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Prevalence and Correlates of Drug-drug Interactions in the Regional Hospital of Gjilan, Kosovo

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ABSTRACT

Aim: Our aim was to assess the prevalence and socioeconomic and clinical correlates of drug-drug interactions among the adult population of transitional Kosovo. **Methods:** A cross-sectional study was conducted including a representative sample of 1921 patients aged ≥18 years (mean age: 57.8±11.2 years; 50.3% women; overall response: 96%) from the regional hospital of Gjilan, Kosovo, during 2011-2013. Potential drug-drug-interactions were assessed and clinical data as well as demographic and socioeconomic information were collected. Binary logistic regression was used to assess the correlates of drug-drug interactions. **Results:** Upon multivariable adjustment for all the demographic and socioeconomic factors as well as the clinical characteristics, drug-drug interactions were positively and significantly related to older age (OR=2.1, 95%CI=1.3-2.8), a lower educational attainment (OR=1.4, 95%CI=1.1-1.9), a longer hospitalization period (OR=2.7, 95%CI=2.1-3.6), presence of three groups of diseases [infectious diseases (OR=1.7, 95%CI=1.3-2.4), cardiovascular diseases (OR=1.8, 95%CI=1.4-2.6), respiratory diseases (OR=1.6, 95%CI=1.2-2.5)], presence of comorbid conditions (OR=3.2, 95%CI=2.3-4.4) and an intake of at least four drugs (OR=5.9, 95%CI=4.6-7.1). **Conclusions:** Our study provides important evidence on the prevalence and socioeconomic and clinical correlates of drug-drug interactions among the hospitalized patients in the regional hospital of Gjilan, Kosovo. Findings from our study should raise the awareness of decision-makers and policy makers about the prevalence and determinants of drug-drug interactions in the adult population of post-war Kosovo.

Key words: drug-drug interaction, Gjilan region, hospitalized patients, Kosovo, Western Balkans.

1. INTRODUCTION

Drug-drug interactions, which refer to modification in the pharmacokinetics or effects of a drug by the presence of another drug (1), may convincingly result in increased or decreased efficacy of the treatment, complete treatment failure, as well as in increased toxicity of the drugs prescribed (2,3). It has been demonstrated that drug-drug interactions are mainly preventable conditions which can be carefully avoided by non-prescription of multiple drugs. As a matter of fact, putative positive effects of multiple-drug treatment should be evaluated vis-à-vis the risk of the occurrence of clinically significant drug-drug interactions (4).

Drug-drug interactions are increasingly acknowledged as an area of major concern in medical care (5), because there have been consistent reports linking them with serious health consequences and significant clinical damage (6,7).

It has been reported that the incidence of potential drug-drug interactions is close to 40% in patients taking five medications, and exceeds 80% in patients taking at least seven drugs (8,9). While several studies have investigated the frequency and nature of drug-drug interactions in community settings (10-12), this issue requires a particular attention in hospital settings, because more medications are usually prescribed simultaneously and more complex schemes and compounds are often used (5). Therefore, the risk of drug-drug interactions is logically higher among hospitalized patients who are often affected due to severe and comorbid conditions associated with chronic polypharmacy effects, which additionally undergo frequent therapeutic alterations (4,5).

As previously noted, the available information on drug interactions and their health effects for Kosovo is scarce, regardless of the anecdotic evidence suggesting a high prevalence of drug interactions and its resultant toxic effect (13). Furthermore, the situation is said to be particularly problematic among the older population subgroup which is highly dependent on multiple drug use given the high prevalence of comorbidity (13).

In this context, the aim of our study was to assess the prevalence and socioeconomic and clinical correlates of drug-drug interactions among the adult population of Kosovo, an independent country in the Western Balkans which is currently undergoing a difficult period of political and socioeconomic transition after a long and devastating war against Serbia.

2. METHODS

This was a cross-sectional study which was carried out in the regional hospital of Gjilan, Kosovo, covering the period 2011-2013.

Study population and sampling

The sampling frame consisted of all the patients aged ≥18 years hospitalized at the departments of Internal Medicine, Cardiology, or Infectious Diseases of the regional hospital in Gjilan from 01-01-2011 until 31-12-2013. Based on this sampling frame, a simple random sample of 2000 patients' records was drawn. Calculation of the sample size was made by use of WINPEPI (Program for Epidemiologists) for several hypotheses related to the prevalence and clinical correlates of drug-drug interactions in our study population. The significance level (two-tailed) was set at 5%, and the power of the study at 80%. Based on the most conservative calculations, the required minimal size for a simple random sample was about 1570 patients' records. We decided to recruit 2000 records in order to account for potential incompleteness of patients' files. Of the 2000 targeted patients' records, there were 79 incomplete files, for which there was also not possible to re-interview the respective patients regarding their socioeconomic characteristics (educational attainment, employment status, income level, or social status). Overall, 1921 patients' records were included in our analysis (response rate: 1921/2000=96%).

Data collection

All patients' records were carefully checked according to a structured checklist including clinical characteristics of the patients and other relevant data related to their hospitalization.

Potential drug-drug-interactions were assessed employing the Drug Interactions Checker within www.drugs.com database (14). The drug-drug interactions evident in our study sample were subsequently classified as major, moderate and minor, depending on their severity of clinical significance and crossover checked manually for the presence of identified interacting agents, according to a few recent reports (4,15). Hence, in our study, drug-drug interactions were identified and classified based on the profile of medications prescribed, as suggested by the recent literature on this field (4,15).

Other important clinical data included type of diagnosis, length of hospitalization and presence of comorbid conditions among patients included in the study.

In addition to clinical information, demographic and socioeconomic data were retrieved from all the patients' records and further verified (double-checked) by re-interviewing the patients (regarding selected socioeconomic factors such as educational attainment, employment status, income level, or social status). Demographic factors included sex and age of the patients, place of residence and marital status at the time of hospitalization. Socioeconomic characteristics included educational attainment (years of formal schooling), employment status, self-perceived income level and self-perceived social status.

The survey was approved by the Kosovo Board of Biomedical Ethics. All individuals who agreed to participate in the study gave their informed consent.

Statistical analysis

Binary logistic regression was used to assess the association of drug-drug-interactions (outcome variable) with the independent variables including demographic and socioeconomic factors [age (<40 years, 40-59 years, ≥60 years), sex (men vs. women), marital status (married vs. single/divorced/widowed), place of residence (urban areas vs. rural areas), education (low, middle, high), employment status (employed, unemployed, retired), income (low, middle, high) and social status (low, middle, high)] and clinical characteristics of the patients [length of hospitalization (1-6 days vs. ≥7 days), diagnosis (infectious diseases, cardiovascular diseases, endocrine diseases, respiratory diseases, gastrointestinal diseases, other diseases), comorbidity (yes vs. no) and number of drugs (1-3 vs. ≥4)]. Crude (unadjusted) and multivariable-adjusted odds ratios (ORs), their 95% confidence intervals (95%CIs) and p-values were calculated. Hosmer-Lemeshow test was used to assess the goodness-of-fit of the logistic regression models. Statistical Package for Social Sciences, version 17.0, Chicago, Illinois, was used for all the statistical analyses.

3. RESULTS

Mean age of the hospitalized patients included in our study sample was 57.8±11.2 years (58.4±10.6 years in men vs. 57.1±9.7 years in women) [Table 1]. About 50% of the patients were aged 60 years and over. Overall, 50% of the patients had a low educational level (48% in men vs. 52% in women). On the whole, 35% of the patients were unemployed with a remarkable sex-difference (28% in men vs. 42% in women). About 40% were from urban areas vs. 60% from rural areas of Kosovo. The absolute majority of individuals (87%) were married. About 37% and 35% of the patients perceived as low their income level

Characteristic	Men (N=954)	Women (N=967)	Total (N=1921)
Age (years)	58.4±10.6*	57.1±9.7	57.8±11.2
Age-group:			
<40 years	139 (14.6)†	123 (12.7)	262 (13.6)
40-59 years	348 (36.5)	353 (36.5)	701 (36.5)
≥60 years	467 (48.9)	491 (50.8)	958 (49.9)
Educational attainment:			
Low	458 (48.0)	506 (52.3)	964 (50.2)
Middle	402 (42.1)	382 (39.5)	784 (40.8)
High	94 (9.9)	79 (8.2)	173 (9.0)
Employment status:			
Employed	324 (34.0)	192 (19.8)	516 (26.9)
Unemployed	268 (28.1)	404 (41.8)	672 (35.0)
Retired	362 (37.9)	371 (38.4)	733 (38.1)
Place of residence:			
Urban area	372 (39.0)	401 (41.5)	773 (40.2)
Rural area	582 (61.0)	566 (58.5)	1148 (59.8)
Marital status:			
Married	813 (85.2)	859 (88.8)	1672 (87.0)
Single/divorced/widowed	141 (14.8)	108 (11.2)	249 (13.0)
Income level:			
Low	337 (35.3)	381 (39.4)	718 (37.4)
Middle	463 (48.5)	447 (46.2)	910 (47.4)
High	154 (16.1)	139 (14.4)	293 (15.2)
Social status:			
Low	321 (33.6)	358 (37.0)	679 (35.3)
Middle	495 (51.9)	503 (52.0)	998 (52.0)
High	138 (14.5)	106 (11.0)	244 (12.7)

*Table 1. Distribution of demographic and socioeconomic characteristics in a representative sample of hospitalized patients in Gjilan region, Kosovo, 2011-2013. *Mean values ± standard deviations. † Absolute numbers and column percentages (in parentheses).*

Clinical characteristics	Drug-drug interactions (N=1192)	No drug-drug interactions (N=729)	Total (N=1921)
Length of hospitalization:			
1-6 days	406 (34.1)*	458 (62.8)	864 (45.0)
≥7 days	786 (65.9)	271 (37.2)	1057 (55.0)
Diagnosis:			
Infectious diseases	174 (14.6)	93 (12.7)	267 (13.9)
Cardiovascular diseases	329 (27.6)	168 (23.0)	497 (25.9)
Endocrine diseases	157 (13.2)	104 (14.3)	261 (13.6)
Respiratory diseases	231 (19.4)	112 (15.4)	343 (17.8)
Gastrointestinal diseases	158 (13.2)	96 (13.2)	254 (13.2)
Other diseases	143 (12.0)	156 (21.4)	299 (15.6)
Co-morbidity:			
No	469 (39.3)	543 (74.5)	1012 (52.7)
Yes	723 (60.7)	186 (25.5)	909 (47.3)
Number of drugs:			
1-3	359 (30.1)	556 (76.3)	915 (47.6)
≥4	833 (69.9)	173 (23.7)	1006 (52.4)

*Table 2. Distribution of clinical characteristics by drug-drug interaction status in a representative sample of hospitalized patients in Gjilan region, Kosovo, 2011-2013. * Absolute numbers and column percentages (in parentheses).*

or social position, respectively. Clinical characteristics by drug-drug interaction status of the patients are presented in Table 2. There were 1192 patients with drug-drug interactions compared with 729 patients with no evidence of drug-drug interactions. Hence, the overall prevalence of drug-drug interactions in our study sample was 1192/1921=62%. Overall, 45% of the patients were hospitalized for 1-6 days compared with 55% of individuals who were hospitalized for seven days or more. The excessive length of hospitalization (≥7 days) was considerably higher among patients with drug-drug interactions compared with those without drug-drug interactions (66% vs. 37%, respectively). On the whole, 14% of the patients had infectious diseases, 26% cardiovascular diseases, 14% endocrine diseases, 18% respiratory diseases, 13% gastrointestinal diseases, whereas the remaining patients (16%) had other conditions. The prevalence of comorbidity was substantially higher among patients with drug-drug interactions compared with those without drug-drug interactions (61% vs. 26%, respectively). Furthermore, the proportion of individuals who were administered ≥4 drugs was remarkably higher among patients with drug-drug interactions compared with those without drug-drug interactions (70% vs. 24%, respectively).

Table 3 presents the crude (unadjusted) association of demographic and socioeconomic factors and clinical characteristics with drug-drug interactions. There was evidence of a positive association of drug-drug interactions with older age (OR=2.6, 95%CI=1.4-3.3), but no relationship with sex. Furthermore, drug-drug interactions were positively associated with a lower educational attainment (OR=1.7, 95%CI=1.1-2.2), retirement (OR=2.0, 95%CI=1.3-2.9), a lower self-perceived income level (OR=1.6, 95%CI=1.1-2.1) and a lower social status (OR=1.6, 95%CI=1.1-2.2). On the other hand, there was no relationship with place of residence, or marital status. As for the clinical correlates, drug-drug interactions were positively related to an excessive length of hospitalization (OR=3.3, 95%CI=2.7-4.0), presence of selected diseases [infectious diseases (OR=2.0, 95%CI=1.5-2.9), cardiovascular diseases (OR=2.1, 95%CI=1.6-2.9), endocrine diseases (OR=1.7, 95%CI=1.2-2.3), respiratory diseases (OR=2.3, 95%CI=1.6-3.1), or gastrointestinal diseases (OR=1.8, 95%CI=1.3-2.5)], comorbidity (OR=4.5, 95%CI=3.7-5.5) and an excessive number of drug intake (OR=7.5, 95%CI=6.0-9.2).

Variable	OR*	95%CI	P
Age-group:			**<0.001 (2)**†
<40 years	1.00	reference	-
40-59 years	1.87	1.06-2.37	0.027
≥60 years	2.64	1.38-3.29	0.001
Sex:			
Men	1.00	reference	0.471
Women	1.08	0.83-1.29	
Educational attainment:			**0.002 (2)**
High	1.00	reference	-
Middle	1.12	0.76-1.41	0.673
Low	1.73	1.14-2.19	0.002
Employment status:			**0.005 (2)**
Employed	1.00	reference	-
Unemployed	1.22	0.89-1.52	0.273
Retired	2.04	1.31-2.95	0.034
Place of residence:			
Urban area	1.00	reference	0.293
Rural area	1.13	0.91-1.37	
Marital status:			
Married	1.00	reference	0.638
Single/divorced/widowed	0.94	0.64-1.42	
Income level:			**0.004 (2)**
High	1.00	reference	-
Middle	1.09	0.73-1.85	0.714
Low	1.64	1.08-2.11	0.026
Social status:			**0.005 (2)**
High	1.00	reference	-
Middle	1.12	0.81-1.72	0.672
Low	1.59	1.13-2.23	0.029
Length of hospitalization:			
1-6 days	1.00	reference	<0.001
≥7 days	3.27	2.70-3.96	
Diagnosis:			**<0.001 (5)**
Infectious diseases	2.04	1.45-2.87	<0.001
Cardiovascular diseases	2.14	1.59-2.86	<0.001
Endocrine diseases	1.65	1.18-2.30	0.004
Respiratory diseases	2.25	1.63-3.10	<0.001
Gastrointestinal diseases	1.79	1.28-2.52	0.001
Other diseases	1.00	reference	-
Co-morbidity:			
No	1.00	reference	<0.001
Yes	4.50	3.67-5.51	
Number of drugs:			
1-3	1.00	reference	<0.001
≥4	7.46	6.04-9.21	

*Table 3. Association of demographic and socioeconomic factors and clinical characteristics with drug-drug interactions; crude (unadjusted) odds ratios (ORs) from binary logistic regression. * Odds ratios (ORs): drug-drug interactions vs. no drug-drug interactions. † Overall p-values and degrees of freedom (in parentheses).*

Upon multivariable adjustment for all the demographic and socioeconomic factors as well as the clinical characteristics, drug-drug interactions were positively and significantly related to older age (OR=2.1, 95%CI=1.3-2.8), a lower educational attainment (OR=1.4, 95%CI=1.1-1.9), a longer hospitalization period (OR=2.7, 95%CI=2.1-3.6), presence of three groups of diseases [infectious diseases (OR=1.7, 95%CI=1.3-2.4), cardiovascular diseases (OR=1.8, 95%CI=1.4-2.6), or respiratory diseases (OR=1.6, 95%CI=1.2-2.5)], presence of comorbid conditions (OR=3.2, 95%CI=2.3-4.4) and an intake of at least four drugs (OR=5.9, 95%CI=4.6-7.1) [data not shown in the tables].

4. DISCUSSION

The prevalence of drug-drug interactions in our study, which included a large representative sample of patients' records form the regional hospital in Gjilan, was high (62%). Major demographic and socioeconomic correlates of drug-drug interactions in this study sample consisted of older age and a lower educational level. Conversely, the most important clinical correlates included an excessive length of hospitalization, presence of comorbidity and, particularly, the excessive number of drug intake.

A recent study conducted in Ethiopia reported a high prevalence of potential drug-drug interactions in the internal medicine ward in the University Teaching Hospital of Gondar (4). Thus, among all patients included in this study (N=78), the prevalence of at least one potential drug-drug interaction, regardless of its severity, was 78% (4). Furthermore, in Kenya, about 33.5% of the patients receiving antiretroviral medications were reported to be exposed to clinically significant drug interactions with their antiretroviral medications (16). On the other hand, a study conducted in Switzerland reported that about 56% of the patients were exposed to one or more major or moderate drug-drug interaction in the internal medicine ward (17). At a broader level, a literature review reported that 0.054% of emergency department visits, 0.57% of hospital admissions and 0.12% of re-hospitalizations were caused by drug-drug interactions (18).

It has been suggested that patient safety may be improved by decreasing the frequency of preventable adverse drug events (5). From this point of view, computerized alerts have been suggested as a useful warning sing for drug-drug interactions (5). However, such instruments of early detection of drug-drug interactions may also lead to excessive alerts, especially when the system produces an overload of signals that are of minor clinical relevance (5,19).

Our study may have some limitations which include the possibility of selection bias and potential information biases. As for the selection bias, we drew a simple random sample of patients' records based on a pre-defined and well-established sampling frame available from the regional hospital in Gjilan, which consisted of all the patients' records hospitalized during the study period (that is 2011-2013). Therefore, the inclusion of a large and representative sample of patients' files provides reassurance for the absence of selection bias in our study sample. Regarding the possibility of information bias, we should point out that the assessment of socioeconomic characteristics was based on self-reported information, which bears the risk of differential reporting among categories of individuals distinguished by selected demographic and socioeconomic profiles. Notwithstanding the lack of evidence for such a differential reporting among individuals with different demographic and socioeconomic characteristics, we cannot fully exclude the possibility of differential reporting among these population categories. In addition, relationships observed in cross-sectional studies are not assumed to be causal and, therefore, future cohort studies in Kosovo should confirm and expand findings from our cross-sectional survey.

5. CONCLUSION

Our analysis provides important evidence on the prevalence and socioeconomic and clinical correlates of drug-drug interactions among patients hospitalized in the regional hospital of Gjilan, in transitional Kosovo. Findings from our study should raise the awareness of decision-makers and policy makers about the prevalence and determinants of drug-drug interactions in the adult population of post-war Kosovo.

CONFLICT OF INTEREST: NONE DECLARED.

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