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THE IMPACT OF REPEAT ADMISSIONS ON DRUG-DRUG INTERACTION RISK IN HEART FAILURE PATIENTS

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ABSTRACT

Background: Drug-drug interactions (DDIs) pose a significant risk to hospitalized patients, particularly those with heart failure who often have complex medication regimens. . However, it remains unclear how this interaction risk profile—specifically its frequency and severity—evolves with recurrent hospitalizations. Therefore, this study aimed to determine the occurrence and characteristics of potential DDIs, focusing on changes in their frequency and severity across multiple admissions. **Method:** This retrospective observational study analyzed data from the electronic medical records of 332 heart failure patients who had 494 hospitalizations between 2022 and 2023 at Universitas Sebelas Maret Teaching Hospital. The study aimed to determine the occurrence and characteristics of potential DDIs, focusing on changes in their frequency and severity across multiple admissions. **Result:** A total of 7,562 potential DDIs were identified. The majority (81.4%) were classified as "Monitor Closely," while "Serious" interactions accounted for 8.0%. The overall frequency of DDIs remained stable across subsequent hospitalizations. Critically, the number of serious drug interactions showed a statistically significant decrease with each successive admission. The most frequent "Serious" interaction was between aspirin and captopril. **Conclusion:** Potential DDIs are highly prevalent in hospitalized heart failure patients, but their overall frequency does not increase with repeat hospitalizations. The significant reduction in serious DDIs with subsequent admissions suggests that current clinical safety systems and interventions are effective at progressively mitigating the most dangerous medication-related risks over time.

Keywords: drug-drug interactions, heart failure, medication safety, polypharmacy, hospitalization

INTRODUCTION

Heart failure is a complex chronic condition that necessitates management with multiple medications, placing patients at a heightened risk for drug-drug interactions (DDIs). These interactions represent a significant public health concern, particularly within inpatient settings where complex, multi-drug regimens are common. The prevalence of clinically evident DDIs among hospitalized patients is substantial, with one meta-analysis estimating it at approximately 17.17%. The clinical and economic burden of these events is equally considerable. In the United States alone, DDIs are estimated to contribute to over 245,000 hospitalizations annually, incurring costs that exceed $1.3 billion (Aksoy and Ozturk, 2023).

Such preventable events can lead to adverse drug reactions, prolong hospital stays, and increase re-hospitalizations, significantly strain healthcare systems (Moura, Acurcio and Belo, 2009; Dechanont et al., 2014).

The risk of DDIs is not uniform and is amplified in populations characteristic of heart failure patients. Polypharmacy, the concurrent use of five or more medications, is a primary risk factor, as the probability of significant interactions increases sharply with each prescribed drug (Das et al., 2019). This is especially pertinent for elderly patients with heart failure, who are more susceptible due to age-related physiological changes that alter drug metabolism (Ahmed, Nanji and Patel, 2015; Khandeparkar and Rataboli, 2017). As a chronic cardiovascular disease, heart failure inherently elevates DDI risk due to its complex therapeutic regimens, which often include drugs with narrow therapeutic indices (Ramos-Esquivel, Víquez-Jaikel and Fernández, 2017; Diksis et al., 2019).

The consequences of DDIs extend well beyond a single hospital admission, contributing significantly to patient morbidity, mortality, and readmission rates (Prasad et al., 2024). The phenomenon known as the "prescription cascade," where a medication's side effect is mistakenly treated with another prescription, can further exacerbate polypharmacy and heighten the risk of adverse outcomes that necessitate more hospital visits (Choi et al., 2023). This highlights that DDIs are not isolated incidents but are deeply interwoven with a patient's overall health journey. Mitigating these medication errors requires applying human factors and systems-based error theories, with medication reconciliation playing a vital role during care transitions (Uitvlugt et al., 2021). Furthermore, the integration of Clinical Decision Support Systems (CDSS) within Electronic Health Records (EHRs) is a pivotal strategy for improving patient safety by providing real-time alerts for potential DDIs (Zikos and DeLellis, 2018; Erawantini et al., 2022).

Despite the well-documented risks, a crucial research gap exists in understanding how these interactions evolve throughout a heart failure patient's care continuum, particularly for those with recurrent hospitalizations. It remains unclear whether DDIs accumulate with each subsequent visit or if clinical interventions effectively mitigate these risks over time (Devani, Patel and Modi, 2022). Therefore, this study aims to determine drug-drug interactions in heart failure patients and characterize these interactions by category. By examining the frequency and severity of DDIs, this research seeks to provide a deeper understanding of how pharmacotherapeutic complexity contributes to DDI risk in this vulnerable population, ultimately identifying opportunities to improve patient safety and outcomes.

METHOD

This observational descriptive study was conducted using a retrospective cohort design at UNS Hospital. De-identified data was collected from the hospital's electronic medical records for patients admitted between 2022 and 2023. The study received ethical approval from the institutional ethics committee (1.573/XII/HREC/2022), ensuring the confidentiality and privacy of all patient information.

The study population included patients aged 18 years or older who were diagnosed with heart failure (ICD-10: I50) and had their first hospitalization for coronary heart disease (ICD-10: I25). Inclusion required documented left ventricular systolic dysfunction (≤50%), receipt of standard heart failure medications, and complete medical records. Patients were excluded if they had congenital heart defects, valve disease, end-stage renal disease, HIV, active malignancy, or an autoimmune disease. Data on patient demographics, prescriptions, and diagnoses were extracted, with focusing on identifying and categorizing potential drug-drug interactions. All data analysis and graph generation were performed using Microsoft Excel and RStudio.

RESULT

This study analyzed potential drug-drug interactions (DDIs) among 332 unique patients over 494 hospitalization visits. The frequency of hospitalizations varied, with many patients having a single visit, while several were hospitalized up to three times.

Distribution and Severity of Drug Interactions

A total of 7,562 potential drug-drug interactions were identified across all hospitalizations. The interactions were classified into four categories based on severity. The overwhelming majority of these interactions, 6,155 (81.4%), fell into the "Monitor Closely" category, indicating that while a potential interaction exists, it can typically be managed with careful patient monitoring. "Minor" interactions accounted for 795 (10.5%) of the total, and "Serious" interactions, which carry a higher risk of adverse events, were observed 606 times (8.0%) (Figure 1). The most critical category, "Contraindication," where the concurrent use of drugs is advised against, was scarce, occurring only 6 times (<0.1%) (Table 1). This distribution underscores that while potential DDIs are common in this patient population, most are of a nature that requires clinical vigilance rather than immediate discontinuation of therapy.

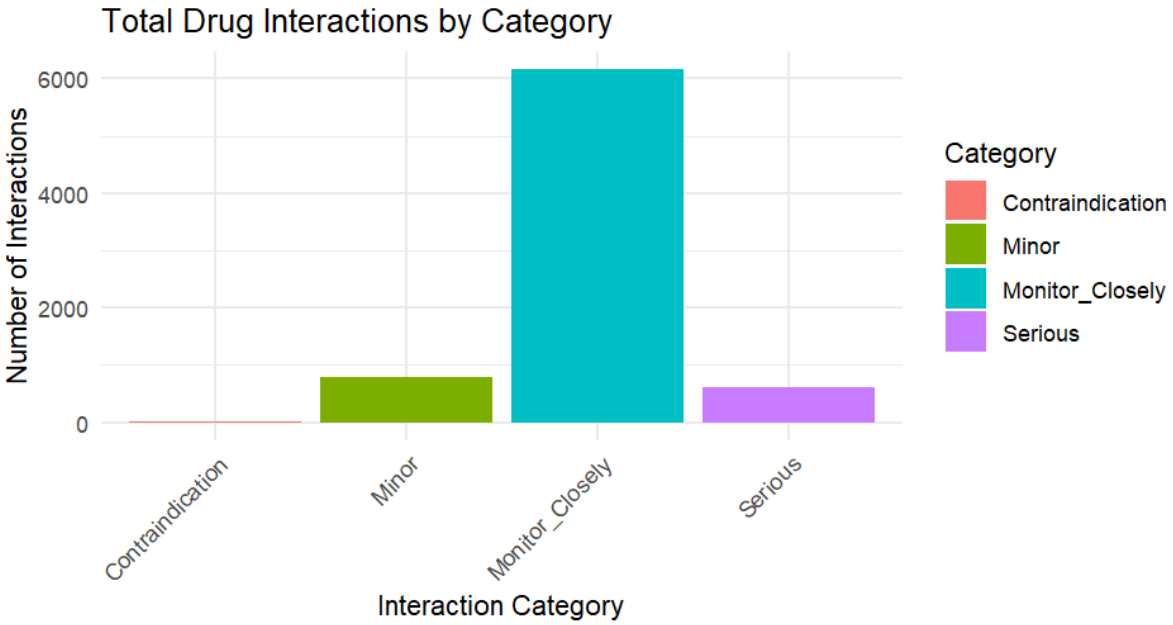

Figure 1. Total Drug Interactions by Category

Table 1. Distribution of Variabel

Category	Count
Monitor_Closely	6155
Minor	795
Serious	606
Contraindication	6

The number of interactions experienced per hospitalization showed significant variability, ranging of 0 to a maximum of 72. The data was right-skewed, with a median of 12.5 interactions per hospitalization and a slightly higher mean of 15.31. This indicates that most hospitalizations involved a manageable number of interactions, but a subset of cases presented a much higher and more complex DDI burden.

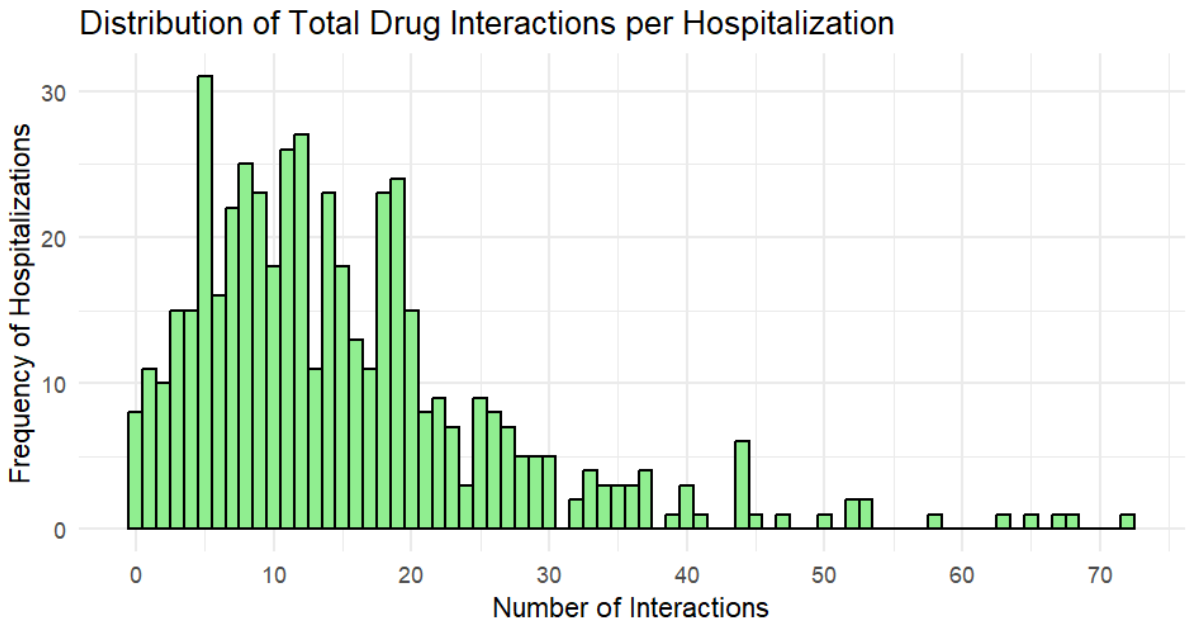

Figure 2. Distribution of Total Drug Interaction per Hospitalization

Most Frequent Interacting Drug Pairs

Analysis of specific drug combinations revealed several recurring pairs. The most frequent interaction observed was between aspirin and furosemide, which occurred 398 times. This was followed by the combination of aspirin and clopidogrel (219 instances) and valsartan and aspirin (190 instances). The prevalence of aspirin in the most common pairs highlights its central role in the therapeutic regimen for heart failure and coronary heart disease.

When broken down by severity, the aspirin + furosemide pair was the most common in both the "Monitor Closely" (220 instances) and "Minor" (178 instances) categories. The most frequent combination for "Serious" interactions was aspirin + captopril, identified in 133 instances. The rare "Contraindication" interactions were primarily attributed to ceftriaxone + calcium carbonate, which occurred twice.

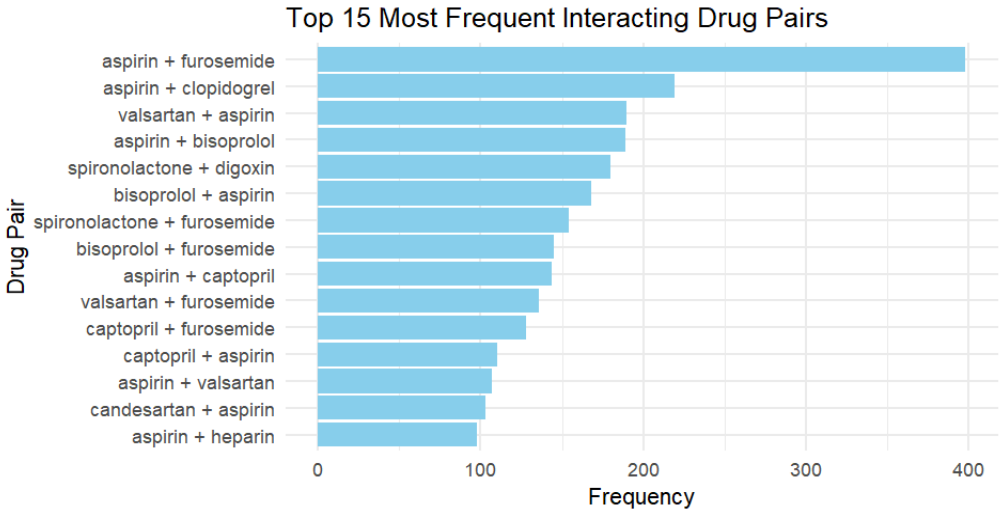

Figure 3. Top 15 Most Frequent Interaction Drug Pairs

DISCUSSION

The primary objective of this research was to determine the occurrence and characteristics of potential drug-drug interactions (DDIs) in hospitalized heart failure patients, with a specific aim to understand how the frequency and severity of these interactions evolve with recurrent hospitalizations.

Main Findings

This study found that while potential drug-drug interactions (DDIs) are highly prevalent in hospitalized heart failure patients, the most clinically significant finding is a negative association between the number of serious interactions and the number of hospitalization visits. Our analysis demonstrated a statistically significant decrease in serious DDIs with each subsequent hospitalization.

Conversely, the total number of interactions does not significantly increase with subsequent hospitalizations. We identified 7,562 potential DDIs, with the vast majority (81.4%) falling into the "Monitor Closely" category. We also found a strong positive correlation between "Monitor Closely" and "Minor" interactions, demonstrating that patients with a higher number of one type of interaction are likely to have others. Furthermore, "Contraindication" interactions were exceptionally rare (less than 0.1% of the total).

Clinical Implications and Comparison with Literature

The high general prevalence of pDDIs (with 81.4% in "Monitor Closely") reflects the clinical reality of managing complex, comorbid conditions where polypharmacy is often necessary (Masnoon et al., 2017). Our prevalence rates align with those of other studies in complex cardiology patients, which report prevalence rates ranging from 72.9% to 97.2%. However, the *severity* distribution varies significantly across the literature; some studies report "Major" interactions as the majority (52.6% or 32.5%), which differs from our finding of 8.0% "Serious". Our lower rate of serious DDIs is, however, comparable to another research that also found them to be rare (e.g., 3.26%).

The finding that total DDIs remain stable is consistent with studies that also found no significant change in *total* pDDIs between admission and discharge. However, our most significant finding—the *decrease* in *serious* DDIs with subsequent visits—contrasts with some literature. For instance, one study found that clinically significant (Type C and X) interactions actually *increased* at discharge, suggesting a potential failure in the de-prescribing process. Our divergent findings are optimistic and strongly suggest that clinical interventions, such as robust medication reconciliation and therapeutic adjustments made during the initial hospital stay, effectively mitigate the most harmful interactions in the long term.

This challenges the assumption that more hospital visits equate to greater DDI risk. Instead, it suggests that improvements in clinical DDI management, such as clinical decision support systems (CDSS) and pharmacist-led medication reconciliation, may be successfully mitigating a potential rise in total DDIs over time (Erawantini et al., 2022; Zheng et al., 2024). The observed reduction suggests a proactive, targeted approach to DDI management can have a lasting, positive impact on patient safety (Hughes et al., 2017). This trend is consistent with systems-based safety theories, where interventions such as CDSS and the involvement of a multidisciplinary team, including clinical pharmacists, enhance medication safety and improve care transitions over time (Fischer and Schwappach, 2022; Ranković, Milentijević, and Janković, 2024; Guntschnig et al., 2025).

The rarity of "Contraindication" interactions (less than 0.1%) likely reflects the success of safety systems in flagging and preventing these well-known, high-risk combinations (Song, Shin and Shin, 2017). Furthermore, our results suggest that while an initial hospitalization may introduce polypharmacy and increase the risk of a prescription cascade, subsequent visits

provide crucial opportunities for healthcare providers to review, de-prescribe, and interrupt this cascade (Yaghmaei et al., 2023).

Limitations

Despite these critical insights, our study has several limitations. The retrospective nature of the data prevents us from establishing a causal link between hospitalization visits and DDI trends. The dataset also had a limited number of patients with three or more hospitalizations, which may affect the generalizability of our findings for patients with very frequent admissions. We could not account for all potential confounding factors, such as changes in a patient's overall health status or the specific reasons for readmission.

Future Work

Future research should prioritize prospective, longitudinal studies with larger cohorts to confirm these findings and integrate patient-reported outcomes and medication literacy assessments to better quantify the impact of DDI management on clinical care and patient engagement (Dechanont et al., 2014; Chao et al., 2018).

CONCLUSION

In this cohort of hospitalized heart failure patients, potential drug-drug interactions were highly prevalent, but their overall frequency did not increase with repeat hospitalizations. Critically, the incidence of serious DDIs significantly decreased with subsequent admissions. This suggests that current clinical safety systems, including medication reconciliation processes and multidisciplinary team oversight, effectively mitigate the most dangerous medication-related risks for patients requiring recurrent care.

Suggestions for future practice include strengthening pharmacist-led medication reviews at every care transition point. Further research should focus on prospective studies to confirm a causal link and identify the clinical interventions that are most effective in reducing high-risk DDIs, thereby enhancing patient safety.

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