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Clinical parameters that predict the need for medium or intensive care admission in intentional drug overdose patients: A retrospective cohort study

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ABSTRACT

Introduction: Many patients with intentional drug overdose (IDO) are admitted to a medium (MC) or intensive care unit (IC) without ever requiring MC/IC related interventions. The objective of this study was to develop a decision tool, using parameters readily available in the emergency room (ER) for patients with an IDO, to identify patients requiring admission to a monitoring unit.
Methods: Retrospective cohort study among cases of IDO with drugs having potentially acute effects on neurological, circulatory or ventilatory function, admitted to the MC/IC unit between 2007 and 2013. A decision tool was developed, using 6 criteria, representing intubation, breathing, oxygenation, cardiac conduction, blood pressure, and consciousness. Cases were labeled as 'high acuity' if one or more criteria were present.
Results: Among 255 cases of IDO that met the inclusion criteria, 197 were identified as "high acuity". Only 70 of 255 cases underwent one or more MC/IC related interventions, of which 67 were identified as 'high acuity by the decision tool (sensitivity 95.7%).
Conclusion: In a population of patients with intentional drug overdose with agents having potentially acute effect on vital functions, 95.7% of MC/IC interventions could be predicted by clinical assessment, supplemented with electrocardiogram and blood gas analysis, in the ER.

1. Introduction

Patients with intentional drug overdose (IDO) are often admitted to a monitoring ward, even if they appear stable in the emergency room (ER) and in no imminent need of interventions that are usually provided in a medium care (MC) or intensive care (IC) environment [1]. This practice is based on the assumption that risk of deterioration cannot reliably be predicted by the clinical course in the first few hours. As a result, many low-acuity patients are admitted to an MC/IC setting without requiring specific interventions.

Although the in-hospital mortality of patients admitted to care facilities with IDO is low (2.1% in a recent Dutch survey) [2], some patients do develop serious complications. Also, absorption of the agents involved may be delayed, resulting in late manifestation of symptoms. A complicating factor in the stratification of patients presenting after an act of self-intoxication is that a proper history of the nature and amount of drugs ingested is often lacking or unreliable [3]. This uncertainty may lead to an overestimation of the likelihood of late events after drug overdose.

As unnecessary MC/IC admissions may harm patients and generate high medical costs, it is important to recognize at an early stage which patients will benefit from monitoring facilities.

We hypothesized that the need for MC/IC admission of patients with drug overdose can reliably be predicted by clinical observations made while the patient is in the ER. This prediction must be highly sensitive to identify all patients that require MC/IC related interventions.

The aim of the present study was to develop a decision tool, using readily available parameters in the ER for patients with an IDO, to identify high-acuity patients for admission to a monitoring unit.

Abbreviations: CVVH, Continuous venovenous haemofiltration; ECG, Electrocardiogram; ER, Emergency room; GCS, Glasgow Coma Score; IC, Intensive care; IDO, Intentional drug overdose; MC, Medium care; NSAID, Non-steroidal anti-inflammatory drug; PO_2, Partial pressure of oxygen in blood; QRS, Complex of Q-, R- and S-waves in the electrocardiogram; QTc, QT-time on electrocardiogram corrected for heart rate; RF, Respiratory frequency; SBP, Systolic blood pressure; SpO_2, Peripheral oxygen saturation; SSRI, Selective serotonin reuptake inhibitor; TCA, Tricyclic antidepressant.

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2. Material and methods

2.1. Population

All admissions with drug overdose to the combined MC/IC unit of the Deventer Hospital, a teaching hospital in the Netherlands, between January 1, 2007, and December 31, 2013, were investigated. Because of multiple admissions, individual patients could be included more than once. Not included were intoxications with pesticides, insecticides or other chemicals. Intoxications with recreational drugs only (eg, ethanol), intoxications with drugs with no potentially acute effects on neurologic, cardiovascular, or ventilator function (eg, paracetamol), and transfers from other hospitals were excluded.

2.2. Data retrieval

An anonymized database containing eligible cases was built using Microsoft Access. The following data were extracted from ER records, laboratory results and MC/IC unit charts: gender, age, serum drug levels, slow release preparation, ER interventions, and intensive care unit (ICU) interventions. Estimated time of intake, drug groups, drug names, estimated drug doses, were based on patient's history, or on circumstantial evidence such as medicine packages found on the scene. Furthermore, vital parameters present at the ER were registered including temperature, first, lowest and highest measured respiratory rate, lowest measured oxygen saturation, highest F_{IO_2} administered, arterial blood sample, first, lowest and highest heart rate recorded, first, lowest and highest measured systolic and diastolic blood pressure, abnormalities on electrocardiogram, QRS duration, corrected QT interval (QTc), Glasgow Coma Scale and the presence or absence of seizures. When electrocardiogram (ECG) and blood gas results were unavailable, they were assumed to be normal. Serum drug levels were not measured routinely, but only if it was thought they would influence the treatment. ER and ICU admission and discharge times, and discharge destination after MC/IC admission were obtained from hospital administrative data.

2.3. Predictors

We designed a decision tool based on a small number of Boolean (true or false) type criteria. The structure of this tool is such that one positive criterion predicts high acuity, resulting in admission to a monitored ward. The algorithm only predicts low acuity, indicating outpatient care or admission to a general medicine bed or psychiatric unit as the appropriate level of care, if all criteria are negative. By design, such a decision algorithm will results in a cumulative sensitivity much higher than the sensitivity of the individual predictors, at the expense of specificity. For the purpose of identifying IDO patients at risk, high test sensitivity was desired and decreased specificity was considered acceptable. In addition, a decision model with a 'yes-or-no' design is easy to use in daily practice. The design of our decision tool resembled triage algorithms for IDO patients published earlier [1,4]. The choice for this particular design precluded the use of logistic regression to build a formal prediction model in which the weighed sum of various parameters is calculated.

To build the decision tool, parameters were first selected on the basis of clinical suitability, which in this case meant that the parameter should be easily measurable in the emergency room. Cut-off values for these parameters were determined with the use of receiver operating curves, but were also chosen so that they matched national and international MC/IC admission guidelines [5,6], published trigger criteria for rapid response teams [7], normal ECG conduction times, as well as our own unit's admission criteria.

Parameters were then eliminated in a stepwise fashion from the decision tool until sensitivity started to decrease. Criteria were also selected to reflect all vital functions. This resulted in the selection of 6 criteria displayed in Table 1, representing intubation, breathing, oxygenation, cardiac conduction, blood pressure, and consciousness. Prolonged QTc was defined as ≥450 ms in males and ≥460 ms in females.

2.4. Outcome measure: MC/IC intervention

All interventions that require frequent or continuous monitoring of consciousness, ECG, SpO_2, or blood pressure were considered MC/IC related. The list consisted of tracheal intubation, invasive or non-invasive mechanical ventilation, fluid resuscitation (a fluid bolus ≥1000 ml, or a fluid bolus ≥500 ml explicitly administered for hypotension), intravenous administration of vasoactive agents, antiarrhythmics, sedatives, magnesium, calcium, atropine, naloxone or flumazenil, treatment of convulsions, defibrillation, hemofiltration or dialysis.

2.5. Statistical analysis

For the prediction of MC/IC interventions, we considered all predictors in Table 1 to be equally important. Cases were labeled as "high-acuity" if they scored positive on one or more of the criteria in Table 1. "Low-acuity" was defined as being negative on all 6 clinical criteria. The MC/IC interventions were dichotomized (intervention applied yes/no).

General patient characteristics, ER interventions, prevalence of ingested substances and MC/IC interventions were compared between high-acuity and low-acuity cases using Chi-square and Fisher's Exact Tests in case of categorical variables and Student *t* test for continuous variables (after normality of the data was confirmed). Using univariate logistic regression analysis, the relationship between each of the individual predictors as well as the dichotomous variable high/low acuity and outcome measure (IC intervention required yes/no) was investigated. Sensitivity and specificity of each individual predictor, as well as for the combination of predictors, were calculated using crosstabs. For all analyses, IBM SPSS statistical software version 22 was used. $P < .05$ was considered statistically significant.

3. Results

During this retrospective 7-year evaluation period, 363 MC/IC unit admissions with drug overdose were registered. After application of the exclusion criteria, 255 cases remained for analysis (Fig. 1). The median time spent in the ER was 2:15 h (interquartile range 1:27 to 3:15 h); 41% of patients received some form of emergency treatment aimed at decreasing the effect of the intoxicants. This treatment was not provided when the estimated time interval between intake and presentation was too long to expect any benefit. The median time spent in the MC/IC unit was 18:02 h (interquartile range, 13:20 to 31:29 h) h. Mortality in our study cohort was 1 (0.4%) of 255 cases. One patient died due to cardiac arrest before arrival to the ER, after an overdose with antipsychotics. This patient was admitted to the IC unit while being resuscitated, and died when chest compressions were stopped.

Of the 255 eligible cases, 197 (77%) were defined as 'high-acuity', meaning one or more of the 6 defined predictors (Table 1) were present. The patient characteristics are presented in Table 2, stratified according to acuity (high vs. low). A comparison between patients defined as high-acuity and patients defined as low-acuity showed that low-acuity patients were significantly younger and were more likely to be treated with activated charcoal or intestinal lavage on the ER as compared to high-acuity patients. In addition, only high acuity patients received antidotes in the ER.

Benzodiazepines were involved in 63.9% of all IDO cases (Table 2). Also common were ethanol, antidepressants, antipsychotics and analgesics (ethanol and paracetamol were common co-ingestants, overdose with ethanol or paracetamol alone was excluded). Tricyclic antidepressants were involved in 13.3% of cases, and 11.4% of cases consisted of slow-release preparations. None of the intoxications with

Table 1
Proposed decision tool

Patient considered 'high-acuity' if one or more of these criteria are positive			
Intubation			
Abnormal oxygenation	SpO_2 <90%	or	PO_2 <8.0 kPa
Abnormal breathing	RF <8/min	or	RF >30/min
Abnormal cardiac conduction	QRS >0.12 s	or	QTc prolonged
Abnormal blood pressure	SBP <90 mmHg	or	SBP >200 mmHg
Abnormal consciousness	GCS <14	or	Agitation

slow release preparations required any interventions. No significant differences in ingested substances between high and low acuity patients were observed. Serum drug levels were measured in 84 cases, and were elevated in 72.6%. Nontoxic (ie, normal or therapeutic) drug levels were found in 8/58 (13.8%) low-acuity cases and in 15 (7.6%) of 197 cases labeled as 'high acuity'.

One or more MC/IC related interventions were required in 70 (27.4%) of 255 cases. Intravenous sedation was the most common intervention, followed by tracheal intubation, fluid resuscitation, continuous administration of antagonists, and continuous intravenous administration of vasopressors. All these interventions were done significantly more often in patients identified as high acuity by the decision tool.

Table 3 shows the Odd's ratios, sensitivity and specificity of the individual criteria used to identify acuity as high or low. Abnormal oxygenation, blood pressure, consciousness and agitation were significantly associated with MC/IC interventions, with odds ratios ranging between 2.47 and 5.94. The parameter with the highest sensitivity was abnormal cardiac conduction (47.1%). Tracheal intubation had a specificity of 100%, due to the fact that all patients intubated in the ER subsequently received artificial ventilation.

When the 6 individual criteria were combined into one acuity score ('high' when one or more individual predictors are present), the odds ratio for IC interventions was 9.45 (2.84-31.33). Sensitivity of this combined variable (our proposed "decision tool") was 95.7%, specificity was 29.7% (Table 3). In three cases, interventions were carried out after admission to the MC/IC unit in patients who would have been predicted as low-acuity. These patients are described in more detail in Table 4.

4. Discussion

The aim of this study was to investigate whether the need for MC/IC admission of patients with drug overdose could be predicted by clinical observations made during the first several hours. The results showed that when a patient is not intubated in the ER, and abnormalities in oxygenation, breathing, cardiac conduction, blood pressure, and consciousness are absent, the need for MC/IC related interventions later on can be excluded with a high degree of safety (sensitivity 95.7%). We therefore concluded that in a retrospective cohort of patients with intentional drug overdose with agents having potentially acute effects on vital functions, MC/IC interventions could have been reliably predicted by clinical assessment, supplemented with ECG and blood gas analysis, in the ER.

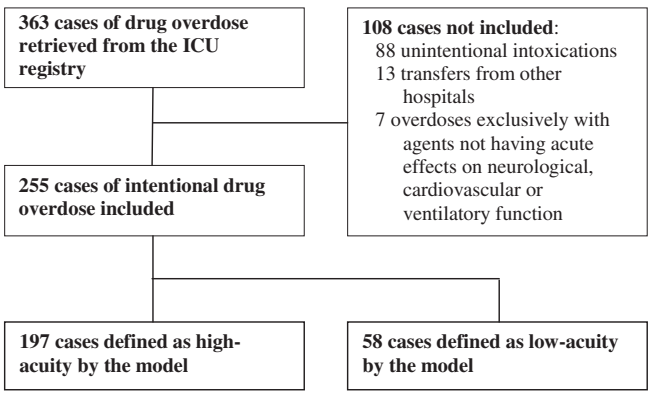

Fig. 1. Flow chart of the inclusion of patients.

Before the study, we decided that failure to recognize a patient who could have benefited from admission to a monitoring ward would be considered more harmful than unnecessary admission. The decision tool that we developed, that is, a combination of 6 easily observable clinical criteria, would have identified over 95% of MC/IC interventions. In three patients, the need for MC/IC admission was not predicted by the decision tool. However, closer analysis of these cases revealed that two of them (patients B and C in Table 4) were not intoxicated at presentation. Both of these patients received intravenous sedatives in order to keep them in bed comfortably while being continuously monitored. In fact, these patients suffered from side effects of an unnecessary MC/IC admission, rather than from drug overdose. Without these two cases the sensitivity of the decision tool would increase from 95.7% to 98.5%.

Partly as a result of the high sensitivity, the specificity of our proposed decision tool was low (29.7%), indicating that the majority of patients predicted as high-acuity did not require any interventions, and their MC/IC admission could therefore be considered unnecessary. However, this tool was tested in patients that were already admitted to the MC/IC unit, constituting a selected population. If the decision tool were to be applied to all cases presenting to the ER, a population in which the incidence of invasive interventions is much lower, specificity would be likely to increase. Future research should be aimed at testing the 6 clinical criteria and the composite 'acuity score' in a prospective design. Despite specificity being low, the use of these criteria during the study period would have eliminated 55 (>20%) of 255 MC/IC admissions for IDO in our hospital.

The notion that severity of symptoms at presentation might predict the course in patients with deliberate intoxication is not new. The Poisoning Severity Score, which combines symptoms from 12 organ systems into one severity grading [8] has been shown to predict later deterioration in mixed poisoning cases [9], and fatal outcome in pesticide poisoning [10]. However, the inclusion of non-vital functions in the score would reduce its value in predicting the need for MC/IC admission. APACHE II, a severity score specifically designed for the IC population, has been shown to predict mortality in severe poisoning [11], but can only be completed after 24 hours of observation. To our knowledge, these scales have not been evaluated for their discriminative value in predicting the need for life-saving interventions at the time of presentation. Moreover, these scales require the use of a table or a spread-sheet program to calculate the score, and are therefore not readily applicable.

Seemingly, the only study that investigated the value of clinical criteria in the ER to predict MC/IC interventions was published by Brett in 1987 [1]. In that study, a decision model was developed using clinical parameters slightly different from ours, but likewise easy to assess in the ER. Brett's model had a sensitivity of 100% in their original study, but was never validated by others in 27 years. Brett defined only 5 strongly invasive interventions as ICU related. Secondary analysis showed that applying the model of Brett to our data resulted in 71% sensitivity and 65% specificity (data not shown). Differences in the definition of what should be considered a MC/IC related intervention prohibited a direct comparison with our tool. The main conclusion of their study, however, was that it is feasible and useful to predict the

Table 2
Patient characteristics, ingested substances and MC/IC interventions

Cases (n)	High acuity 197	Low acuity 58	Total population 255	*P*: low vs high acuity
Age in years (mean, SD, range)	40 (13; 16–74)	35 (12; 15–60)	39 (13; 15–74)	.009
Male Gender (n (%))	75 (38.1)	17 (29.3)	92 (36.1)	.22
Ingested substances (n (%))				
Ethanol	88 (44.7)	19(32.8)	107 (42.0)	.11
Benzodiazepines	128 (65.0)	35(60.0)	163 (63.9)	.52
Antidepressants				
SSRIs	44 (22.3)	16(27.6)	60 (23.5)	.41
TCAs	28 (14.2)	6 (10.3)	34 (13.3)	.45
Other antidepressants	13 (6.6)	5 (8.6)	18 (7.1)	.57
Antipsychotics	79 (40.1)	20(34.5)	99 (38.8)	.44
Analgesics				
Paracetamol	32 (16.5)	9 (15.5)	41 (16.1)	.90
NSAIDs	20 (10.2)	6 (10.3)	26 (10.2)	.97
Opioids	28 (14.2)	3 (5.2)	31 (12.2)	.06
Phenothiazines	20 (10.2)	4 (6.9)	24 (9.4)	.46
Antihypertensives	22 (11.2)	5 (8.6)	27 (10.6)	.58
Stimulants	17 (8.6)	6 (10.3)	23 (9.0)	.69
Antiepileptics	16 (8.1)	2 (3.4)	18 (7.1)	.38
Antihistamines	6 (3.0)	1 (1.7)	7 (2.7)	1.00
Benzodiazepine likes	5 (2.5)	0 (0.0)	5 (2.0)	.60
Other	25 (12.7)	12 (20.7)	37 (14.5)	.13
Unknown	5 (2.5)	1 (1.7)	6 (2.4)	1.00
Slow release preparations	20 (10.2)	9 (15.5)	29 (11.4)	.26
Interventions performed in the ER (n (%))				
Activated charcoal	71 (36.0)	34 (58.6)	105 (41.2)	.002
Acetylcysteine	20 (10.2)	5 (8.6)	25 (9.8)	.73
Antidotes	21(10.7)	0 (0)	21 (8.2)	.005
Gastric lavage	14 (7.1)	3 (5.2)	17 (6.7)	.77
Intestinal lavage	2 (1.0)	4 (6.9)	6 (2.4)	.03
MC/IC Intervention (n (%))				
Intravenous sedation	42 (21.3)	2 (3.4)	44 (17.3)	.002
Intubation and mechanical breathing	30 (11.8)	0 (0.0)	30 (11.8)	.002
Fluid resuscitation	23 (11.7)	1 (1.7)	24 (9.4)	.02
Continuous administration of antagonists	14 (5.5)	0 (0.0)	14 (5.5)	.04
Intravenous administration of vasopressive agents	14 (5.5)	0 (0.0)	14 (5.5)	.04
Intravenous administration of magnesium	5 (2.0)	0 (0.0)	5 (2.0)	.59
Intravenous administration of calcium	3 (1.2)	0 (0.0)	3 (1.2)	1.00
Intravenous administration of atropine	2 (0.8)	0 (0.0)	2 (0.8)	1.00
Intravenous administration of antiarrhythmics	1 (0.4)	0 (0.0)	1 (0.4)	1.00
Treatment of convulsions	1 (0.4)	0 (0.0)	1 (0.4)	1.00
CVVH	0 (0.0)	0 (0.0)	0 (0.0)	-
Defibrillation	0 (0.0)	0 (0.0)	0 (0.0)	-

clinical course of patients with IDO by criteria present in the ER, which is in accordance with our findings.

The criteria that make up our decision tool are very similar to the criteria used as early warning signs propagated in medical emergency team programs [7], and to the standard cut-off values used to identify ECG abnormalities. Moreover, these criteria resemble the current admission rules in our combined MC/IC ward. In fact, our data suggest that it would be reasonable to apply routine clinical admission criteria to patients with IDO who have stayed in the ER for 2 to 3 hours. If the intoxication is associated with any disturbance in vital signs, we would be inclined to admit that patient for monitored observation. If not, admission to a general ward (e.g. for preventive treatment in case of paracetamol overdose) or discharge home or to a psychiatric facility would be considered, whichever is most appropriate.

Most publications show that, once a health-care facility has been reached, patients presenting with IDO have a low mortality. The mortality rate of 0.4% in our study population is in accordance with the in-hospital mortality reported in other studies on IDO patients (0%-6%) [1,2,12-17]. During the 7-year period of our study, two additional IDO patients not included in our analysis by virtue of the exclusion criteria (paracetamol poisoning and paraquat poisoning) died in our unit. Such cases can only be properly identified and treated on the basis of serum levels, prompted by adequate medical history-taking.

Paradoxically, the overall mortality of patients who are admitted for drug overdose is not determined by acute toxic events. Most of the mortality in this cohort occurs after hospital discharge. A recent study highlighted a discrepancy between the in-hospital mortality of 2.1%, and a mortality rate of approximately 10% found 24 months after

Table 3
Odds ratio, sensitivity and specificity for individual criteria and combined into acuity (high/low)

Criterium	OR (95% CI)	Sensitivity (%)	Specificity (%)
Intubation	-	7.1	100
Abnormal oxygenation	2.47 (1.14–5.33)	20.0	90.8
Abnormal breathing	2.77 (0.78–9.88)	7.1	97.3
Abnormal cardiac conduction	1.33 (0.77–2.32)	47.1	60.0
Abnormal blood pressure	5.60 (2.66–11.76)	31.4	92.4
Abnormal Consciousness	5.94 (2.86–12.30)	39.2	90.2
Acuity (sum of the above criteria; 'yes' if one of the criteria is present)	**9.45 (2.84–31.33)**	**95.7**	**29.7**

Table 4
Case description of false negative patients

Patient A	53-year old woman, who had taken enalapril 600 mg and temazepam 30 mg, conscious and hemodynamically stable in the ER. Developed hypotension on the MC ward, followed by fluid resuscitation 1500 ml. Organ function remained normal.
Patient B	37-year old woman with psychiatric history, claimed to have taken oxazepam 600 mg, biperiden 14 mg, and zuclopentixol 12 mg. Developed restlessness on the MC ward, treated with 1 mg of haloperidol and 2.5 mg of midazolam iv. Serum levels of zuclopentixol were not elevated.
Patient C	25-year old intellectually disabled man, claimed to have taken unknown amounts of risperidone, seroquel, quetiapine, diazepam, temazepam and paracetamol. Was treated with acetylcysteine on the MC ward. Developed restlessness, treated with a sedative dose of propofol. Serum levels of paracetamol and quetiapine were negative.

discharge. It remains speculative what causes this late mortality, but behavioral factors, social circumstances, and withdrawal from psychiatric care are likely to play a role [2]. From that perspective, admitting patients during a mental crisis to a high tech environment like a MC/IC ward does not appear to be helpful, unless there is a necessity.

The strength of our study lies in the fact that the subgroup of patients that might benefit from admission to a MC/IC ward can be defined reliably by applying a fast and simple set of parameters. All that is needed to use the decision tool is clinical examination, ECG and blood gas analysis. Before it can be concluded that a patient's vital signs are stable, a safe observation period is required. The median observation period in our study was 2:15 h, but it cannot be concluded that this is a safe period. Other studies have addressed this [4].

Use of the decision tool could have prevented unnecessary MC/IC admissions in over 20% of cases, with considerable potential cost savings. Equally important, however, is that it might have saved 55 patients the psychological burden of an admission in a hostile environment. This burden is illustrated by patients B and C (Table 4), who were given medical treatment for behavior that was more likely to be induced by failure to attend to their mental needs, than by a presumed intoxication. The decision tool would have identified these patients as low-acuity.

Some limitations apply to the results of this study. Firstly, the results are only applicable to the population included in this analysis. A decision tool based on clinical parameters can only be expected to predict effects of drugs that induce changes in these parameters. Therefore, only IDO cases with drugs having potentially acute effects on neurologic, cardiovascular, or ventilatory function were included in this study. As a consequence, the feasibility of the decision tool does not extend to overdose with recreational substances, or intentional intoxications with, for instance, paracetamol.

Secondly, one could wonder whether a clinical tool designed in one hospital would work equally well in other institutions. The fact that this was a single-center study limits the generalizability of the decision tool. The validity of our tool might benefit from retrospective testing in a separate cohort. However, the prevalence of ingested drugs, summarized in Table 3, was representative of the nature of intoxications in many other surveys [1-4,18], suggesting that our patient population was not much different from others.

In addition, this study was performed in a retrospective cohort. Validation of this decision tool in a prospective setting would yield more insight in the robustness of the test characteristics. The specificity of 29.7% of the decision tool seems rather low, but it must be borne in mind that our patient cohort was already admitted to the ICU, and therefore selected. We were unable to obtain a reliable estimate of the total number of patients coming to the ER or the number of patients who were admitted elsewhere or sent home with mild or absent intoxication symptoms in the period from which we collected our data, because shortcomings in our clinical record system made it difficult to capture these patients. However, if we assume that patients not admitted to the MC/IC unit did not have abnormal test criteria, and did not require MC/IC interventions, specificity would turn out considerably higher. We think that the most appropriate way to test the robustness of our decision tool would be to perform a prospective study in the ER population of IDO patients. This might also lead to fine-tuning of the cut-off values in the decision tool. Statistical methods, such as multivariate analysis, may assist in this process. Until the validity has been confirmed in further studies, this tool should be applied with caution when used to guide decisions. Clinical judgment should always override the decision tool when doubt exists.

5. Conclusion

The results of our study support the hypothesis that the clinical course of patients with IDO can be predicted after several hours of observation. A set of 6 criteria that are readily available in the ER, could have identified patients requiring MC/IC interventions with 95.7% sensitivity. In our setting, the use of this decision tool would have eliminated more than 20% of MC/IC admissions. Future research aimed at validating these 6 criteria in a prospective, multicenter design is needed to further strengthen our results and to prepare the use of these criteria in the clinical setting.

Author contributions

HvdO conceived the study and prepared the manuscript. MvD also designed and conducted the study as part requirement to obtain her medical degree. EvtR advised on methodology and statistics, and prepared these sections of the manuscript. FJ reviewed the study conduction and preparation of the manuscript. All authors read and approved the final manuscript.

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