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Use of Network Analysis for Identifying Drug Combinations to Prevent ADRs

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INTRODUCTION

The identification of drug combinations is critical to prevent adverse events, such as bleeding, often associated with the concomitant use of different active ingredients. Analysis of interactions using graphs is a useful tool for intuitively and quantitatively representing drug-drug relationships in real-world clinical settings.

OBJECTIVES

This study aimed to estimate the prevalence of potentially clinically important drug-drug interactions (DDIs) and the average causal effect of DDI exposure on hospitalization for bleeding related to adverse drug reactions (ADRs). In addition, identify the type of DDI that could lead to bleeding and the most common co-prescribed therapies responsible for ADRs through a network analysis approach.

METHODS

We performed a retrospective cohort single-center study including all consecutive patients admitted to the Internal Medicine Units of the Niguarda Hospital in Milan for bleeding-related complications from 1 January 2015 to 31 December 2018. Clinical characteristics, comorbidities, and pharmacological treatments were collected for each patient. Medication exposure was defined as the therapy assumed by the patient at the moment of admission. Polytherapy was defined by concomitant chronic use of ≥5 drugs. DDIs were identified using the LexiDrug database. Network analysis was applied to go to identify drug-drug interaction. Networks are a widely used tool for describing and analyzing complex systems, such as biological systems, in which relationships between entities-such as molecules, genes or drugs-play a central role [1,2,3]. In the biomedical context, graphs make it possible to visualize and study molecular interactions, such as those between proteins, genes, or drugs. A graph is a structure composed of a set of nodes (also called vertices) and a set of arcs (or edges) connecting pairs of nodes. Each arc can be characterized by a weight, which represents the strength or frequency of the interaction. This approach allows highlighting which drug combinations are most common in the analyzed dataset. There are several types of graphs, but in this analysis we focus on an undirected, weighted graph. This type of representation is particularly suitable when the relationship between two elements is bidirectional or symmetric, as is the case when two drugs are simply taken together by a patient, without implying a direction of effect [1]. One of the main questions that network analysis seeks to address concerns the identification of the most relevant or central nodes. A frequently used metric for this purpose is the degree of a node, which represents the number of connections (i.e., that the number of arcs) it has with other nodes in the network. Nodes with a high degree can be considered potential hubs, that is, central elements that contribute to the connectivity and robustness of the network. Analyses were conducted in R, using packages for data manipulation, graphs and visualization.

RESULTS

Overall, 604 patients, 242 women, and 363 men, were admitted for bleeding: 215 clinically relevant non-major bleeding, 389 major bleeding. Among major bleeding 209 in >80 elderly, 62 in patients between 75-80, 67 between 65-75, and 51 in under 65 patients. Patients using more than 2 drugs were included and they were 87.15% in case of major bleeding and 84.65 with minor bleeding. The most used drugs are proton pump inhibitors, followed by platelet aggregation inhibitors excl heparin, and beta-blocking agents. The dataset contains 392 ddis associated with the risk of bleeding. These associations represent specific combinations of drugs that could be linked to

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bleeding incidents, highlighting the importance of monitoring these combinations in clinical settings. The post frequent ddi associated with bleeding are co-somministrations of cns depressants and agents with antiplatelet properties, but also vitamin k antagonists with omeprazole/ pantoprazole, corticosteroids (systemic) / salicylates, aspirin / selective serotonin reuptake inhibitors, enoxaparin / agents with antiplatelet properties.

A drug x drug adjacency matrix was then constructed, in which each cell represents the absolute frequency with which two drugs were taken in combination by at least one patient. An undirected graph was derived from this matrix, in which the nodes represent the drugs and the arcs represent the observed interactions, with weight proportional to frequency. The degree of each node (number of interactions) was calculated and then the top 10% of the most connected nodes were selected to construct a filtered graph. A highly connected node appears frequently in combination with other active ingredients, while a less connected node is present in only a few associations. The degree of a node corresponds to the number of connections it has with other nodes. In addition, the weight of the arcs is proportional to the number of patients sharing the same drug combination: a thicker arc indicates a recurrent combination, while thinner arcs signal less frequent combinations.

The dataset included 604 patients, with 348 total drugs and 2542 interactions. Limiting the analysis to bleeding-associated interactions, the number of drugs considered drops to 121, with 392 interactions. In this subgraph, warfarin emerges as the most connected node (rank = 46), followed by amiodarone, clopidogrel, enoxaparin sodium, and acetylsalicylic acid. The most frequent interaction is warfarin - omeprazole (17 times). The filtered graph, showing only the 10% most connected drugs in the bleeding risk subgroup, is shown in Figure 1, where the intensity of the arc reflects the frequency of the observed interaction.

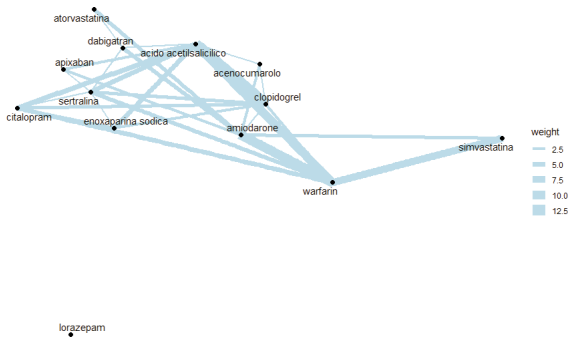

Figure 1. Graph of drug interactions associated with bleeding (10% most connected nodes).

CONCLUSIONS

Potentially clinically important DDIs carry an increased average causal effect on ADR-related admission. Especially by exposure to DDIs that increase bleeding risk, which should be targeted for medicine optimization. The analysis highlighted key drugs in the network of interactions, particularly warfarin, which confirms its clinical relevance as a critical node in high-risk bleeding settings. This approach is a valuable tool for surveillance of drug interactions and can support clinical decisions, especially in polytreatment settings.

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