# Impact of pharmacists' intervention on identification and management of drug-drug interactions in an intensive care setting

*Syed Shahzad Hasan*[1], BPharm, MClin Pharm, *Kim Nai Lim*[2], BPharm, *Mudassir Anwar*[2], BPharm, MSc, *Belagodu Sridhar Sathvik*[2], BPharm, PhD, *Keivan Ahmadi*[3], BPharm, MClin Pharm, *Adelyn Wei Li Yuan*[4], MPharm, *Mokhtar Ahmad Kamarunnesa*[4], BPharm, MClin Pharm

**INTRODUCTION** The primary and secondary objectives of this study were to identify and assess the risks associated with the occurrence of drug-drug interactions (DDIs) and to determine the value of pharmacists' interventions in the management of clinically significant DDIs, respectively.

**METHODS** A prospective, case-control study was carried out on patients admitted to the intensive care unit (ICU), and involved a review of patients' medication chart daily by the pharmacist and the clinical parameters. All identified DDIs were carefully analysed in order to provide recommendations on the management of clinically significant DDIs.

**RESULTS** The majority of DDIs were categorised as Type-C severity level (n = 305, 75.9%). 'Substitution' was recommended in 34 cases of clinically significant DDIs, 'dosage adjustment' in 17 (4.2%) and 'stop or avoid' in 13 (3.2%). The number of drugs prescribed (p = 0.001, rS = 0.539) and length of ICU stay (p = 0.001, rS = 0.364) were significantly associated and positively correlated with the occurrence of DDIs. Patients with DDIs had a longer length of ICU stay than those without DDIs (9.5 days vs. 2.4 days, p = 0.001). No significant difference was found between patients aged below 50 years and those above 50 years (odds ratio 0.488, 95% confidence interval 0.166–1.434) in terms of the risk of DDIs.

**CONCLUSION** A large number of DDIs were identified in this study, but only a small number were clinically significant. Pharmacists' participation in daily ward rounds could play an important role in the detection and management of clinically significant DDIs.

*Keywords: drug interaction, identification, intensive care, management, pharmacist*
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## INTRODUCTION

Drug-drug interactions (DDIs) may be defined as alterations of the pharmacological or clinical responses to the administration of a drug combination.[1-3] In primary healthcare, 9%–70% of patients are reported to be receiving concomitant drugs with the risk of a potential DDI.[4-7] In general, DDIs account for 6%–30% of all adverse drug reactions (ADRs);[5,6] in hospitalised patients, DDIs can make up 5%–9% of ADRs.[3,4] Among inpatients, it has been estimated that 5%–20% of serious DDI-related ADRs have resulted in hospitalisation or death.[7,8] Between 2.2%–65.0% of inpatients receive medications, including those at discharge, that have one or more potential DDIs.[9-12]

Drug-drug combinations may be useful in some situations, e.g. chemotherapy regimens utilise two or more drugs to improve cancer killing rates.[12] However, other drug-drug combinations are best avoided where possible, e.g. the use of fluoxetine and furosemide in patients with hypertension and depression.[13] Unfortunately, available information regarding DDIs may often be incomplete and difficult to interpret with regard to the type of appropriate actions to take. Therefore, the risks of DDIs should be considered by all members of the healthcare team at each step of the drug-delivery process when a new medication is prescribed, dispensed or administered to a patient.[12]

Although combination therapy may lead to DDIs, the concurrent use of multiple drugs has become a trend, as combination therapy is believed to increase therapeutic effectiveness.[14] A retrospective review has reported that patients taking three or more drugs, or patients aged ≥ 50 years taking two or more medications who were admitted to the emergency department had a considerable risk for DDIs.[14] A few studies have also shown an exponential[15,16] or linear relationship between the number of drugs and the probability for DDIs. Factors such as increasing age, multiple illnesses and female gender have been found to be risk factors for potential DDIs.[18-22] The number of literature on DDIs and ADRs has grown steadily over the years, yet there are few studies focusing on physicians' and pharmacists' ability to effectively identify or recall potential DDIs.[23-25]

Currently, there is limited available information about the impact of DDIs in intensive care settings. Indeed, most data is derived from case reports, volunteer studies or investigations of potential DDIs in non-intensive-care patients.[26,27] The primary and secondary objectives in this study were to identify and assess

[1]School of Pharmacy, University of Queensland, Woolloongabba, Queensland, Australia, [2]School of Pharmacy and Health Sciences, International Medical University, Kuala Lumpur, Malaysia, [3]Department of Global Public Health, Monash University, Malaysia, [4]Medical Intensive Care Unit, Hospital Serdang, Selangor, Malaysia
**Correspondence**: Mr Syed Shahzad Hasan, PhD Research Fellow, School of Pharmacy, University of Queensland, 20 Cornwall Street, Woolloongabba, QLD 4102, Australia. shahzad_pharmacy@yahoo.com

**Table I. Classification of DDIs.[28-30]**

| Severity level | Description |
|---|---|
| Type-A | The interaction was found to be life-threatening, and concomitant use of the interacting agents was contraindicated |
| Type-B (major DDI) | The interaction was found to be life-threatening and/or required medical intervention to minimise or prevent serious adverse effects |
| Type-C (moderate DDI) | The interaction resulted in an exacerbation of the patient's condition and/or required an alteration in therapy |
| Type-D (minor DDI) | The interaction had limited clinical effects and did not require a major alteration in therapy |

DDIs: drug-drug interactions

**Table II. Types of recommendations.**

| Recommendation | Description |
|---|---|
| Substitution | Precipitant drugs were substituted with another drug for the same indication |
| Stop/avoid/dosage adjustment | Precipitant drugs were stopped/avoided, followed by substitution of precipitant drugs for the same indication, or adjustments in dose, frequency, timing, duration, etc was required |
| Monitoring | Monitoring of DDIs was sufficient, and continuation of precipitant and object drugs concomitantly was not harmful |
| No change | No change or modification in drug therapy was recommended due to limited clinical significance of DDIs |

DDIs: drug-drug interactions

the risks associated with the occurrence of DDIs, and to determine the value of pharmacists' interventions in the management of clinically significant DDIs, respectively.

## METHODS

This was a prospective case-control study involving patients who were admitted to a 13-bed (ten beds plus three isolation beds) combined (medical, surgical, renal and paediatric) intensive care unit (ICU) of Hospital Serdang, Selangor, Malaysia. All patients were admitted to the unit due to critical illness and/or a need for close monitoring. The study was approved by the Research and Ethics Committee of International Medical University, and registered with the National Medical Research Registry (NMRR), Ministry of Health Malaysia.

Prospective reviews of the patients' medication charts were performed daily for a period of 12 weeks. Patients' demographic characteristics, diagnosis and comorbidities were retrieved from the hospital computerised medical records. All prescribed medications were screened to identify DDIs based on several tertiary references.[28-30] During their stay in the ICU, a patient was categorised under 'Case' if he was identified as having one or more DDIs and 'Control' if no DDIs were identified. The results of laboratory tests, physical and mental examinations, and electrocardiograms (ECGs) of all Case patients were also monitored daily to assess for DDI-related adverse events.

All DDIs identified were analysed for the level of severity (Type-A to Type-D, Table I).[28-30] DDIs that were classified as Type-A or Type-B were considered to be clinically significant. Recommendations made by the pharmacists regarding the management of clinically significant DDIs were compiled on a daily basis. The types of recommendations made are presented in Table II. The numbers of clinically significant DDIs classified under Type-A and Type-B were forwarded to the authorities concerned, i.e. the relevant prescriber(s) through the pharmacist in-charge of the ICU. The patients were followed up and the outcome of the recommendations recorded.

Study risk factors for the DDIs were identified with the help of previous studies,[1,3,7,9-10,14,18-22] and categorised into three main domains: (1) Patient-related risk factors, including age, gender, race, acute illness, renal/hepatic impairment, metabolic disorders and comorbidities; (2) Drug-related risk factors, including the number of drugs, number of therapeutic class, nature of medications being prescribed, drugs with narrow therapeutic windows, hepatic enzyme inducers, hepatic enzyme inhibitors, where the pharmacokinetic and pharmacodynamic properties of each therapeutic agent were considered to be risk factors; (3) Prescriber-related risk factors, including the number of prescribers and the medical specialty of each prescriber. Here, the external factor, i.e. number of prescribers, was considered to be possibly related with the risk of causing DDIs in ICU patients.

Both descriptive and inferential statistics were carried out using the Statistical Analysis for the Social Sciences version 13 (SPSS Inc, Chicago, IL, USA). A p-value $\leq 0.05$ was considered to be statistically significant. The demographic data of the patients were presented as frequency, mean, standard deviation and percentage. For association and correlation between patients' demographics and DDIs, Chi-square or likelihood ratio and Spearman's tests were used. In order to establish the difference, Mann-Whitney and Kruskal-Wallis tests were performed. Lastly, odds ratio with 95% confidence interval (95% CI) was used for risk factor assessment.

## RESULTS

Overall, 82 patients who were prescribed more than one drug were included in the data analysis. Of these, the majority were male (n = 53, 64.6%), aged > 60 years (n = 22, 26.8%) and Malay (n = 46, 56.1%). The age of the patients ranged from four months to 82 years (median 43 years). Of the 82 patients, 41 (50.0%) were documented to have no comorbid conditions, while the other half had one or more comorbidities. There were 31 (43.1%) with impaired renal function and ten (12.2%) with hepatic impairment. 29 (35.4%) patients had medical histories that were significant for metabolic disorders such as diabetes mellitus, hypothyroidism, hyperthyroidism and adrenal insufficiencies. The patients' demographics and occurrence of DDIs are presented in Table III.

Of the 82 patients reviewed, 62 (75.6%) were designated as 'Case' subjects, while the remainder were 'Control' subjects. The Case group had a total of 402 DDIs (an average of 6.5 DDIs per patient or 0.08 DDI per patient per day). Out of these 402 DDIs, 353 (87.8%) were identified using Lexi-Comp Online™ database

**Table III. Demographic characteristics of the study participants (n = 82).**

| Variable | No. (%) | | Association | Correlation |
|---|---|---|---|---|
| | Total | Occurrence of DDIs | | |
| **Gender** | | | | |
| Male | 53 (64.6) | 40 (64.5) | p = 0.969 | $r_s$ = 0.004 |
| Female | 29 (35.4) | 22 (35.5) | | p = 0.969 |
| **Ethnic group** | | | | |
| Malay | 46 (56.1) | 33 (53.2) | p = 0.684 | $r_s$ = 0.119 |
| Chinese | 17 (20.7) | 13 (21.0) | | p = 0.286 |
| Indian | 10 (12.2) | 8 (12.9) | | |
| Others | 9 (11.0) | 8 (12.9) | | |
| **Age group (yrs)** | | | | |
| 0–15 | 14 (17.1) | 10 (16.1) | p = 0.340 | $r_s$ = 0.123 |
| 16–30 | 17 (20.7) | 10 (16.1) | | p = 0.270 |
| 31–45 | 13 (15.9) | 11 (17.7) | | |
| 46–60 | 16 (19.5) | 14 (22.6) | | |
| > 60 | 22 (26.8) | 17 (27.4) | | |

$r_s$: Spearman's correlation value; DDIs: drug-drug interactions

(Pediatric Lexi-Drugs Online™, Hudson, OH, USA), 131 (32.6%) were identified by Micromedex®Healthcare Series (Thomson Micromedex, Greenwood Village, CO, USA), and 72 (17.9%) were identified using Hansten and Horn DDI monographs (Hansten and Horn's Drug Interactions Analysis and Management, St Louis, MO, USA). Two-thirds of the DDIs were identified using more than one compendium.

Pharmacodynamics- and pharmacokinetics-related DDIs were identified in 96.8% and 59.7% of the Case subjects, respectively. Overall, pharmacodynamics-related DDIs were more common (66.9%) than pharmacokinetics-related DDIs (24.2%). A total of 14 (17.1%) patients were prescribed drugs with a narrow therapeutic index. In addition, 43 (52.4%) and 78 (95.1%) patients were prescribed drugs that were found to be hepatic enzyme inducers and hepatic enzyme inhibitors, respectively. However, 42 (10.4%) and 75 (18.7%) incidences of DDIs involved drugs with hepatic enzyme-inducing and -inhibiting activities, respectively.

Within individual demographic groups, the occurrence of DDIs was highest among patients aged > 60 years (n = 17, 27.4%), Malay patients (n = 33, 53.2%), patients with no comorbid condition (n = 29, 46.8%) and male patients (n = 40, 64.5%) (Table I). However, age, ethnicity and gender were not found to be significantly associated with the occurrence of DDIs. Most of the patients with DDIs did not have any evidence of renal impairment (n = 29, 46.8%), hepatic impairment (n = 41, 66.1%) and metabolic disorders (n = 38, 61.3%), with insignificant association. Interestingly, all the patients with DDIs were diagnosed with some form of acute illnesses; of these, more than 90% had different types of infection.

Study factors such as gender, age group and duration of ICU stay were used to identify the differences among groups in terms of the occurrence of DDIs. Although the incidence of DDIs was found to be more frequent in male (n = 40, 64.5%) as compared to female (n = 22, 35.5%) patients, no significant differences were found between male and female patients (p = 0.969), among the Malay, Chinese and Indian patients (p = 0.836), and the different age groups, i.e. 0–30, 31–60, > 60 years (p = 0.148) in terms of the occurrence of DDIs. However, duration of ICU stay < 3 days, 3–7 days and > 7 days showed a significant difference (p = 0.001) in the occurrence of DDIs. Female gender (OR 0.979, 95% CI 0.341–2.814, p = 0.969), age > 50 years (OR 0.488, 95% CI 0.166–1.434, p = 0.340) and ICU stay > 7 days (OR 0.381, 95% CI 0.079–1.845, p = 0.001) were not significantly associated with DDIs.

The median number of drug classes prescribed to the patients was nine (range 1–19), while the number of prescribers and the number of medical specialties involved in each patient was 1–3, with a median of two prescribers and medical specialties, respectively. In total, 37 drug classes were found to be involved in the 402 DDIs. Of these, opioid analgesics (n = 108, 26.9%) were the most common drug class associated with the occurrence of DDIs. Among opioid analgesics, morphine was the most frequent drug involved. However, no significant association was detected between the drug classes and occurrence of DDIs. Their respective clinical significance notwithstanding, the five most common drug combinations involved in DDIs were ranitidine and morphine (n = 21, 5.2%), morphine and magnesium sulphate (n = 13, 3.2%), midazolam and magnesium sulfate (n = 11, 2.7%), erythromycin and ranitidine (n = 9, 2.2%), dobutamine and noradrenaline (n = 8, 2.0%), and dopamine and noradrenaline (n = 8, 2.0%). In terms of the level of clinical significance, the majority of DDIs were categorised as Type-C, resulting in pharmacists most commonly recommending only monitoring for these patients.

The majority (57.3%) of patients in the ICU stayed for 3–7 days, similar to the duration of ICU stay among most patients with DDIs (64.5%). In addition, the duration of ICU stay for patients with DDIs was significantly associated (p = 0.001) and correlated (p = 0.001) with the occurrence of DDIs. Out of the 82 patients, the majority (57.3%) were taking ten drugs. Among patients with DDIs, 71% of them received > 10 different drugs, with 29% receiving 6–10 drugs each and none receiving ≤ 5 drugs. The number of drugs was also found to be significantly associated

**Table IV. Study factors associated with occurrence of DDIs.**

| Variable | Occurrence of DDI* | OR | 95% CI | p-value |
|---|---|---|---|---|
| **Duration of stay (days)** | | | | |
| ≤ 7 | 48 (77.4) | 0.381 | 0.079–1.845 | 0.001 |
| > 7 | 14 (22.6) | | | |
| **No. of drugs** | | | | |
| ≤ 10 | 18 (29.0) | 0.072 | 0.019–0.277 | 0.001 |
| > 10 | 44 (71.0) | | | |
| **Gender** | | | | |
| Male | 40 (64.5) | 0.979 | 0.341–2.814 | 0.969 |
| Female | 22 (35.5) | | | |
| **Age group (yrs)** | | | | |
| ≤ 50 | 33 (53.2) | 0.488 | 0.166–1.434 | 0.340 |
| > 50 | 29 (46.8) | | | |

*Data is presented as no. (%)
DDI: drug-drug interaction; OR: odds ratio; CI: confidence interval

**Table V. Relationships between duration of stay and number of drugs with occurrence of DDIs.**

| Variables | No. (%) | | Association | Correlation |
|---|---|---|---|---|
| | Total (n = 82) | Patients with DDIs (n = 62) | | |
| **Duration of stay (days)** | | | | |
| < 3 | 19 (23.2) | 8 (12.9) | p = 0.001 | $r_s$ = 0.364 |
| 3–7 | 47 (57.3) | 40 (64.5) | | p = 0.001 |
| > 7 | 16 (19.5) | 14 (22.6) | | |
| **No. of drugs** | | | | |
| ≤ 5 | 5 (6.1) | 0 (0) | p = 0.001 | $r_s$ = 0.539 |
| 6–10 | 30 (36.6) | 18 (29) | | p = 0.001 |
| > 10 | 47 (57.3) | 44 (71) | | |

$r_s$: Spearman's correlation value; DDI: drug-drug interaction

**Table VI. Mean number of drug- and prescriber-related factors.**

| Variable | Median (range) |
|---|---|
| Duration of stay | 5.3 ± 3.7* (2–19) |
| No. of drugs prescribed | 11 (2–24) |
| No. of therapeutic classes prescribed | 9 (1–19) |
| No. of prescribers involved | 2 (1–3) |
| No. of medical specialties involved | 2 (1–3) |
| No. of occurrence of drug interactions | 4 (1–26) |

*Data is expressed as mean ± standard deviation

**Table VII. Examples of DDIs that occurred among the study population during the study period.**

| Severity level | Description |
|---|---|
| Type-A | IV ceftriaxone 500 mg twice daily and IV calcium gluconate 5 ml four times daily |
| Type-B (major DDI) | IV potassium hydrophosphate 10 mmol and IV magnesium sulfate 20 mmol |
| Type-C (moderate DDI) | IV morphine 1 mg/1 mL and IV tramadol 50 mg three times daily |
| Type-D (minor DDI) | IV midazolam/morphine 1 mg and IV ranitidine 50 mg three times daily |

DDI: drug-drug interactions; IV: intravenous

(p = 0.001) and correlated (p = 0.001) with the occurrence of DDIs. Number of drugs > 10 (OR 0.072, 95% CI 0.019–0.277, p = 0.001) was significantly associated with the occurrence of DDIs. The list of study risk factors associated with the occurrence of DDIs is presented in Table IV. The number of DDIs identified in the patients was 1–26 (mean 6.5 ± 5.5), while the number of drugs prescribed was 2–24 (median 11). The relationships between duration of stay and number of drugs with the occurrence of DDIs are shown in Table V, while the drug- and prescriber-related factors are presented in Table VI.

Based on their respective levels of severity, the DDIs were categorised as Type-A (0.2%), Type-B (15.7%), Type-C (75.9%) or Type-D (8.2%). As Type-A and -B DDIs were considered clinically significant in this study, they occur in more than one out of every seven DDIs. Regarding the management of clinically significant DDIs, 'substitution of involved drugs' was recommended in 34 (8.5%) cases of DDI, 'dosage adjustment' in 17 (4.2%) and 'stopping or avoiding the drug combinations' in 13 (3.2%) cases. For DDIs that were classified as Type-C, monitoring of the patients (hepatic function, renal function, ECG, blood counts, etc) was recommended by the pharmacists. Some examples of DDIs that occurred among the study population are presented in Table VII.

The mean length of ICU stay was 5.3 ± 3.7 (range 2–19) days. The length of ICU stay was significantly different for patients in the Case (9.5 days) and Control (2.4 days) groups (p = 0.001). The mean duration of drug therapy involved in Type-A DDIs was found to be two days; however, only one drug combination was categorised under Type-A. The mean duration of drug therapy involved in Type-B DDIs was 3.4 ± 2.7 days, and those for Type-C and Type-D were 2.69 ± 2.3 days and 2.5 ± 1.6 days, respectively.

## DISCUSSION

This study reports a high frequency of occurrence of DDIs, but only a small number of them appeared to be clinically significant. A median of four (range 1–26) DDIs occurred and 11 (range 2–24) drugs were prescribed to patients who stayed in the ICU for an average 5.3 ± 3.7 days, with no significant gender difference. This finding was in contrast to several other studies that identified female gender as a risk factor associated with the occurrence of DDIs.[19,22,25] While there is no credible elucidation for gender differences, it is possible that they are due to physiological and pharmacological reasons. For example, Hutson at el suggested that as gastrointestinal (GI) motility is affected by sex hormones, the GI transit time is thus slower in females than in males. The pharmacokinetic profiles of some lipophilic drugs could also be attributed to differences in body fat between the genders, resulting in a larger volume of distribution in females compared to males.[31]

Many studies have documented that the use of medication tends to increase with age due to the prevalence of multiple chronic diseases corresponding with advancement in age and eventually more diagnoses,[32-35] which increases the possibilities of DDIs. In this study, a positive relationship was found between age and the occurrence of DDIs, with patients aged > 50 years more likely to develop DDIs. This finding is in agreement with a large Swedish population-based study, which established a positive correlation between age groups and the occurrence of DDIs.[17] It has also been found that the risk of adverse reactions caused by DDIs is higher in the elderly population due to changes in pharmacokinetic and pharmacodynamic interactions.[34] In our study, more than three-quarters of the patients with renal and hepatic impairments were identified with DDIs.

It is widely accepted that the more comorbid conditions a patient has, the greater the number of drugs that is likely to be taken, and therefore, the higher the risk that a DDI may occur. About 80% of the patients with 1–2 or > 3 comorbidities were identified with DDIs compared to 70% of the patients without comorbidities. Likewise, several studies have reported multiple illnesses as one of the risk factors associated with DDIs.[19-27,31-35] Prescribed drugs with a narrow therapeutic index were not found to be significantly associated with the occurrence of DDIs. In contrast, previous studies have reported that drugs with narrow therapeutic indices, such as oral anticoagulants, hypoglycaemic agents and digoxin, were most often involved in DDIs.[15]

Our study found that the duration of ICU stay was significantly associated with the occurrence of DDIs. This is in accordance with the results from previous studies, which reported that a two-fold increase in the duration of ICU stay resulted in significant DDIs.[36,37] In particular, duration of ICU stay > 7 days was identified as a risk factor associated with the occurrence of DDIs. It has been accepted that an increase in duration of ICU stay would result in an increased number of prescribed drugs, which may in turn prolong the duration of drug therapy, thus exposing patients to a higher probability of DDIs. Moreover, patients who are admitted to the ICU have a considerably higher risk of DDIs than the average patient, as most of them are critically ill and have more medical problems. In addition, the number of drugs prescribed to patients was also significantly associated and correlated with the occurrence of DDIs. This is in agreement with previous findings that multiple drugs would predispose patients to the adverse effects of drug therapy such as DDIs.[6,14-15,17,20,32] Seymour and Routledge document that the number of drugs tends to increase with the number of prescribers involved with the patients.[32] On the average, two prescribers and > 1 medical specialty were involved in the prescription of drugs to patients in this study.

When evaluating DDIs, one primary concern was the clinical significance or level of severity of the interaction. Significance relates to the type and magnitude of the effect and subsequently, the necessity of monitoring the patient or altering the therapy to avoid potentially adverse consequences. Although a large number of DDIs were detected in this study, only 64 of them were considered to be clinically significant. More than half of the DDIs were of moderate significance, where monitoring of the DDI was sufficient and concomitant use of precipitant and object drugs was not harmful. Egger et al likewise reported that the majority of DDIs found in their study were of moderate severity (n = 281, 69.9%).[38] Although a few studies have documented that potentially significant DDIs were highly prevalent, the number of DDIs associated with potentially relevant clinical consequences was relatively low and rare.[2,33,38] Interestingly, a study by Rivkin reported that more than half of all ADRs in the medical ICU resulted from DDIs, and thus concluded that 100% of DDIs could be prevented.[39]

An appropriate approach to the management of DDIs should be based on identifying the potential DDIs and then taking the necessary measures, such as therapeutic drug monitoring or dose adjustment, to reduce the likelihood of clinically relevant consequences. 64 (15.9%) clinically significant DDIs were forwarded with the consultation of the ICU pharmacist in this study. However, more than half of the study patients were still administered the same drugs found to be involved in clinically significant DDIs (Type-A and Type-B). This may be due to the fact that some DDIs are clinically important for the proper treatment of certain diseases, although their combination may bring unfavourable outcomes. Indeed, monitoring and follow-up are crucial in order to minimise negative health outcomes in such situations, especially for drugs whose therapeutic effects may be augmented or diminished if given together.[20,40] While some drug interactions do result in laboratory changes (i.e. drug-lab interactions), they may be acceptable if no clinically significant outcomes are produced.[40] It has been previously documented that the clinical significance of a potential DDI is not easily established and may require individual assessment.[12] Pharmacists, along with physicians and nurses, are an integral part of the healthcare system, and they can play an important role in establishing the clinical significance of DDIs and its management. It has also been reported that the participation of a

pharmacist on medical rounds can reduce the risk of adverse drug events such as DDIs.[41]

In conclusion, a relatively high frequency of occurrence of DDIs among patients on daily follow-up was identified in this study. However, most of them were of minor-to-moderate clinical significance, where monitoring of the patient was adequate to prevent harmful consequences. Female gender, age > 50 years, use of > 10 drugs and duration of ICU stay > 7 days were identified as risk factors (either patient- or drug-related) associated with the occurrence of DDIs. It has been proven that the participation of a well-trained pharmacist on medical rounds can aid in recognising the risk of adverse drug events such as DDIs. Thus, physicians, pharmacists and nurses should be more vigilant toward potential DDIs among patients, especially those admitted to critical care. The point-of-care pharmacist has fewer limitations compared to drug interaction software programmes in terms of dosage, time of administration, duration of treatment and underlying diseases, which cannot be controlled by a DDI programme.

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