Prevalence of clinically relevant drug-drug interactions in Cardiac Intensive Care Units in tertiary care hospitals in the United States and Pakistan

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Abstract

Objective To determine the prevalence of clinically relevant drug-drug interactions in an intensive care unit of a tertiary care hospital in the United States and to compare to an intensive care unit at a Pakistani hospital, which lacks electronic medical record-based drug-drug interaction screening. Study setting A retrospective cross-sectional analysis was conducted in the cardiovascular intensive care unit (CVICU) at Michigan Medicine (MM), Ann Arbor, MI, USA between Jan 2018 – Jan 2019. Study Design Analysis of 300 MM patients was conducted to identify drug-drug interactions using Micromedex® and Lexicomp®. Descriptive statistics and multivariate binary logistic regression was used. Independent samples t-test was used to compare prevalence between MM and in a similar cohort of patients in the cardiac intensive care (CCU) at KTH, Pakistan from a previously published study. Data Collection Data was collected for patients who were admitted to the CVICU for at least 24 hours and were prescribed at least 2 drugs from the electronic health record of MM. Principal Findings In the intensive care unit of the US hospital, 58% of patients had at least one drug-drug interaction, while 16% had a clinically relevant drug-drug interaction. Significantly fewer patients had drug-drug interactions at the US hospital than the Pakistani hospital (58% vs. 95%, $p < 0.01$). Polypharmacy and length of stay increased drug-drug interaction occurrence in the US hospital ($p < 0.01$). Conclusion The prevalence of drug-drug interactions in the intensive care unit at the US hospital was high but lower than the Pakistani hospital, likely due to electronic medical record-based screening. Despite electronic medical record-based screening at the US hospital, 8 clinically relevant drug-drug interaction pairs were undetected.

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Data was collected for patients who were admitted to the CVICU for at least 24 hours and were prescribed at least 2 drugs from the electronic health record of MM.

Principal Findings

In the intensive care unit of the US hospital, 58% of patients had at least one drug-drug interaction, while 16% had a clinically relevant drug-drug interaction. Significantly fewer patients had drug-drug interactions at the US hospital than the Pakistani hospital (58% vs. 95%, $p < 0.01$). Polypharmacy and length of stay increased drug-drug interaction occurrence in the US hospital ($p<0.01$).

Conclusion

The prevalence of drug-drug interactions in the intensive care unit at the US hospital was high, but lower than the Pakistani hospital, likely due to electronic medical record-based screening. Despite electronic medical record-based screening at the US hospital, 8 clinically relevant drug-drug interaction pairs were undetected.

KEY WORDS: Drug-drug interactions, intensive care units, electronic medical record-based screening, clinically relevant drug-drug interactions.

What is known on this topic:

DDIs are high in critical care units

EMR based DDI screening may reduce DDIs in a hospital

What this study adds:

Despite the presence of EMR based DDI screening, clinically relevant DDIs occur.

Presence of an EMR based DDI screening likely reduces the potential clinically relevant DDIs in cardiac intensive care units.

INTRODUCTION

Cardiovascular disease (CVD) is the leading causes of death worldwide, with an estimated 17.9 million deaths annually [1]. Patients with CVD often have a constellation of comorbidities requiring polypharmacy for symptom control and avoidance of clinical deterioration[2]. Polypharmacy can lead to drug related problems including drug-drug interactions (DDIs)[3], which occur when co-administration of two drugs affects their pharmacological response [4]. DDIs can reduce treatment efficacy or increase toxicity, so preventing DDI is critical to optimize treatment outcomes [5].

Patients admitted to intensive care units (ICUs) have serious medical conditions and are often managing multiple co-morbidities requiring polypharmacy, elevating their risk of DDIs [6]. DDI avoidance in this population is critically important as fluctuations in drug concentrations and effects may be particularly harmful to ICU patients [7]. The prevalence of DDIs in intensive care units ranges from 27% to 95% [8-11], depending on the ICU setting, study population, hospital's systems for DDI detection, and severity level that is considered a DDI.

DDIs can be prevented by combining systems for DDI detection with pharmacists to manage detected DDIs [12]. Computerized order entry systems built into electronic medical records (EMR) that provide automatic DDI warnings enhance patient safety[13] by reducing medication errors [14], DDIs and their resultant adverse events [15]. At Michigan Medicine (MM) a tertiary care hospital in the United States, the DDI screening

tool incorporated within its EMR provide DDI alerts to the pharmacists, nurses and physicians who make decisions based on patient's individualized therapy.

The primary objective of this study was to determine the prevalence of clinically relevant DDIs in a Cardiac ICU unit at MM, equipped with automated DDI screening within its EMR. A secondary objective was to compare the prevalence of DDIs at MM with a Cardiac ICU at Khyber Teaching Hospital (KTH) in Pakistan, a tertiary care hospital that lacks an EMR and automated DDI screening software.

METHODS

Study design and data collection

A retrospective cross-sectional analysis of the prevalence of DDIs and was conducted in the cardiovascular intensive care unit (CVICU) at MM, Ann Arbor, MI, USA. A cohort of 1,320 patients admitted to the CVICU between Jan 2018 – Jan 2019, was obtained from DataDirect, a tool providing access to EMR data from patients at MM. The sample size for this representative analysis was calculated using the formula for known populations [16], (the anticipated prevalence was considered as 50% (P = 0.5); 5% margin of error was considered (d = 0.05); and 95% confidence level (Z = 1.96) was used)[11], resulting in a sample of 298 patients, which was rounded to 300. Three hundred patients who were admitted to the CVICU for at least 24 hours and prescribed 2 or more drugs were randomly selected from the cohort for inclusion in the study and their full medication profile during their CVICU stay were obtained from MiChart, the EMR of MM, while only concomitant medications were included in the analysis for DDIs. Topical medications, sterile bulk preparations and medications administered on an as needed basis were excluded from the analyses.

Drug-drug Interactions

DDIs were analyzed using Micromedex® (Watson health, IBM Corporation), and categorized on the basis of severity (contraindicated, major, moderate, minor) and documentation (excellent, good, fair). DDIs were included in the analyses if they fit into either of two categories: Category 1: severity of contraindicated, or severity of major with excellent/good documentation; or Category 2: severity of moderate with excellent/good documentation. DDI that did not satisfy criteria for inclusion in category 1 or 2 were not included in these analyses. DDIs were also screened for clinical relevance by Lexicomp® (Wolters Kluwer Health, Hudson, OH), based on having a severity category D or X, which was selected due to its superior performance for detecting clinically relevant DDIs.[17] Commonly identified DDIs were further included for analysis. Finally, DDI that generated an alert in MiChart were classified as having been detected by the EMR **(Figure 1).**

Statistical analysis

Descriptive statistics were used to report means with standard deviation and percentages. Multivariate binary logistic regression was used to identify predictors of DDI (category 1 or 2) occurrence including number of prescribed drugs, length of ICU stay, and patient gender and age. Number of prescribed drugs and length of ICU stay were dichotomized by the median for analysis.

DDIs in a similar cohort of patients in the cardiac intensive care (CCU) at KTH, Pakistan from a previously published study [11]was analyzed using criteria similar to current study and the number of DDIs were compared using independent samples t-test. To maintain consistency with the prior analysis, prevalence of category 1 and 2 DDI were compared between the two institutions. Statistical analyses were performed using IBM SPPS Statistics for Windows, Version 25 (Armonk, NY: IBM Corp.).

Ethics Approval

The study was determined to be exempt subject research by the Institutional review board (IRBMed) of MM (HUM00166927).

RESULTS

Demographics

Medication profiles of 300 MM CVICU patients were evaluated, of which 65.7% were males **(Table 1)** . The mean age was 62 (standard deviation: ± 13) years, number of prescribed drugs was 6.0 (± 2.55), and stay in the ICU was 3.97(± 3.70) days. The previous study of patients at KTH included 260 patients, of which 59.2% were males. The mean age was 56 ± 13 years, which was significantly lower than in MM ($p< 0.01$), but there was a similar number of prescribed drugs (5.79 ± 1.67) and stay in the CCU (3.73 ± 1.44 days).

Prevalence of DDIs

At least one DDI was detected in 58% of patients and at least one category 1 DDI was detected in 47.3% of patients. Further screening by Lexicomp® indicated that 16.3% of patients had a clinically relevant DDI and 13% of patients had a DDI that was detected by the EMR**(Table 2)** .

Compared with KTH, fewer patients at MM had a DDI (58% vs. 95%,$p < 0.01$) and nominally fewer patients had a category 1 DDI (47% vs. 65%), though the difference was not statistically significant ($p > 0.05$). At MM, 1.57 DDIs per patient were observed while at KTH 3.09 DDIs per patient were observed.

Predictors of DDIs

In the multivariate binary logistic regression analysis, the presence of DDIs at MM was 7.2 (95% confidence interval: 3.89 – 13.33) times greater in patients prescribed >6 drugs and 3.9 (95% CI: 2.21 – 7.19) times greater in patients with an ICU stay >3 days. In KTH, the presence of DDIs was 2.8 (95% CI: 1.49 – 5.23) times greater in patients prescribed 6 or more drugs, while stay in the ICU had no significant effect ($p>0.05$). Age and gender of the patients had no effect on the presence of DDIs in either hospital**(Table 3)** .

Drug Interacting Pairs

Table 4 lists the 17 unique DDI pairs observed at MM that were confirmed to be clinically relevant by Lexicomp®. These 17 pairs occurred 66 times and the EMR detected 9 of these pairs, which occurred 52 times. Two unique drug pairs accounted for 57.1% of the undetected DDIs: omeprazole-tacrolimus and amiodarone-simvastatin. In KTH, two unique pairs were responsible for 75.5% of DDIs: clopidogrel-esomeprazole and aspirin-enoxaparin.

DISCUSSION

Polypharmacy is common in patients with cardiovascular disease[13], increasing risk of DDIs[8] that worsen treatment outcomes [18]. DDI screening tools embedded within EMR can assist with DDI identification and management, however, DDIs are still highly prevalent [14]. The objective of the current study was to evaluate the prevalence of DDIs in the CVICU at MM and to compare it to the prevalence in an ICU in KTH, Pakistan. Our study confirmed a high prevalence of DDIs in MM (58%), but a significantly lower prevalence than KTH (95%, $p< 0.01$).

Estimates of DDI prevalence worldwide varies from 38% to 71%, depending on the study setting, population and tools employed to evaluate DDIs [8, 19, 20]. At MM 1.57 DDIs per patient were present, which is lower than the DDIs per patient at KTH (3.09) or reported from an ICU in Serbia (˜6). The lower prevalence of DDI at MM likely reflects the effectiveness of DDI screening by the EMR, as there is no computerized DDI screening system at KTH or Serbia [21].

Polypharmacy and longer ICU stay increased risk of DDIs in MM (both,$p < 0.01$), while in KTH only polypharmacy increased DDI risk ($p < 0.01$). Polypharmacy and length of stay have been previously reported to increase DDI risk in various studies conducted in the US and worldwide [22-25]. Gender and age have also been reported to be associated with DDIs[22-25] but were not associated with DDIs in MM or KTH ($p > 0.05$). Prior reports of association may have been due to analyzing cohorts from mixed treatment units with mixed disease states, which could introduce issues with confounding.

Of the total clinically relevant DDI observed in MM CVICU patients, only 21% (14/66) were undetected by the MM EMR. In comparison, 100% of clinically relevant DDIs are undetected at KTH due to the lack of any DDI screening system. Recent studies highlighted the effectiveness of EMR based DDI detection

tools and pharmacists in reducing medication errors and DDIs [26-28]. Thus implementation of an EMR based DDI screening tool and pharmacist screening could help prevent DDIs at KTH. At MM, a subset of clinically relevant DDIs were not detected by the EMR. Of the 8 DDI pairs that were not detected, 2 pairs resulted in 57% of observed DDIs. The DDI of tacrolimus and omeprazole is important in transplant patients as omeprazole may increase tacrolimus concentrations leading to increased risk of hepatotoxicity and nephrotoxicity [29, 30]. EMR DDI detection systems could be further improved by enhancing information display and contextualization, and providing DDI management recommendations that are tailored to the individual provider and unit [31].

Strengths of the study include a large sample size, inclusion of all concurrently administered drugs and use of multiple tools to analyze clinical relevance of DDIs. However, several limitations should be considered. This study was conducted in a single unit of a single tertiary care hospital, limiting the generalizability of these findings. Additionally, the retrospective study design precludes meaningful analyses of the number of DDIs that were detected and appropriately managed.

CONCLUSION

In conclusion, 47.3 % of ICU patients at MM had a clinically significant DDIs, and ICU patients at MM had lower rates of DDIs than patients at KTH, likely due to the presence of EMR based screening. Additional studies at a variety of units and institutions are needed to determine the relative effectiveness of EMR-based screening tools and pharmacists. Outcome studies are also needed to validate that clinically relevant DDIs have meaningful effects on patient outcomes. Finally, improvements are needed to EMR-based DDI screening tools and systems to detect and manage DDIs to ensure all patients receive safe and effective treatment.

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Table 1: Patient general characteristics

Variables	US Hospital n (%) n = 300	Pakistani Hospital n (%) n=260	p value
Gender (%) Male Female	197 (65.7) 103 (34.3)	154 (59.2) 106 (40.8)	0.16
Age (years) Mean ± SD Range [?] 18 19-59 [?] 60	62.45 ± 13.35 24 – 89 – 104 (34.7) 196 (65.3)	56 ± 13.49 17 – 100 2 (0.8) 137 (52.7) 121 (46.5)	< 0.01*
Prescribed drugs Mean ± SD Range [?] 4 5-6 [?] 7	6 ± 2.55 2 – 14 105 (35) 82 (27.3) 113 (37.7)	5.79 ± 1.67 2 – 12 60 (23.1) 117 (45.0) 83 (31.9)	0.24
Stay (days) Mean ± SD Range [?] 2 3-4 [?] 5	3.97 ± 3.70 1 – 29 139 (46.3) 73 (24.3) 88 (29.4)	3.73 ± 1.44 2 – 13 35 (13.5) 171 (65.8) 54 (20.7)	0.29

SD standard deviation

* Statistically significant

Table 2: Stepwise distribution of drug interaction data

Variable
Patients with DDI Total patients Category 1 or 2 DDIs Category 1 DDIs Clinically relevant DDIs EMR-Detected DDIs

DDIs Drug-drug interactions, EMR electronic medical record

*not reported for cohort

Table 3: Multivariate Logistic Regression Analysis

Variable	**OR (95%CI)**
	US Hospital
Prescribed drugs [?] 6 > 6 Duration of stay [?] 3 > 3 Gender Male Female Age [?] 60 >60	Reference 7.196 (3.885-13.330)

OR odds ratio, CI confidence interval

* Statistically significant

Table 4: Drug-drug interactions observed in the cardiovascular intensive care unit of the US hospital confirmed by Lexicomp ®

Interacting drug pair	n	Outcome
amiodarone-colchicine	1*	Increased colchicine plasma concentrations and increased risk of colchicine toxicity
amiodarone-digoxin	4*	Digoxin toxicity (nausea, vomiting, cardiac arrhythmias) and potentiated effects of amioda
amiodarone-fluconazole	8*	Increased amiodarone exposure and an increased risk of cardiotoxicity
amiodarone-rifampin	3*	Decreased efficacy of amiodarone
amiodarone-warfarin	15*	Increased risk of bleeding
clopidogrel-omeprazole	12*	Reduced plasma concentrations of clopidogrel active metabolite and reduced antiplatelet a
fluconazole-tacrolimus	2*	Increased tacrolimus exposure and risk of tacrolimus toxicity, including QT-interval prolon
fluconazole-warfarin	6*	Increased risk of bleeding
isosorbide-sildenafil	1*	Potentiation of hypotensive effects
amiodarone-simvastatin	3	Increased exposure to simvastatin and an increased risk of myopathy or rhabdomyolysis
amlodipine-simvastatin	1	Increased simvastatin exposure and increased risk of myopathy, including rhabdomyolysis
atorvastatin-colchicine	1	Increased colchicine exposure; an increased risk of myopathy or rhabdomyolysis
atorvastatin-diltiazem	1	Increased risk of rhabdomyolysis
esomeprazole-tacrolimus	1	Increased tacrolimus exposure
lamotrigine-primidone	1	Decreased lamotrigine efficacy
metronidazole-warfarin	1	Increased risk of bleeding
omeprazole-tacrolimus	5	Increased tacrolimus exposure

***** EMR detected DDIs

Figure Legends

Figure 1: Stepwise analysis of drug-drug Interactions

Representation of analysis of drug-drug interactions in the US hospital patients categorized using Micromedex® and further screened by Lexicomp®. Comparison made to Pakistani hospital patients at level of category 1 or 2 drug-drug interactions.

DDIs Drug-drug interactions

*Drug-drug interactions were considered clinically relevant if they were category X or D in Lexicomp®