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# The Effect of the Number of Potential Drug-Drug Interactions and Prescribed Medications on Length of Stay and Mortality Rate of Patients in The Intensive Care Unit

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## Abstract:

**Introduction:** The incidence rate of potential drug-drug interactions (PDDIs) in medical prescriptions was reported from 5.4% to 63% depending on the studied population, duration of the study, and different methods used to classify them. The importance of DDIs is in terms of their impact on clinical outcome. The main aim of this retrospective study was the evaluation of the impact of DDIs on ICU outcome i.e. ICU Length of stay (ICULS) and mortality.

**Methods and Results:** The prescribed medications of 262 patients older than 18 years with ICULS more than 48 hours admitted to the ICU during 8 months were evaluated for the risk of PDDIs. We detected a significantly increased ICULS (from 7.03 ± 5.49 days to 19.14 ± 17.64 days, $p$=0.035) and mortality rate (OR, 3.76; 95% CI 1.47-9.62; $p$=0.006) in patients with at least one D or X interaction compared to those without them. The frequency of these interactions was 73.6%. We also observed a significant association between the number of prescribed medications (r=0.79, $p$=0.001) and PDDIs (r=0.86, $p$=0.001) with increased ICULS.

**Conclusion:** According to the high prevalence of PDDI among ICU patients due to their large number of prescribed medications, long time of treatment, and complicated diseases, and its significant positive correlation with ICULS and mortality, it is recommended to monitor the medications of patients who received more than 5 drugs for interactions to increase the chance of prevention of significant PDDIs and decrease LOS, costs, and mortality.

**Keywords:** Drug-Drug Interactions; Length of Stay; Mortality; Prescribed Medications; Outcome

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## 1. Introduction

Drug-drug interactions (DDIs) occur when the effect of one drug is altered by the presence of another drug that could result in increased toxicity or reduced therapeutic efficacy [1]. The incidence rate of potential DDIs (PDDIs) in medical prescriptions was reported from 5.4% to 63% depending on the studied population, duration of the study, and different methods used to classify

them [2-8]. DDIs are classified into pharmacokinetic(PK) and pharmacodynamic(PD) interactions. PK interactions when happening with one drug affects the absorption, distribution, metabolism, or excretion of another drug. PD interactions are those which the effects of one drug are changed by the presence of another [9]. DDIs can fail treatment and cause adverse drug reactions (ADRs) [9]. ADRs have clinical and economic outcomes such as the increased likelihood of hospitalization, prolonged hospital stay, increased costs of health services, and can lead to an increase in morbidity and mortality rate [10]. The importance of DDIs in terms of their impact on clinical outcome was reported by some studies [8, 11-13].
The risk of PDDIs was reported higher among ICU patients due to a large number of prescribed medications, long duration of therapy, and comorbidities such as renal and liver failure that is the alterating PK and PD properties of drugs [11, 12].
The main aim of the study was the evaluation of the impact of DDIs on ICU outcome i.e. ICU Length of stay (ICULS) and mortality, the frequency of PDDIs among the ICU patients, and the correlation between the number of prescribed medications and PDDIs with ICULS.

## *2.* Materials & Methods

### 2.1. Setting and study population

This retrospective study was conducted at a medical-surgical ICU, Imam Hossein Medical Center affiliated with Shahid Beheshti University of Medical Sciences (SBMU), Tehran, Iran. The prescribed medications of all patients older than 18 years with ICULS more than 48 hours admitted to the ICU between September 2017 and April 2018 were evaluated for the risk of PDDIs. Determination of PDDIs was carried out using the online Lexi-Interact™ 2017.
Baseline characteristics of eligible patients including age, sex, Acute Physiological Chronic Health Evaluation (APACHE) II score, and also their outcome i.e. ICULS and mortality rate were recorded. Daily prescriptions were gathered in a pre-designed Microsoft Access database.

### 2.2. Definitions

The severity of PDDIs is categorized as classes A, B, C, D, and X. In general, PDDIs categorized as A or B are academic, but not a clinical concern. Those rated C, D, or X always require the physician's attention [12].
Significant DDIs were considered as the experience of at least one D or X interaction.
Patient-days were calculated as the total number of patients occupying beds in the ICU for all days in the study period.

### 2.3. Outcome

The impact of significant DDIs on ICU outcome i.e. ICULS and mortality rate was assessed as the main aim of the study. The frequency of PDDIs among the ICU patients and the correlation between the number of prescribed medications and PDDIs with ICULS were considered as secondary outcomes.

### 2.4. Statistical analyses

All statistical analyses were performed using the STATA software (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LP). Categorical variables were reported as count (percentage, %) and Continuous variables as mean± standard deviation (SD). Quantitative data were tested for normality of distributions by the Kolmogorov–Smirnov test and then compared by unpaired student's t-test and Mann–Whitney U test for normal and non-normal distribution data, respectively. A Pearson's correlation coefficient was computed to assess the relationship between variables. Cox proportional hazard model was used for evaluating the association between the patient outcome and predictor variables that were reported as Hazard ratios (HR) and their 95% confidence intervals (CIs). A *P*-value of $< 0.05$ was considered statistically significant.

## 3. Results

From 262 patients who were eligible for the study, 12 patients were excluded due to lack of prescription information, and data from 250 patients with 3986 patient-days were analyzed. The baseline characteristics of participants were presented in Table1.

**Table1.** Baseline characteristics of participants

| | | |
|---|---|---|
| **Sex** | **Male, n (%)** | 156 (62.40) |
| | **Female, n (%)** | 94 (37.60) |
| Age (year), mean±SD | | 52.42±22 |
| APACHE II* score (day), mean±SD | | 27.08±24.27 |
| ICULS** (day), mean±SD | | 15.16±9.3 |
| Mortality, n (%) | | 74 (29.60) |

* APACHE II score, Acute Physiological Chronic Health Evaluation II score; ** ICULS, ICU Length of stay

We detected that from 250 included patients, 184 ones (73.6%) experienced at least one significant DDIs. The ICULS was 19.14 ± 17.64 days in these patients compared to 7.03 ± 5.49 days in patients without D or X interactions (*P*=0.035). The Kaplan-Meier curves showed the probability of discharge from the ICU and ICULS in patients with and without D or X interactions

(Figure 1). The evaluation of the impact of X interactions on ICULS also showed a significantly higher ICULS in 60 patients (24%) who had at least one X interaction (25.67±20.86 days) compared to those who did not (12.87±13.19 days) (*P*=0.049).

The assessment of the correlation between the D or X interactions with mortality rate by the Cox proportional hazard model showed APACHE II as a significant intervening variable. By adjusting the APACHE II score, the mortality rate in patients with at least one D or X interaction was 3.76 times more than patients without any D or X interactions (OR, 3.76; 95% CI 1.47-9.62; *P*=0.006).

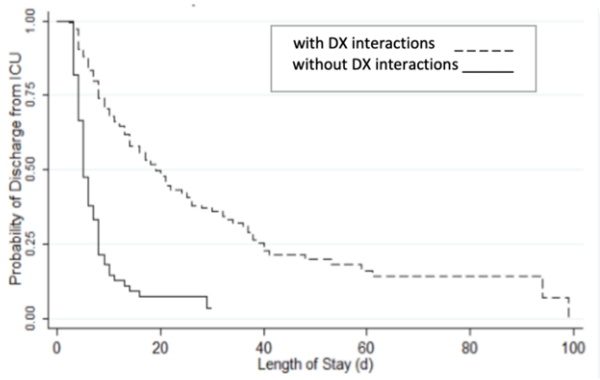


**Figure 1. Kaplan-Meier curves for patients with and without D or X interactions,** the probability of discharge from the ICU and ICULS in patients with and without D or X interactions.

From all medications administered during the 3986 patient-days, we recorded a total of 50364 PDDIs that 14.16% and 2.73% categorized as D and X interactions, respectively. The frequency of DDIs in A to X categories was showed in Figure 2. Significant DDIs were detected among 73.6% of ICU patients.

We observed a significant association between the number of prescribed medications (r=0.79, *P*=0.001) and PDDIs (r=0.86, *P*=0.001) with increased ICULS.

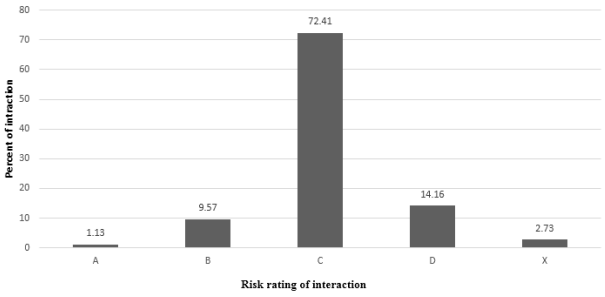


**Figure 2. Percent of interactions,** The frequency of drug-drug interactions in A to X categories.

## 4. Discussion and Conclusion

This study showed a significantly increased ICULS (from 7.03 ± 5.49 days to 19.14 ± 17.64 days, *P*=0.035) and mortality rate (OR, 3.76; 95% CI 1.47-9.62; *P*=0.006) in patients with at least one D or X interaction compared to those without them. The frequency of these interactions was 73.6%. The overall prevalence of PDDIs in the ICU has been reported to range between 44.3% and 87.9% with other studies based on the differences in study design, and software sensitivity, and specificity [13-15]. The correlation between the significant PDDIs with clinical outcomes was also reported by some studies [8, 11-13]. The median ICULS was 12 days in patients with at least one PDDIs during their hospitalization in comparison to 5 days for patients without that (*P*<0.01) [12]. Also, Reis et al. reported a significantly higher ICULS among patients who experienced one or more PDDIs in the first 24 hours of hospitalization than others (*P*<0.001) [13].

We observed a significant association between the number of prescribed medications (r=0.79, *P*=0.001) and PDDIs (r=0.86, *P*=0.001) with increased ICULS. This significant correlation between the ICULS and the number of PDDIs (*P*<0027) was also reported by Rodrigues et al [16]. The number of prescribed medications was considered as a high positive predictive value for the increased risk of PDDIs [11, 13, 16]. It is showed that the use of more than 6 drugs/day was associated with an increased risk of significant PDDIs by 9.8 times [11]. These results demonstrate the fact that more drugs were administered in patients with a longer hospital stay such as critically ill patients, resulting in a higher probability of PDDIs. Also, critically ill patients with higher severity of illness are more likely to have polypharmacy and the potential to develop PDDIs.

In conclusion, the incidence of PDDIs among ICU patients is high. A large number of prescribed medications, long time of treatment, and complicated diseases are risk factors for developed PDDIs. The significant positive correlation between PPDIs with ICULS and mortality is a reason for monitoring the potential PDDIs in patients who received more than five drugs to increase the chance of prevention of significant PDDIs and decrease ICULS, the huge cost burden on healthcare, and mortality.

## List of abbreviations

ADRs: Adverse drugs reactions
DDIs: Drug-Drug Interactions
PDDIs: Potential DDIs
PD: Pharmacodynamic

PK: Pharmacokinetic
ICULS: Length of Stay in the Intensive Care Unite
APACHE II score: Acute Physiological Chronic Health Evaluation II score

## Author Contributions:

MS, MM, MK, MMM, and MH designed the study. DM reviewed the literature and gathered data. Drafting of the proposal was done by DM and MS. RH analyzed and interpreted data and EP wrote the manuscript and edited it according to the guide to the author of the journal. All authors helped to manuscript improvement and finalize the article for publication.

## Conflict of interest

All authors declare no potential conflicts of interest for the research, authorship, and/or publication of this article.

## Ethics

Although the article does not contain a corresponding regional or institutional code of ethics, the IPA decision on publishing this retrospective article resulted from the review of patients' files is based on the COPE and NEAC guidelines for these circumstances

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