Potential drug-drug interactions in the intensive care

Frequency, clinical relevance and improvement strategy

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CHAPTER 2

Heterogeneity in the identification of potential drug-drug interactions in the intensive care unit: a systematic review, critical appraisal, and reporting recommendations

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ABSTRACT

Patients admitted to the intensive care unit (ICU) are frequently exposed to potential drug-drug interactions (pDDIs). However, reported frequencies of pDDIs in the ICU vary widely between studies. This can be partly explained by significant variation in their methodological approach. Insight into methodological choices affecting pDDI frequency would allow for improved comparison and synthesis of reported pDDI frequencies. This study aimed to evaluate the association between methodological choices and pDDI frequency and formulate reporting recommendations for pDDI frequency studies in the ICU. The MEDLINE database was searched to identify papers reporting pDDI frequency in ICU patients. For each paper, the pDDI frequency and methodological choices such as pDDI definition and pDDI knowledge base were extracted, and the risk of bias was assessed. Each paper was categorized as reporting a low, medium, or high pDDI frequency. We sought associations between methodological choices and pDDI frequency group. Based on this comparison, reporting recommendations were formulated. Analysis of methodological choices showed significant heterogeneity between studies, and 65% of the studies had a medium to high risk of bias. High risk of bias, small sample size, and use of drug prescriptions instead of administrations were related to a higher pDDI frequency. The findings of this review may support researchers in designing a reliable methodology assessing pDDI frequency in ICU patients. The reporting recommendations may contribute to standardization, comparison, and synthesis of pDDI frequency studies, ultimately improving knowledge about pDDIs in and outside the ICU setting.

INTRODUCTION

A drug-drug interaction (DDI) occurs when a drug affects the pharmacokinetics and/or the pharmacodynamics of another drug.[1] A potential DDI (pDDI) can be defined as two potentially interacting drugs administered concomitantly.[2] Such a pDDI may lead to an actual DDI, which could result in patient harm.

Patients admitted to the intensive care unit (ICU) are more likely experience DDIs because of often present polypharmacy, impaired absorption and reduced renal and hepatic function.[3] Moura et al.[4] found that pDDIs are associated with a longer ICU length of stay (LOS). Freeman et al.[5] showed that ICU patients with pDDIs related to QT-prolonging drugs have a higher ICU mortality rate and longer ICU LOS, compared to patients without these pDDIs.

A recent systematic review by Fitzmaurice et al.[6] estimated that 58% of ICU patients are exposed to pDDIs, with the number of pDDIs per patient ranging between one and five. However, the pDDI frequency found in the included studies, varied widely from 0.5 pDDIs per patient to 33.5 pDDIs per patient. Differences in setting, patient characteristics and other methodological choices such as pDDI knowledge bases and pDDI definition, have been suggested as contributing to the variation in reported pDDI frequencies.[6-9] Such variation in methodology hinders meaningful comparison and synthesis of the results.[6-9]
To our knowledge, a comprehensive analysis of methodological choices and their impact on the measured pDDI frequency has not been reported previously. More insight into the influence of methodological choices on pDDI frequency would allow for better comparison and data synthesis regarding pDDI frequency in the ICU.[6-9] Understanding the true extent of pDDI problems in ICU patients is important because, based on the extent of medication safety risks such as pDDIs, hospitals introduce preventive measures such as clinical decision support systems (CDSSs). Furthermore, currently no reporting guidelines are available for studies investigating pDDI frequency in general or in ICU patients. The reporting guideline for observational routinely collected health data in pharmacoepidemiology (RECORD-PE), is not specifically aimed at studies reporting pDDI frequencies.[10,11] Reporting guidelines are an important tool, as they increase the reproducibility and comparability of study results, as well as the quality of evidence synthesis.

The aim of this study was to evaluate the association between methodological choices and pDDI frequency in the ICU and use these findings to formulate reporting recommendations for pDDI frequency studies in the ICU setting.

METHODS

This study is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (Supplementary file, online).[12]

Eligibility criteria

Original papers in English reporting the frequency of pDDIs in ICU patients, published between January 2010 and January 2021 were included. Studies in pediatric ICUs were excluded. To identify potential papers, we searched the MEDLINE database through PubMed. Appendix 2.1 (this thesis) provides details on the search strategy. Case studies, letters, opinions, conference papers, dissertations and systematic reviews were excluded. Studies focusing on only one drug or pDDI type were excluded, as well as studies focusing on interactions with herbs, diseases or nutrients.

Study selection and data collection

Two reviewers (JK and TB) screened articles for inclusion based on title and abstract using the web application Rayyan.[13] Discrepancies were discussed and resolved by the two reviewers. Next, full-text screening for inclusion was done by one reviewer (TB). Then, a data extraction form (Supplementary file, online) was developed to extract relevant information regarding five methodological domains, all potentially influencing the reported pDDI frequency:

- Setting and design: study design, study period, sample size, hospital type, ICU type, and presence of a CDSS.
- Eligibility criteria for patient inclusion: criteria based on the patient's LOS, or selection of specific admission days, for example only the third day of admission.
- Patient characteristics: age, sex, diagnosis, and LOS.
- pDDI characteristics and outcomes: included drug types evaluated, number of prescribed drugs, type of pDDIs evaluated, assessment of clinical relevance of pDDIs, total number of pDDIs, number of pDDIs per patient, and percentage of patients with at least one pDDI. When explicitly reported, the number of pDDIs per patient was taken directly from the paper, otherwise, it was derived using reported information.
- pDDI detection strategy: pDDI definition, the drug data source used for pDDI detection, the pDDI knowledge base used, and whether pDDI detection was automated or manually.
- The use of a reporting guideline, if stated by the authors.

Whether drug prescriptions or administrations were used to detect pDDIs is referred to as "the drug data source". The pDDI definition includes whether or not pDDIs were counted more than once per patient, and the time frame in which two drugs have to be administered/prescribed to deem it a pDDI. This time frame will be further referred to as "gap time".

Quality assessment

The quality of studies was assessed by one reviewer (TB) with the Risk of Bias (ROB) Tool, designed to assess bias in population-based prevalence studies.[14] This assessment was validated by a second reviewer (JK). The ROB tool assesses the methodological quality of the study and the extent to which results may be biased. The tool comprises 10 items addressing four domains, and a summary assessment. Items 1 to 4 assess the external validity by assessing the domains selection bias and response bias. Items 5 to 9 assess the internal validity by

assessing the domains measurement bias and bias related to the analysis. Response options for individual items were either high risk or low risk. The summary assessment evaluates the overall ROB based on responses to the 10 items. Response options for the summary assessment were low, moderate or high ROB.[14] Before the quality assessment was carried out, two reviewers (TB and JK) defined for each item in the tool how this item should be interpreted in the context of pDDI detection. The interpretation is explained in Appendix 2.2 (this thesis).

Summary measures

To evaluate the influence of methodological choices on the measured pDDI frequency, each study's pDDI frequency was categorized based on the number of pDDIs per patient. A Pareto chart was used to identify natural clusters of studies that share similar pDDI frequencies. As there were no visible clear-cut groups on the Pareto chart, we categorized the studies' frequencies based on tertiles. Each study was categorized as high, medium, or low frequency. Studies evaluating severe pDDIs were categorized separately. Studies evaluating a specific pDDI subtype or patient population were excluded from categorization, because their pDDI frequency may deviate from the general frequency of all pDDI types in all ICU patients. Next, the groups were analyzed for differences in the above stated methodological domains.

Based on the findings of this analysis, recommendations for standardized reporting of the methods and results of studies investigating pDDI frequency were formulated, for the ICU setting. Factors that could influence the measured pDDI frequency should be clearly stated and therefore are included in our recommendations.

RESULTS

Study selection

In total, 2381 potential articles were identified, of which finally 26 articles were included. Figure 1 shows a flow diagram of the selection process.

Study characteristics

Characteristics of the included studies are presented in Table 1 and 2. All 26 studies were observational studies, of which 12 were prospective, 10 were retrospective and 4 did not report being either. Four studies were multicenter studies, while 22 (85%) were single-center studies. Studies were mostly conducted in non-Western countries (62%). Seventeen studies evaluated pDDIs in adult patients (65%), five studies included all ages (19%), one study evaluated pDDIs in the elderly population (4%), and three studies did not report any age restrictions (12%). Several ICU types were represented, including mixed ICUs (27%), medical ICUs (15%), cardiac ICUs (15%), cardiosurgical ICUs (12%) and medicosurgical ICUs (12%). Five studies (19%) focused on the frequency of a specific pDDI subgroup or patient group. None of the studies reported the use of a reporting guideline.

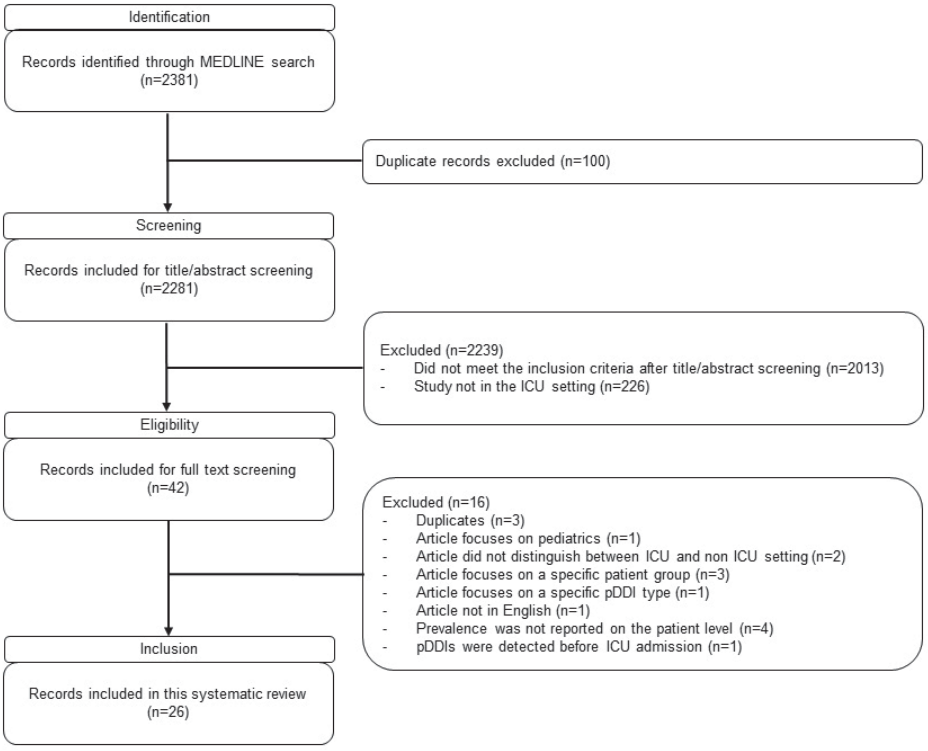

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram

Table 1 Study characteristics and pDDI frequency of studies evaluating all pDDI types

Study	Number of patients	ICU type	Country	Selection of pDDIs	Number of pDDIs	% patients with a pDDI	Number of pDDIs per patient
Khan et al.[17]	649	Cardiac	Pakistan	QT prolonging pDDIs	361	27.9%	0.6[a]
Alvim et al.[18]	82	Medical	Brazil	pDDIs with antimicrobial drugs	98	46%	1.2[a]
Uijtendaal et al.[2]	1659	Mixed	Netherlands	All pDDIs	2887	54%	1.7
Ali et al.[31]	232	Medical + surgical	Palestine	All pDDIs	422	72%	1.8
Smithburger et al.[20]	240	Mobile	USA	All pDDIs	457	Not reported	1.9[a]
Ray et al.[32]	400	Medical + surgical	India	All pDDIs	800[a]	Not reported	2.0
Reis et al.[33]	299	Not reported	Brazil	All pDDIs, including drug-enteral interactions	1st 24h 552 Halfway 753 Discharge 610	68.6% 73.9% 69.6%	1.9[a] 2.5[a] 2.0[a]
Shakeel et al.[34]	1044	Mixed	Pakistan	All pDDIs	3019	71%	2.9[a]
Wagh et al.[35]	400	Not reported	India	All pDDIs	1171	Not reported	2.9[a]
Smithburger et al.[36]	400	Cardiac	USA	All pDDIs	1150	Not reported	2.9[a]
Amkreutz et al.[16]	252	Medical	Germany	All pDDIs in kidney transplant patients	Meona 298 Mediq 1224	99.2%	Meona 1.2[a] Mediq 4.9[a]
Ismail et al.[37]	416	Medical	Pakistan	All pDDIs	1686	74.5%	4.1[a]
Vanham et al.[26]	275	Medical + surgical	Belgium	All pDDIs	1120	79%	4.1[a]
Hasan et al.[38]	82	Mixed	Singapore	All pDDIs	402	76%	4.9[a]
Shakeel et al.[39]	520	Cardiac	Pakistan	All pDDIs	2548	96%	4.9[a]
Rodrigues et al.[22]	369	Mixed	Brazil	All pDDIs	1844	89%	5.0[a]
Jain et al.[40]	500	Cardiac	India	All pDDIs	2849	Not reported	5.7[a]
Farzanegan et al.[21]	195	Cardiac + surgical	Iran	All pDDIs	1405	79.5%	7.2[a]
Armahizer et al[15]	187	Cardiac + surgical	USA	QT prolonging pDDIs in patients with QT prolongation	1843	Not reported	9.9[a]
Janković et al.[41]	201	Mixed	Serbia	All pDDIs	Micromedex 2109[a] Epocrates 3349[a] Medscape 5915[a]	99.0%	Micromedex 10.5 Epocrates 16.7 Medscape 29.4
Łoj et al.[42]	43	Not reported	Poland	All pDDIs	1442	Not reported	33.5[a]

[a] As this number was not reported, we calculated it based on available data.

ICU = Intensive Care Unit; pDDI = potential Drug-Drug Interaction; USA = United States of America.

Table 2 Study characteristics and pDDI frequency of studies evaluating pDDI types with at least moderate severity

Study	Number of patients	ICU type	Country	Selection of pDDIs	Number of pDDIs	% patients with a pDDI	Number of pDDIs per patient
Rodrigues et al.[22]	369	Mixed	Brazil	Contraindicated	129[a]	Not reported	0.4[a]
Amkreutz et al.[16]	252	Medical	Germany	Major/contraindicated in kidney transplant patients	Meona 58 Mediq 154	94.4%	Meona 0.2[a] Mediq 0.6[a]
Smithburger et al.[20]	240	Mobile	USA	Major/Contraindicated	114	Not reported	0.5[a]
Farzanegan et al.[21]	195	Cardiac + surgical	Iran	Major/contraindicated	248	Not reported	1.3[a]
Askari et al.[43]	9644	Mixed	Netherlands	Severe and clinically relevant pDDIs	16122	11.2%[a]	1.7
Oğlu et al.[44]	101	Medical	Turkey	Moderate/Major/Contraindicated	173	45.5%	1.7[a]
Baniasadi et al.[45]	184	Cardiac + surgical	Iran	Major/contraindicated	496	38%	2.7[a]
Moura et al.[4]	236	Mixed	Brazil	Moderate/Major	787	55%	3.3[a]
Ramos et al.[19]	62	Not reported	Brazil	Moderate/Major/Contraindicated in HIV/AIDS patients	331	Not reported	5.3[a]

[a] As this number was not reported, we calculated it based on available data.

ICU = Intensive Care Unit; pDDI = potential Drug-Drug Interaction; USA = United States of America.

pDDI frequency

In total, 21 studies assessed the frequency of all pDDI types, without any selection on pDDI severity (see Table 1). In this group, the mean number of pDDIs per patient varied widely, ranging from 0.6 to 33.5. The percentage of patients with at least one pDDI varied from 28% to 96%. Of these 21 studies, we categorized the pDDI frequency as low in 5 studies, as moderate in 5 studies and as high in 7 studies (see Table 3). The remaining four studies were not categorized because of their specific pDDI subtype and were therefore excluded from analysis of methodological choices.[15-18]

In total, 9 studies assessed the frequency of pDDIs with a severity level of at least moderate (see Table 2). In this subgroup, the mean number of pDDIs per patient varied from 0.2 to 3.33, and the percentage of patients with at least one pDDI varied from 11% to 94%. Of these 9 studies, we categorized the pDDI frequency as low in 2 studies, as moderate in 3 studies and as high in 2 studies (see Table 4). The remaining two studies were not categorized because of their specific pDDI subtype and were therefore excluded from analysis of methodological choices.[16,19]

Four studies reported the pDDI frequency of all pDDIs types and the pDDI frequency of pDDIs with a severity level of at least moderate[16,20-22], and were therefore represented in both Table 1 and Table 2.

Quality assessment

Hoy et al.'s ROB Tool[14] was easy to use and appropriate to assess the quality of pDDI frequency studies. The additional notes provided in the appendix of their article were helpful, also in applying the items to our review.

For 9 studies (35%) the ROB was rated as low, for 7 studies (27%) as medium, and for 10 studies (38%) as high. The medium and high ratings for ROB were mostly due to the single-center nature of the studies (selection bias) and the use of drug prescriptions, which are seen as a proxy as opposed to drug administrations (measurement bias). Table 5 shows the ratings of each article.

Variation in patient characteristics and setting

Table 3 shows the methodological choices pertaining to patient characteristics and setting in relation to pDDI frequency, for studies evaluating all pDDI types. From Table 3, the following can be observed. First, studies with a high pDDI frequency had fewer restrictions on admission days or LOS. In the high frequency group, two studies had a restriction on LOS, while in the low frequency group, 4 studies had a restriction on LOS and 1 on admission days. Second, patients in high pDDI frequency group received more drugs per patient (median = 11) compared to the medium (median = 6) and low frequency (median = 9) groups. Third, regarding sample size, high pDDI frequency studies had smaller sample sizes (mean = 272) compared to low pDDI frequency studies (mean = 566). Regarding ICU type, cardiac ICUs seem to be represented more often in the high pDDI frequency group compared to the medium and low pDDI frequency group. Regarding age and country, no significant differences were observed among the three pDDI frequency groups.

Table 4 shows the methodological choices pertaining to patient characteristics and setting in relation to pDDI frequency, for studies evaluating pDDI types with at least moderate severity. Despite the small numbers in this subgroup, the same patterns apply to this subgroup.

Variation in pDDI detection and ROB

Table 6 shows the methodological choices pertaining to pDDI detection strategy and ROB in relation to pDDI frequency, for studies evaluating all pDDI types. From Table 6 the following can be observed. First, studies reporting a high pDDI frequency had a high ROB (71%), while in the low frequency group only one study had a high ROB (20%). Second, in the high pDDI frequency group, drug prescriptions were used more often to detect pDDIs, as opposed to drug administrations. In the high pDDI frequency group, no study detected pDDIs based on drug administrations, while in the low pDDI frequency group two out of five studies did. Third, studies reporting low or medium pDDI frequencies more often used Micromedex[23] or a combination of Micromedex and Lexi-interact[24] as pDDI knowledge base(s). Regarding manual or automated detection, no significant differences were observed among the frequency groups.

Table 7 shows the methodological choices pertaining to pDDI detection strategy and ROB in relation to pDDI frequency, for studies evaluating pDDI types with at least moderate severity. Despite the small numbers in this subgroup, the same patterns apply.

Another important observation is that only three studies specified whether or not a gap time was applied. Two studies defined a pDDI as two simultaneously administered interacting drugs, while another study defined a pDDI as two interacting drugs prescribed within 24 hours. Furthermore, only two studies reported how pDDIs were counted. Both reported that a specific pDDI was counted only once per patient.

Reporting recommendations

Based on the analysis of methodological choices, the reported results in the included studies, and the ROB evaluation, a set of recommendations was defined for studies reporting pDDI frequency in the ICU. Table 8 summarizes the recommendations. The recommendations focus on the Methods and Results section and are an addition to the existing RECORD-PE guideline.[10]

Reporting recommendations: Methods section

ICU type: Describe the type of the ICU(s) from which the patient sample was drawn. For example, the sample could be drawn from a medical ICU, surgical ICU or cardiac ICU, representing different patient populations with different drug profiles.

Restrictions on the LOS: Indicate whether patients were excluded based on restrictions regarding their ICU LOS. Some studies exclude ICU patients with a LOS of less than 24 hours. In a previous study, we showed that patients with a minimum LOS of 24 hours have a higher pDDI frequency compared to patients with a shorter LOS.[25]

Table 3 Setting, patient characteristics and pDDI frequency category of studies evaluating all pDDI types

Study	Frequency all pDDIs	Number of patients	ICU type	Country	Selection of pDDIs	Age	Number of drugs	Selection admission days	Selection in LOS
Uijtendaal et al.[2]	Low	1659	Mixed	Netherlands	All pDDIs	62 (median)	Not reported	No	LOS >= 24h
Ali et al.[31]	Low	232	Medical + surgical	Palestine	All pDDIs	53 (median)	4 (mean)	No	LOS >= 48h
Smithburger et al.[20]	Low	240	Mobile	USA	All pDDIs	60 (mean)	Not reported	No	No
Ray et al.[32]	Low	400	Medical + surgical	India	All pDDIs	61 (mean), 63 (median)	9 (median)	No	LOS >= 48h
Reis et al.[33]	Low	299	Not reported	Brazil	All pDDIs, including drug-enteral interactions	57 (median)	12 (median)	Yes[b]	LOS >= 5 days
Shakeel et al.[34]	Medium	1044	Mixed	Pakistan	All pDDIs	68 (mean)	6 (mean)	No	LOS >= 24h
Wagh et al.[35]	Medium	400	Not reported	India	All pDDIs	55 (mean)	8 (mean)	No	No
Smithburger et al.[36]	Medium	400	Cardiac	USA	All pDDIs	Not reported	Not reported	No	No
Ismail et al.[37]	Medium	416	Medical	Pakistan	All pDDIs	Not reported	Not reported	No	No
Vanham et al.[26]	Medium	275	Medical + surgical	Belgium	All pDDIs	Not reported	6 (median)[a]	Day 3	LOS >= 72h
Hasan et al.[38]	High	82	Mixed	Singapore	All pDDIs	43 (median)	9 (median)	No	No
Shakeel et al.[39]	High	520	Cardiac	Pakistan	All pDDIs	58 (mean)[a]	6 (median)	No	LOS >= 24h
Rodrigues et al.[22]	High	369	Mixed	Brazil	All pDDIs	57 (median)	13 (mean)	No	LOS >= 24h
Jain et al.[40]	High	500	Cardiac	India	All pDDIs	56 (mean)	7 (mean)	No	No
Farzanegan et al.[21]	High	195	Cardiac + surgical	Iran	All pDDIs	48 (median)	Not reported	No	No
Janković et al.[41]	High	201	Mixed	Serbia	All pDDIs	66 (mean)	23 (mean)	No	No
Łoj et al.[42]	High	43	Not reported	Poland	All pDDIs	62 (mean)	22 (median)	No	No

[a] As this number was not reported,we calculated it based on available data. [b] pDDIs were evaluated at 3 time points: the first 24 h, the 50th percentile, and at discharge.
ICU, intensive care unit; LOS, length of stay; pDDI, potential drug-drug interaction.

Table 4 Setting, patient characteristics and pDDI frequency category of studies evaluating pDDI types with at least moderate severity

Study	Frequency all pDDIs	Number of patients	ICU type	Country	Selection of pDDIs	Age	Number of drugs	Selection admission days	Selection in LOS
Rodrigues et al.[22]	Low	369	Mixed	Brazil	Contraindicated	57 (median)	13 (mean)	No	LOS >= 24h
Smithburger et al.[20]	Low	240	Mobile	USA	Major/Contraindicated	60 (mean)	Not reported	No	No
Farzanegan et al.[21]	Medium	195	Cardiac + surgical	Iran	Major/contraindicated	48 (median)	Not reported	No	No
Askari et al.[43]	Medium	9644	Mixed	Netherlands	Clinically relevant pDDIs	63 (mean)	Not reported	No	No
Oğlu et al.[44]	Medium	101	Medical	Turkey	Moderate/Major/ Contraindicated	61 (mean)	10 (mean)[a]	Yes[b]	LOS >= 24h
Baniasadi et al.[45]	High	184	Cardiac + surgical	Iran	Major/contraindicated	48 (median)	10 (mean)[a]	Day 1 and 2	No
Moura et al.[4]	High	236	Mixed	Brazil	Moderate/Major	50 (mean)	Not reported	No	No

[a] As this number was not reported,we calculated it based on available data. [b] Only the first visit analyzed.
ICU, intensive care unit; LOS, length of stay; pDDI, potential drug-drug interaction.

Table 5 Quality assessment according to the Risk of Bias Tool by Hoy et al.

	Was the target population of the study a close representation of the general population	Was the sampling frame a true or close representation of the target population	Was some form of random selection used to select the sample or was a census taken	Was the likelihood of non-response bias minimal	Were data collected directly from the subjects, as opposed to a proxy	Was an acceptable case definition used in the study	Was the study instrument that measured the parameter of interest shown to have reliability and validity	Was the same mode of data collection used on all subjects	Was the length of the shortest prevalence period for the parameter of interest appropriate	Were the numerator and denominator for the parameter of interest appropriate	Overall assessment
Ali et al.[31]	Yes	Yes	Yes	Not applicable	No	Yes	Yes	Yes	Not applicable	Yes	Low
Alvim et al.[18]	No	No	Yes	Not applicable	No	Yes	Yes	Yes	Not applicable	Yes	High
Amkreutz et al.[16]	No	Yes	Yes	Not applicable	Yes	Yes	Yes	Yes	Not applicable	Yes	Low
Armaziher et al.[15]	No	Yes	Yes	Not applicable	Yes	Yes	Yes	Yes	Not applicable	Yes	Low

Askari et al.[43]	No	Yes	Yes	Not applicable	Yes	Yes	Yes	Yes	Not applicable	Yes	Low
Baniasadi et al.[45]	No	Yes	Yes	Not applicable	No	Yes	Yes	Yes	Not applicable	Yes	Medium
Farzanegan et al.[21]	No	Yes	Yes	Not applicable	No	Yes	Yes	Yes	Not applicable	Yes	Medium
Oğlu et al.[44]	No	No	Yes	Not applicable	No	Yes	Yes	Yes	Not applicable	Yes	High
Hasan et al.[38]	No	No	Yes	Not applicable	No	Yes	Yes	Yes	Not applicable	Yes	High
Ismail et al.[37]	No	No	Yes	Not applicable	No	No	Yes	Yes	Not applicable	Yes	High
Jain et al.[40]	No	Yes	Yes	Not applicable	No	No	Yes	Yes	Not applicable	Yes	High
Janković et al.[41]	No	Yes	Yes	Not applicable	No	No	Yes	Yes	Not applicable	Yes	High
Khan et al.[17]	Yes	Yes	Yes	Not applicable	Yes	Yes	Yes	Yes	Not applicable	Yes	Low
Łoj et al.[42]	No	No	Yes	Not applicable	No	No	Yes	Yes	Not applicable	Yes	High
Moura et al.[4]	No	Yes	Yes	Not applicable	No	Yes	Yes	Yes	Not applicable	Yes	Medium
Ramos et al.[19]	No	Yes	Yes	Not applicable	Yes	Yes	Yes	Yes	Not applicable	Yes	Low
Ray et al.[32]	No	Yes	Yes	Not applicable	No	Yes	Yes	Yes	Not applicable	Yes	Medium
Reis et al.[33]	No	Yes	Yes	Not applicable	Yes	Yes	Yes	Yes	Not applicable	Yes	Low
Rodrigues et al.[22]	No	Yes	No	Not applicable	No	Yes	Yes	Yes	Not applicable	Yes	High
Shakeel et al.[34]	Yes	Yes	Yes	Not applicable	Yes	Yes	Yes	Yes	Not applicable	Yes	Low
Shakeel et al.[39]	Yes	Yes	No	Not applicable	No	Yes	Yes	Yes	Not applicable	Yes	Medium
Smithburger et al.[20]	No	No	Yes	Not applicable	No	Yes	Yes	Yes	Not applicable	Yes	High
Smithburger et al.[36]	No	No	Yes	Not applicable	No	Yes	Yes	Yes	Not applicable	Yes	High
Uijtendaal et al.[2]	No	Yes	Yes	Not applicable	Yes	Yes	Yes	Yes	Not applicable	Yes	Low
Vanham et al.[26]	No	Yes	Yes	Not applicable	No	Yes	Yes	Yes	Not applicable	Yes	Medium
Wagh et al.[35]	No	Yes	Yes	Not applicable	No	Yes	Yes	Yes	Not applicable	Yes	Medium

Table 6 pDDI detection strategy and pDDI frequency category of studies evaluating all pDDI types

Study	Frequency all pDDIs	Selection of pDDIs	Prescriptions or administrations	Manual or automated detection	Gap time	Unique DDIs counted	pDDI knowledge base	#KB	Study rating (ROB)
Uijtendaal et al.[2]	Low	All pDDIs	Administrations	Automated	Simultaneous administrations[a]	Not reported	G-standard	1	
Ali et al.[31]	Low	All pDDIs	Unclear	Manual	Not reported	Not reported	Drugs.com	1	
Smithburger et al.[20]	Low	All pDDIs	Prescriptions	Manual	Not reported	DDIs were only counted once per patient	Micromedex, Lexi-interact	2	
Ray et al.[32]	Low	All pDDIs	Prescriptions	Manual	Not reported	Not reported	Epocrates & Medclik	2	
Reis et al.[33]	Low	All pDDIs, including drug-enteral interactions	Administrations	Manual	Not reported	Not reported	Micromedex	1	
Shakeel et al.[34]	Medium	All pDDIs	Administrations	Manual	Simultaneous administrations	Not reported	Micromedex	1	
Wagh et al.[35]	Medium	All pDDIs	Prescriptions	Manual	Not reported	Not reported	Micromedex	1	
Smithburger et al.[36]	Medium	All pDDIs	Prescriptions	Manual	Not reported	Not reported	Micromedex, Lexi-interact	2	
Ismail et al.[37]	Medium	All pDDIs	Not reported	Manual	Not reported	Not reported	Micromedex	2	
Vanham et al.[26]	Medium	All pDDIs	Prescriptions	Manual	Not reported	Not reported	Stockley, Micromedex, Lexi-interact	3	
Hasan et al.[38]	High	All pDDIs	Prescriptions	Manual	Not reported	Not reported	Lexi-interact, Micromedex, Hansten & Horn	3	
Shakeel et al.[39]	High	All pDDIs	Prescriptions	Manual	Not reported	Not reported	Micromedex, Drug interaction facts	2	
Rodrigues et al.[22]	High	All pDDIs	Prescriptions	Manual	Not reported	Not reported	Micromedex	1	
Jain et al.[40]	High	All pDDIs	Not reported	Manual	Not reported	Not reported	Medscape drug interaction checker	1	
Farzanegan et al.[21]	High	All pDDIs	Prescriptions	Manual	Not reported	Not reported	Lexi-interact	1	
Janković et al.[41]	High	All pDDIs	Not reported	Manual	Not reported	Not reported	Medscape, Micromedex, Epocrates	3	
Łoj et al.[42]	High	All pDDIs	Not reported	Manual	Not reported	Not reported	Stockley	1	

[a] Administrations for a specific drug were attributed to 1 drug record if the time gap did not exceed 12 h for continuously administered drug or 36 h for discontinuously administered drug.
ICU, intensive care unit; KB, knowledge base; pDDI, potential drug-drug interaction; ROB, Risk of Bias.

Table 7 pDDI detection strategy and pDDI frequency category of studies evaluating pDDI types with at least moderate severity

Study	Frequency all pDDIs	Selection of pDDIs	Prescriptions or administrations	Manual or automated detection	Gap time	Unique DDIs counted	pDDI knowledge base	#KB	Study rating (ROB)
Rodrigues et al.[22]	Low	Contraindicated	Prescriptions	Manual	Not reported	Not reported	Micromedex	1	🟥
Smithburger et al.[20]	Low	Major/Contraindicated	Prescriptions	Manual	Not reported	DDIs were only counted once per patient	Micromedex, Lexi-interact	2	🟥
Farzanegan et al.[21]	Medium	Major/contraindicated	Prescriptions	Manual	Not reported	Not reported	Lexi-interact	1	🟧
Askari et al.[43]	Medium	Clinically relevant pDDIs	Administrations	Automated	24 hours	Not reported	G-standard	1	🟩
Oğlu et al.[44]	Medium	Moderate/Major/ Contraindicated	Prescriptions	Manual	Not reported	Not reported	Lexi-interact, Micromedex	2	🟥
Baniasadi et al.[45]	High	Major/contraindicated	Prescriptions	Manual	Not reported	DDIs were only counted once per patient	Lexi-interact	1	🟧
Moura et al.[4]	High	Moderate/Major	Prescriptions	Automated	Not reported	Not reported	Drug Interactions Facts	1	🟧

ICU, intensive care unit; KB, knowledge base; pDDI, potential drug-drug interaction; ROB, Risk of Bias.

Restrictions on admission days: Specify if pDDI detection was restricted to specific admission day(s). This may influence pDDI frequency in two ways. First, a short detection period may lead to an underestimation of pDDI frequency. Second, ICU patients are more at risk of a pDDI in the first day(s) of admission.[25] For example, Vanham et al.[26] only detected pDDIs on the third admission day. Therefore, they may report a lower pDDI frequency per patient compared to studies detecting pDDIs on all admission days.

pDDI prevention strategies: Describe any type of pDDI prevention strategy in the ICU, such as a computerized decision support system or active participation of clinical pharmacists in the ICU. Prevention strategies are expected to decrease the pDDI frequency, and therefore may be relevant in comparing pDDI frequencies among studies.[27,28]

Set of Drugs: Describe the set of drugs included in the pDDI evaluation. Indicate whether a selection of drugs was used, based on drug type, medical indication, or any other factor. The pDDI frequency is expected to be lower when a selection of drugs is evaluated. Additionally, some drugs are involved in many pDDIs, which could also affect the pDDI frequency.

Drug Data Source: Describe the drug data source from which pDDIs are detected, such as drug orders or clinical notes. Clearly indicate whether drug prescriptions or drug administrations were used. Using prescriptions instead of administrations could result in an overestimation of pDDI frequency, because not all prescribed drugs may be actually administered. Especially when there are concerns about a pDDI, exposure to a pDDI may be prevented by cancelling prescriptions and not actually administering the medication.

Set of pDDIs: Describe the set of pDDIs evaluated in the study and indicate which pDDI knowledge base was used to detect pDDIs. As there is little concordance between different pDDI knowledge bases[26], differences between studies in the use of a pDDI knowledge base may complicate comparison. The use of different pDDI knowledge bases, and therefore the use of different names and pDDI classifications, further complicates the comparison of frequently occurring pDDIs between studies. For example, some pDDI knowledge bases use names based on drug group level, while others use names based on specific drug level. Regarding the set of pDDIs used, describe whether the severity of pDDIs was used as inclusion or exclusion criterion. Also, state how severity was assessed, for example, by using severity levels defined in a pDDI knowledge base or via expert based consensus.[29] Using severity as defined in pDDI knowledge bases may bias the results, because pDDI knowledge bases are not tailored to the ICU setting.

pDDI Detection Strategy: State the process for detecting pDDIs and indicate whether the process was manual or automated.

Gap Time: Specify any time restrictions used to define a pDDI. Indicate whether two drugs should be given simultaneously or that a gap in time between them is allowed to deem it a pDDI. Specify the gap time, for example one admission day, or a period of 24 hours, or 72

hours. With a longer gap time, more pDDIs will be detected. While a long gap time may overestimate the number of pDDIs, using simultaneously administered drugs may underestimate the number of pDDIs. Although challenging to implement, the optimal strategy would be taking into account the half-life of drugs for each pDDI to reduce both under- and overestimation.

Counting of the pDDIs: Describe how pDDIs were counted, indicate whether specific pDDIs or pDDI types were counted, and indicate whether a pDDI was counted more than once per patient. For example, the pDDI type nonsteroidal anti-inflammatory drugs + corticosteroids can be represented by 10,000+ combinations of drug subtypes, such as the combination of ibuprofen with dexamethasone or diclofenac with hydrocortisone.[30] Counting all instances of combinations of drug subtypes will result in a substantially higher pDDI frequency, compared to counting only the pDDI type once. Each instance of a pDDI increases the risk of harm, therefore, reporting each instance seems more appropriate.

Table 8 Summary of recommendations for reporting the frequency of pDDIs in the ICU

Section/Topic	Item No	Item
Methods		
ICU type	1	Describe the type of the ICU(s) the patient sample was drawn from.
Set of pDDIs	2	Describe the set of pDDIs evaluated in the study. Indicate which pDDI knowledge base was used to detect these pDDIs. Indicate whether a selection of pDDIs was made based on clinical relevance, severity level, pDDI type or any other factor.
Set of drugs	3	Describe the set of drugs included in the evaluation of pDDIs. Indicate whether a selection of drugs was made, based on medication type, medical indication or any other factor.
Drug data source	4	Describe the drug data source on which pDDI detection was performed e.g. drug orders, clinical notes. Clearly indicate whether drug prescriptions or drug administrations were used.
Detection algorithm	5	State the process for detecting pDDIs and indicate whether the process was manual or automated.
pDDI definition		
Gap time	6	Specify what time restrictions were used to define a pDDI. Indicate whether drugs should be given simultaneously or that a gap time is used to deem them a pDDI. Indicate whether the gap time takes half-life into account. Specify the gap time, e.g. 24 hours.
Counting of the pDDIs	7	Describe how pDDIs were counted, indicate whether specific pDDIs or pDDI types were counted and indicate whether a pDDI was counted more than once in one patient or not.
Restrictions admission days	8	Specify if pDDI detection was restricted to specific admission day(s).
Restrictions length of stay	9	Indicate whether patients were excluded based on restrictions regarding their ICU length of stay.
pDDI prevention strategies	10	Describe if the ICU uses any type of pDDI prevention strategy, such as a computerized decision support system.
Results		
Number of patients	1	Report the number of patients in the patient sample.

Section/Topic	Item No	Item
Participants	2	Characterize the patient sample in terms of relevant variables e.g. age, sex, diagnosis, comorbidities, (predicted) mortality.
Number of pDDIs	3	Report the total number of pDDIs detected.
Number of patients with at least one pDDI	4	Report the number and percentage of patients with at least one pDDI.
Number of drugs	5	Report the total number of drugs evaluated.
Total length of stay	6	Report the total length of stay of all patients in days.

ICU = Intensive Care Unit; pDDI = potential Drug-Drug Interaction.

Reporting recommendations: Results section

General: Researchers should report raw numbers in addition to summary measures. Providing raw numbers enables the calculation of alternative outcome measures and facilitates comparison between studies.

Participants: Characterize the patient sample in terms of relevant variables for example age, sex, diagnosis, comorbidities, and (predicted) mortality. These factors may relate to the number of pDDIs identified; for example patients with comorbidities in general use more drugs and may therefore be more prone to pDDIs.

Number of Patients: Report the total number of patients in the patient sample.

Number of pDDIs: Report the total number of pDDIs detected.

Number of Patients with at least one pDDI: Report the number and percentage of patients with at least one pDDI. This outcome measure is often used in pDDI studies, therefore, reporting it facilitates comparison between studies.

Number of Drugs: Report the total number of drugs evaluated. For example, give the total number of drug administrations or the total number of drug prescriptions. Clearly indicate how drugs were counted, whether drug subtypes were counted and whether a drug could be counted twice or more per patient.

Total Length of Stay: Report the total LOS of all patients in days. This enables the calculation of outcome measures per patient day.

DISCUSSION

Main findings

This study evaluated the relation between methodological choices and pDDI frequency and formulated reporting recommendations for pDDI detection studies in the ICU. In line with the recent systematic review by Fitzmaurice et al.[6], the frequency of pDDIs found in the lit-

erature varied widely, from 0.6 pDDIs per patient to 33.5 pDDIs per patient. Comparison of methodological choices (patient characteristics, setting, pDDI detection strategy), and ROB showed significant heterogeneity between studies. Noteworthy is that 65% of the studies had a medium or high risk of bias and none reported the use of a reporting guideline.

Associations of methodological choices and ROB with pDDI frequency

In general, studies with a high pDDI frequency had a higher ROB, used drug prescriptions to detect pDDIs as opposed to drug administrations, had fewer restrictions regarding LOS or the inclusion of specific admission days, had a higher number of drugs per patient, and had smaller sample sizes. Regarding ICU type, cardiac ICUs are represented more often in the high pDDI frequency studies compared to the medium and low pDDI frequency studies. A recent study on pDDIs in the ICU[25] shows that pDDIs between QT-prolonging drugs are the most frequently occurring pDDI type. As QT-prolonging drugs may be administered more frequently in cardiac ICUs, this may partly explain higher pDDI frequencies in cardiac ICUs. Regarding country and median age, no apparent differences among the three pDDI frequency groups were found.

What is missing in pDDI frequency studies?

Important methodological choices including gap time and whether pDDIs are counted more than once per patient were rarely reported, despite the considerable influence these factors may have on the measured pDDI frequency. Applying the same gap time for each pDDI does not take into account half-life and might lead to an overestimation of pDDIs involving drugs with a short half-life or an underestimation of pDDIs involving drugs with a long half-life. Taking into account the half-life of drugs is complex, but could be a worthy future direction. In addition, no study considered the half-life of drugs or the duration of a pDDI. These factors are important modulators of actual DDI manifestation[31] as pharmacokinetic/pharmacodynamic mechanisms are often time dependent. For example, for pDDIs with an underlying liver metabolism induction mechanism, it takes several days to produce an induction effect on the enzymes involved.[32]

Strengths and limitations

This study has several strengths. First, the included articles span over a period of 11 years. Second, to our knowledge, this is the first study to analyze different sources of heterogeneity influencing pDDI frequency. Third, to analyze heterogeneity, a comprehensive set of methodological choices potentially influencing pDDI frequency was evaluated and our findings were translated into reporting recommendations. Our recommendations extend the RECORD-PE guideline.[10] Fourth, the quality of all included articles was assessed with a well-established ROB tool. Finally, the results and recommendations presented in this study are not only applicable to studies investigating pDDI frequency in ICU patients, but can be generalized to hospitalized adult patients in general, since standardization in pDDI definitions and detection methods is also lacking there.[9]

This study has some limitations. First, to review the literature, only the MEDLINE database was used, and the search was limited to studies in English. However, the large sample of studies we searched and found seems to be representative of other databases as it covers 73% of articles included in a recently published systematic review by Fitzmaurice et al.[6] who searched several databases. Second, as the included studies show significant heterogeneity, it was not feasible to perform a statistical analysis, and the effect of the potential sources of heterogeneity on pDDI frequency was assessed based on qualitative patterns. Third, recommendations formulated were primarily based on what was found in the reviewed articles and therefore might not include other relevant factors not reported by these studies. Hence, the recommendations cover the current literature but might need adaptation in the future.

Future research and implications

The results and recommendations presented in this study can support researchers in designing a robust and transparent methodology to evaluate and report pDDI frequency in the ICU or hospital setting. Additionally, along with RECORD-PE, the recommendations can be used by reviewers of peer-reviewed journals for quality assessment of studies reporting pDDI frequency. Future development of a standardized, international classification of pDDIs, covering different pDDI knowledge bases, would further enable comparison of pDDI frequency across settings and countries and understanding the true extent of the pDDI problems in ICU patients.

CONCLUSION

This systematic review showed significant heterogeneity between pDDI frequency studies in ICU patients, and 65% of the studies had a medium to high risk of bias, which complicates the comparison of study outcomes. Methodological choices such as the drug data source, sample size, and the choice of pDDI knowledge base are associated with reported pDDI frequency. To improve comparability of pDDI frequency studies, the reporting quality of studies should be improved. A set of reporting recommendations was formulated that extend established guidelines. Our recommendations may contribute to standardization, reproducibility, comparison, and evidence synthesis of pDDI frequency studies in and outside the ICU setting, ultimately improving our knowledge about pDDIs in hospitalized (ICU) patients. This in turn may inform pDDI prevention strategies such as CDSSs, contributing to improved medication safety.

ONLINE SUPPLEMENTARY FILES

Scan the QR-code to find the online supplementary files for this chapter.

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