing on the Preventability of Adverse Drug Reactions," *Hospital Pharmacy* 27 (1992): 538.

16. PCNE, The PCNE Classification V 8.03, 2019, https://www.pcne.org/upload/files/318_PCNE_classification_V8-03.pdf.

17. J. Bergs, S. Verelst, J. B. Gillet, and D. Vandijck, "Evaluating Implementation of the Emergency Severity Index in a Belgian Hospital," *Journal of Emergency Nursing* 40 (2014): 592–597.

18. M. E. Charlson, P. Pompei, K. L. Ales, and C. R. MacKenzie, "A New Method of Classifying Prognostic Comorbidity in Longitudinal Studies: Development and Validation," *Journal of Chronic Diseases* 40 (1987): 373–383.

19. J. Hias, L. Hellemans, S. Nuyts, et al., "Predictors for Unplanned Hospital Admissions in Community Dwelling Adults: A Dynamic Cohort Study," *Research in Social & Administrative Pharmacy* 19 (2023): 1432–1439.

20. B. Mertens, J. Hias, L. Hellemans, et al., "Drug-Related Hospital Admissions in Older Adults: Comparison of the Naranjo Algorithm and an Adjusted Version of the Kramer Algorithm," *European Geriatric Medicine* 13 (2022): 567–577.

21. D. A. Grimes and K. F. Schulz, "Refining Clinical Diagnosis With Likelihood Ratios," *Lancet* 365 (2005): 1500–1505.

22. P. Peng and A. Coyle, "Likelihood Ratios for the Emergency Physician," *Academic Emergency Medicine* 25 (2018): 958–965.

23. K. Ouchi, C. Lindvall, P. R. Chai, and E. W. Boyer, "Machine Learning to Predict, Detect, and Intervene Older Adults Vulnerable for Adverse Drug Events in the Emergency Department," *Journal of Medical Toxicology* 14 (2018): 248–252.

Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Supplementary 1. Supplementary 2. Table S1:** pds70265-sup-0003-TableS1.pdf. **Table S2:** pds70265-sup-0004-TableS2.pdf. **Table S3:** pds70265-sup-0005-TableS3.pdf. **Table S4:** pds70265-sup-0006-TableS4.pdf.