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Research Article

Assessing drug-drug interactions: Prevalence, predictors, and their impact on in-hospital mortality in hospitalised haemodialysis patients

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Abstract

This retrospective observational study was conducted in Libya to examine the frequency and determinants of drug-drug interactions (DDIs) among hospitalised haemodialysis inpatients between January 2018 and June 2020. The study highlighted a notable prevalence of DDIs among HD patients, with a prevalence rate of 71.1%. Regarding the identification of DDI predictors and their correlations with extended hospital stays and polypharmacy, regression analysis was conducted to identify predictors and outcomes. The study found that DDIs were associated with prolonged hospital stays and were independently linked to polypharmacy in HD patients. Furthermore, a significant clinical impact of DDIs on HD patients was observed, particularly in relation to in-hospital mortality.

Keywords

drug-drug interactions, haemodialysis, in-hospital mortality, Libya

Introduction

End-stage renal disease (ESRD) is characterised by a significant decrease in glomerular filtration rate (GFR) to 15 ml/min/1.73² (Kalantar et al. 2021). ESRD and death are two potential outcomes and prognoses associated with chronic kidney disease (CKD) (Abbasi et al. 2011). In the countries of the Middle East, the prevalence and incidence of the disease ranged from 818 cases per million people (pmp) in Lebanon to 55 cases pmp in Iraq, and from 49.9 cases pmp in Iran to 276 cases pmp in Turkey, respectively. According to the findings of a review study that was carried out in Turkey, the prevalence that was measured for the Middle East was 393 pmp. It would indicate that the incidence of ESRD in this part of the world is not as common as it is in other nations (Malekmakan et al. 2018).

There were 2417 adult patients in Libya receiving maintenance dialysis for end-stage kidney disease (ESKD), according to a study published in 2012 on the epidemiology and aetiology of dialysis-treated ESRD in Libya. With a total adult population of 3,873,000 in 2009, the prevalence of ESKD requiring dialysis was predicted to be 624

cases pmp. Prevalence varied marginally throughout Libya's regions, with the North West area seeing the highest rate (628 per 100,000 people), which is also the most populous area of the country. Other regions recorded rates of 623 in the North East and 597 in the South of Libya (Alashek et al. 2012a).

Drug-drug interactions (DDIs) occur when the effects of one drug are altered by the presence of another drug. There is a notable incidence of hospitalisation due to DDIs (>1%), and epidemiological estimates place the prevalence of probable DDIs in the elderly between 35 and 60%. Of these, 5–15% are responsible for adverse effects that are mostly avoidable or treatable (Burato et al. 2021). A systematic review of DDI in the Middle East concluded that errors involving drug-to-drug interactions were the least prevalent type of prescription medication. According to reports, Iran has the highest rate of interaction errors in the Middle East, at 1.54%. Saudi Arabia ranked second with a reported rate of 1.08% (Aidah et al. 2021). DDIs and death-related hospital discharges are prevalent among the elderly (Carrero et al. 2018), and DDIs accounted for 10–16% of all preventable adverse events in intensive care unit (ICU) patients, and 5% were expected to experience an adverse drug reaction (ADR) due to a DDI during hospitalisation (Cashion et al. 2021). However, data on the frequency of potential drug-drug interactions (pDDIs) among haemodialysis (HD) patients, especially in Libya, is lacking. Although studies on ESRD and dialysis have shown a high frequency in Libya (Alashek et al. 2012a), no studies have examined DDIs. Due to their complex medication schedules and reduced kidney function, HD patients are at increased risk for DDIs; therefore, this study aims to assess the prevalence of DDIs and their predictors among Libyan haemodialysis patients.

Methods and materials

Study design

This retrospective observational study was carried out at the Al-Hawari Kidney Services Centre, which has 100 beds and is the main nephrology centre in Benghazi, Libya. It covers most eastern parts of Libya, containing haemodialysis clinics (99 HD machines), ICUs, outpatient clinics, transplant clinics, peritoneal dialysis clinics, and inpatient wards for males and females (Information Health Center 2014). The inclusion criteria were: ESRD patients who are on regular haemodialysis, admitted to Al-Hawari Kidney Services centre within study period, all adult patients (>18 years), and admitted for 24 hours. The exclusion criteria were all patients who have medical records that have missing data and patients who had acute kidney injury (AKI). Prior to the start of the study, the medical research and ethics committee of AL-Hawari Kidney Services granted ethical approval issued at 1.1.2021, and because there is no direct connection with patients, consent was not obtained because it was deemed unnecessary by the committee.

Sample size

According to the data kept by the Statistical Department in the Al-Hawari Centre in the year 2020 in Libya, there were a total of 500 HD patients across the Al-Hawari Kidney Services Benghazi facility. In order to determine the requisite sample size for this study, the Taro Yamane formula (1967) was utilised (Chaokromthong et al. 2021).

$$\text{The formula is } n = N/ (1+N (e)^{2})$$

n signifies the sample size, N signifies the population under study, and e signifies the margin error (it could be 0.05) at CI 95. Plug in the values in the formula n = 500/2.25 = 222. The result of this calculation was 222 patients.

Data collection

This study includes data from paper-based medical records of patients on regular HD (ESRD) who were hospitalised on a ward between January 2018 and June 2020 and encountered DDIs. A total of 1490 medical records of patients admitted to word were reviewed for this study during a 30-month period. The data were gathered retrospectively by the researcher from the patients' medical records by using a predesigned data collection form for each individual patient; the period of data collection spanned from January 1, 2021, to December 31, 2021. The following categories of information were gathered: (a) demographic features; (b) the presence of comorbid conditions; (c) laboratory test results; and (e) medications consumed while in the hospital. Only medicines that were prescribed while the patient was in the hospital were taken into consideration. The sociodemographic data include age, gender, admission date, discharge date, marital status, and smoking status. Clinical data include comorbid diseases like diabetes mellitus (DM), hypertension (HTN), cardiovascular disease (CVD), stroke, chronic obstructive pulmonary disease (COPD), and cerebrovascular accident (CVA). Laboratory results include urea, serum creatinine at admission, fasting blood sugar, and complete blood count. The primary outcome of this study is the identification of DDIs among hospitalised HD patients. The identification process for DDIs was done by using Lexicomp (Kluwer). Lexicomp is an extensively utilised drug interaction database and decision support system that aids in the identification and management of DDIs. It provides crucial information regarding potential drug interactions, allowing clinicians to make informed decisions and enhance patient safety during medication management. Each interaction was assigned a risk rating of A, B, C, D, or X by this system. Risk rating A indicates there is no known interaction, B requires no action, C requires monitoring of therapy, D requires consideration of therapy modification, and X indicates that the combination should be avoided.

The following information was collected for each recognised DDI that developed while the patient was hospitalised: (a) the date of start and end of the identified drug treatment; (b) the name of the substance that caused the

interaction. The secondary outcomes include in-hospital mortality, which is defined as any death that occurred during hospitalisation.

Statistical analysis

The statistical analysis was done with IBM SPSS version 22, which was developed by SPSS Inc. in Chicago, Illinois. Descriptive analysis was used where the categorical variables were presented as frequencies and percentages, while continuous variables were reported as means with standard deviations or medians with interquartile ranges, depending on whether they were normally distributed. The normality of the data was examined using the Kolmogorov-Smirnov statistic, where a p value of < 0.05 indicated a non-normal distribution of the data. Regression analysis was used first, and univariable analysis was used to assess the association between independent variables and categorical nominal outcomes (DDIs). Next, multivariable logistic regression analysis was employed to identify independent predictors of the above-mentioned outcome among hospitalised HD patients. Variables with a p-value of < 0.25 in the univariable analysis were included in the multivariable model to identify independent predictors for DDIs. The significant association in the multivariable model was considered when the p value was < 0.05.

Results

Socio-demographic and clinical features of drug-drug interactions among haemodialysis patients

Overall, the median age was 54 years old (with an interquartile range (IQR) of (41–65), and 131 of the patients were male (54.8%). The majority (217) are married (90.8%), and 229 of patients were non-smokers (95.8%). Regarding haemodialysis frequency, 218 patients were on a three times per week schedule (91.2%). The majority of patients 213 had at least one comorbid condition (89.1%), with 192 of patients having hypertension (80.3%) and 93 of patients having diabetes (38.9%) being the most prevalent. In relation to the laboratory data, the median Scr value was 8.4 mg/dL, with a reference range of 0.70–1.40 mg/dL and an IQR of (6.4 to 11.2). The urea level was recorded as 139 with a reference range of 15–45 mg/dL and an IQR of (96, 175). The fasting blood sugar (FBS) level was measured at 117 with a reference range of 70–120 mg/dL and an IQR of (93, 163). The white blood cell count was observed to be 7.8 with a reference range of 4–9 103/μL and an IQR of (5.6, 11.5). Haemoglobin was found to be 8.2, with a reference range of 12–18 g/dL and an IQR of (7.1, 9.3). The mean corpuscular volume was determined to be 82.8 with a reference range of 80–100 fl and an IQR of (79.9, 85.9). Lastly, the platelet count was recorded as 218, with a reference range of 150–350 103/μL and an IQR of (150, 280).

In relation to hospitalisation, the median hospital stay was 6 with (IQR) (4.9). Admission to ICU was 5.4%. The all-cause mortality rate in hospitals was 11.7% (Suppl. material 1).

Estimation of drug-drug interactions among haemodialysis patients

In the context of Lexicomp, the categories of DDIs are categorised as A, B, C, D, and X. Group A signifies no known interaction, and for the sake of this study, we will exclude this risk group of DDIs. The prevalence of DDIs within our population is 170 cases, accounting for 71.1% of the total. These cases encompass DDIs falling under categories B, C, D, and X. Based on the risk rating classification, the findings of this study indicate that the proportions for risk categories C, B, D, and X were 61.5%, 34.7%, 21.3%, and 0.8%, respectively (Fig. 1).

The most frequently observed DDI, occurring in 74 (31.0%) of patients, included the combination of calcium carbonate and alfacalcidiol. This was followed by the combination of calcium carbonate and amlodipine, which was observed in 41 (17.2%) of patients.

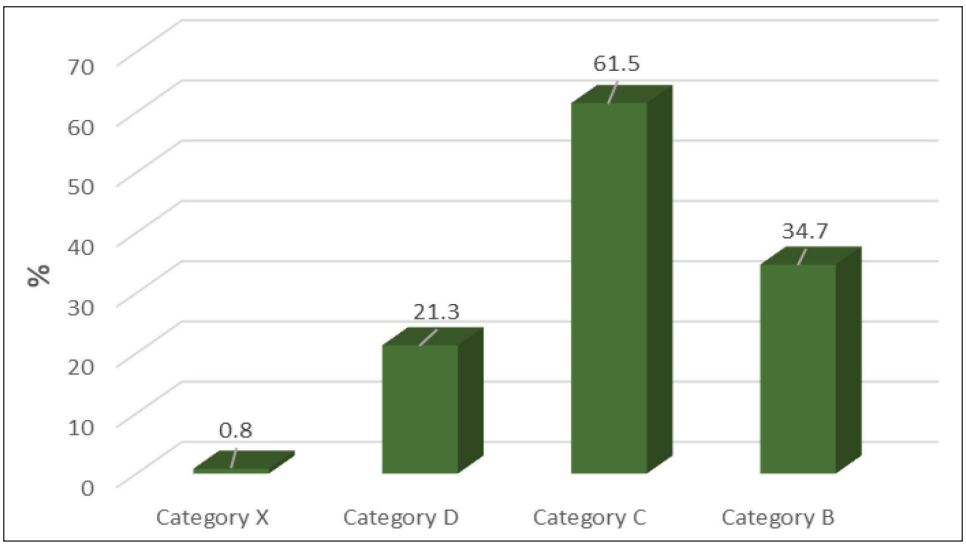

Figure 1. Frequency of top 10 potential drug-drug interactions among hospitalised haemodialysis patients.

Other notable DDIs included bisoprolol with insulin isophane 18 (7.5% of patients), warfarin with heparin 16 (6.7% of patients), and calcium carbonate with ciprofloxacin 13 (5.4% of patients). Furosemide with allopurinol had a lower incidence of DDIs, observed in just 8 patients, accounting for 3.3% of the total population. It is noteworthy that two patients had x-category DDIs, namely quetiapine with metoclopramide and quetiapine with tiotropium. The top 10 class C/D drug-drug interactions among hospitalised haemodialysis patients are shown in Table 1.

Table 1. The top 10 class C/D drug-drug interactions among hospitalised haemodialysis patients.

Drug/drug interaction	Frequency	%	Risk Category
CaCo3/alfacalcidiol	74	31.0%	C
Caco3/amlodipine	41	17.2%	C
Bisoprolol/insulin isophane	18	7.5%	C
Warfarin/heparin	16	6.7%	C
CaCo3/ciprofloxacin	13	5.4%	D
CaCo3/allopurinol	11	4.6%	D
Warfarin/ceftriaxone	10	4.2%	C
Metoclopramide/ciprofloxacin	9	3.8%	C
Bisoprolol/nifedipine	9	3.8%	C
Furosemide/allopurinol	8	3.3%	C

Factors associated with potential drug-drug interactions among haemodialysis patients

The results of the univariable analysis indicate a statistically significant association between hospitalisation and DDIs (p value = 0.005). Additionally, a significant relationship was seen between polypharmacy (defined as the use of five or more medications) and DDIs (p value < 0.001). However, the multivariable analysis indicated that polypharmacy was an independent predictor for pDDIs among hospitalised HD patients (OR = 11.209, 95% CI = 5.21–24.12, p value = < 0.001) (Table 2).

Association between drug-drug interactions and in-hospital mortality among modialysis patients

With regards to the association between pDDIs and mortality, the logistic regression analysis revealed a significant positive association between the number of DDIs and in-hospital mortality after adjusting for pre-known covariates (B = 0.172, SE = 0.085, p value = 0.042) (Table 3).

Discussion

Sociodemographic and clinical characteristics of haemodialysis patients

The current study found that hospitalised HD patients had a median age of 54 years, and the percentage of males was much greater than the percentage of females. These findings are in line with the findings of other research that was carried out in Libya (Alashek et al. 2012a; Habas et al. 2019; Rafiu et al. 2019) and globally (Weigert et al. 2020; Shankar et al. 2024). Differences between men and women have a significant bearing on the prevalence and treatment options for a number of diseases, including CKD (Carrero et al. 2018). There is a fast decrease in eGFR and a higher occurrence of Renal Replacement Therapy(RRT) in men than women(Neugarten et al. 2000; Nitsch et al. 2015; Minutolo et al. 2020). Animal models have shown proof that oestrogens have nephroprotective effects by opposing the activity of transforming growth factor and downregulating the renin-angiotensin system, whereas testosterone exerts effects in the kidney that are proinflammatory, proapoptotic, and profibrotic (Oktanella et al. 2023). Numerous comorbidities, including HTN, DM, CVD, and HCV, were identified as prevalent in this study. ESRD can be caused by a variety of factors; however, HTN was by far the most common contributing factor in our study, followed by DM and CVD. This outcome is consistent with prior studies conducted in Libya (Alashek et al. 2012b; Goleg et al. 2014) and the Middle East (Al-Ramahi et al. 2016; Hammoud et al. 2022). Hypertension is considered a risk factor and underlying cause of ESRD (Leiba et al. 2019; Duan et al. 2020; Weldegiorgis et al. 2020), and hypertension and diabetes are responsible for eighty percent of all cases of ESRD (Koye et al. 2018). Regarding the frequency of dialysis, the majority of our patients adhere to a thrice-weekly regimen, which aligns with findings from other research (Rama et al. 2012; Hijazeen et al. 2020). This practice is substantiated by a systematic analysis that compares more frequent dialysis sessions with three weekly sessions. The research's findings indicate that there are no significant changes in terms of reducing mortality, but there is evidence of improved patient self-care (PSC) with more frequent dialysis sessions (Slinin et al. 2015).

Prevalence and classification of drug-drug interactions among haemodialysis patients

In this study, the prevalence of pDDIs in HD patients' medications was 71.1%, which is consistent with findings from India (76%), and Pakistan (78.5%) (Rama et al. 2012; Saleem et al. 2017). In contrast, prevalence was higher in studies conducted in Palestine and the United Arab Emirates, where the incidence of DDIs was 89.1% and 85.3%, respectively (Al-Ramahi et al. 2016; Hammoud et al. 2022). The discrepancy in incidence rates may be attributed to variations in study methodologies, equations employed for estimating renal function, definitions of DDIs, and approaches utilised to assess the frequency or incidence rates of DDIs (Sgnaolin et al. 2014; Fasipe et al. 2017). Numerous diverse methodologies have been employed in prior research to assess and categorise DDIs in individuals with CKD. In this research, we employed Lexicomp as a tool for identifying potential DDIs in patients with HD. The majority of identified pD-

Table 2. Factors associated with potential drug-drug interactions among hospitalised haemodialysis patients.

Variable	Univariable analysis		Multivariable analysis	
	P value	OR	P value	OR
Age	0.292	0.991 (0.975–1.008)	–	–
Gender (ref, female)				
Male	0.932	0.977 (0.576–1.660)	–	–
Marital status (ref, single)				
Married	**0.072**	0.359 (0.117–1.097)	0.082	0.305 (0.080–1.164)
Frequency of dialysis (times/week) (ref, < 3)				
3	0.760	0.863 (0.334–2.226)	–	–
HTN	0.763	1.106 (0.573–2.136)	–	–
DM	0.968	0.989 (0.576–1.697)	–	–
CVD	0.573	0.781 (0.331–1.842)	–	–
SCr	0.436	0.972 (0.902–1.045)	–	–
Urea	**0.217**	1.003 (0.998–1.007)	0.190	1.004 (0.998–1.009)
FBS	0.576	0.999 (0.996–1.002)	–	–
WBC`	0.461	0.983 (0.939–1.029)	–	–
Hb	0.502	0.959 (0.849–1.084)	–	–
Hct	0.654	0.988 (0.938–1.041)	–	–
MCV	0.868	0.997 (0.957–1.038)	–	–
PLT	0.440	1.001 (0.998–1.003)	–	–
Hospitalisation	**0.005***	1.103 (1.031–1.180)	0.074	1.071 (0.993–1.155)
ICU admission	0.313	1.972 (0.528–7.367)	–	–
Polypharmacy	**<0.001**	10.73 (5.44–21.18)	**<0.001**	11.209 (5.21–24.12)

Note. HTN: hypertension; DM: diabetes mellitus; CVD: cardiovascular disease; HCV: hepatitis C; SLE: systemic lupus erythematosus; COPD: chronic obstructive pulmonary disease; HBV: hepatitis B; RA: rheumatoid arthritis; PLT: platelet; RBC: red blood cells; RBS: random blood sugar; SCr: serum creatinine; WBC: white blood cells; Hb: haemoglobin; Hct: haematocrit; MCV: mean corpuscular volume; ICU: intensive care unit.

Table 3. shows the association between drug-drug interactions and in-hospital mortality among haemodialysis patients.

Variable	P value	Crude OR	CI 95%	P value	Adjusted OR[a]	CI 95%
DDIs numbers	0.074[#]	1.160	(0.986–1.364)	0.042	1.188[##]	(1.006–1.403)

[a] Adjusted for age, cardiovascular diseases;
[#] B = 0.148, SE = 0.083;
[##] B = 0.172, SE = 0.085.

DIs (61.5%) were classified as class C based on their risk rating, indicating the need for therapeutic monitoring. A medication change was indicated for (21.3%) pDDIsdue to their classification as D risk levels, and B class of DDIs was accounted for (34.7%). This observation aligns with the results reported in previous study (Fasipe et al. 2017). Various studies have employed distinct identification tools called Micromedx and Medscape, which have revealed that a significant proportion of DDIs are classified as moderate interactions according to their risk rating (Rama et al. 2012; Saleem et al. 2017). Therefore, it is imperative to closely monitor and carefully assess patients with CKD in order to manage and reduce DDIs. This can be accomplished through effective collaboration between clinical pharmacists and physicians. Monitoring potential drug interactions is crucial for enhancing the quality of prescribing and dispensing practices, as well as promptly implementing preventive measures (Arellano et al. 2015).

Predictors of potential drug-drug interaction among haemodialysis patients

The present study has successfully established a correlation between DDIs and various other factors. Through the univariable analysis conducted in this study, it has been determined that hospitalisation (duration of hospitalisation) is one of the factors significantly associated with harmful pDDIs. This finding aligns with a similar study conducted in the United Arab Emirates, where 150 patients with CKD were prospectively examined to assess the prevalence of DDIs (Hammoud et al. 2022). Furthermore, our investigation has uncovered another characteristic that is associated with DDIs among HD patients, namely polypharmacy. This finding aligns with previous studies conducted in Brazil, Palestine, Jordan, and the United Arab Emirates (Sgnaolin et al. 2014; Al-Ramahi et al. 2016; Hijazeen et al. 2020; Hammoud et al. 2022). The present study identifies polypharmacy as the independent variable related to DDIs among hospitalised HD patients by multivariate analysis. Existing literature has clearly established a correlation between DDIs and two important factors: a longer length of hospital stay (Dechanont et al. 2014; Kardas et al. 2021) and polypharmacy (Maher et al. 2014; Oliveira et al. 2024). Both are recognised as contributing factors to pDDIs. Deprescribing is a viable approach for mitigating the issues of polypharmacy and poor medication utilisation. Deprescribing is a defined practice involving the gradual reduction, cessation, or withdrawal of medications with the aim of controlling polypharmacy and enhancing patient outcomes (Scott et al. 2015). There are currently depression

tools that can be categorised into two major groups: particular tools and general tools. General tools offer a framework for evaluating a patient's existing drugs, whereas particular tools focus on discontinuing specific prescriptions using algorithms that are based on evidence of the safety and effectiveness of these drug regimens (Cashion et al. 2021). An algorithm has been devised specifically for HD patients. This algorithm aims to deprescribe certain medications, including loop diuretics, alpha-1 blockers, proton pump inhibitors, statins, and quinine, in patients undergoing HD (Lefebvre et al. 2020). Patients, caregivers, care teams, and systems may face barriers to deprescribing, such as lack of support, time, or guidance from clinicians. Clinicians face problems such as low self-efficacy, inadequate comprehension, and low prescribing feasibility. System-level obstacles include limited resources (e.g., time, administrative assistance) and a lack of policies promoting personalised medication management (Mohottige et al. 2021). This process is typically facilitated through collaboration between the pharmacy department and the nephrology team (McIntyre et al. 2017). The integration of clinical pharmacists within a multidisciplinary team in the context of the HD population has the potential to mitigate issues related to polypharmacy and medication utilisation, as well as the frequency and rate of hospitalisations (Daifi et al. 2021; Talib and Mudhafar 2021).

Association between in-hospital mortality and drug-drug interaction among haemodialysis patients

This study examined the relationship between DDIs and in-hospital mortality. While the unadjusted analysis did not find a significant association, the adjusted analysis revealed a significant relationship. This suggests that DDIs are an independent variable for in-hospital mortality among patients undergoing HD.

In contrast to the research (Rivkin and Yin 2011; Teramura et al. 2016; De Vincentis et al. 2020) that failed to establish a correlation between probable DDIs and mortality, this study reveals a noteworthy association between pDDIs and the occurrence of "in-hospital mortality" among patients undergoing HD. The association between DDIs and mortality is subject to conflicting findings. One study identified a correlation between DDIs and in-hospital mortality (Rosas-Carrasco et al. 2011), while another study did not find an association between DDIs and short-term mortality but did see a relationship with long-term mortality (Maguire et al. 2007). The observed variations in findings can be attributed to disparities in hospital care, variations in methodology employed for categorising DDIs, the absence of a universally accepted definition of DDIs, and discrepancies in patient profiles, as certain studies are based on community samples with fewer drugs being utilised.

The independent variable in our study pertains to DDIs, which have been identified as a contributing factor to mortality and can be explained by the fact that DDIs can lead to harmful consequences, including potential adverse drug reactions that may prove fatal, particularly among elderly patients with comorbidities. Additionally, the likelihood of experiencing adverse drug reactions increases as the number of medications prescribed to a patient increases. DDIs and polypharmacy have an obvious impact on mortality (Huang et al. 2021; Zerah et al. 2021).

According to previous research, age and cardiovascular disease are the most common and significant confounding factors linked to mortality and DDIs (Rosas-Carrasco et al. 2011; Sultana et al. 2019); these variables were utilised to adjust the regression analysis in this study.

This study has some limitations, as when conducting a retrospective study, it is important to acknowledge and address some constraints that may arise when reviewing the findings of this particular section. First, the study allows only to collect data retrospectively, which is poor in documentation and may introduce missing data based on the availability of data. Secondly, it is a single centre study, which yields less generalisability of results. Thirdly, the drug interactions are determined based on a computer-based method, which does not reflect clinical drug interaction interpretation. Additionally, in the in-regression analysis, we did not consider the long-term mortality; we only focused on all-cause in-hospital mortality as an outcome. Furthermore, this study did not include erythropoietin-stimulating drugs due to economic limitations. Finally, it should be noted that certain biochemical data, such as serum albumin levels, were not included in the analysis due to data deficiency caused by cost constraints. It is important to acknowledge that these missing data may have an association with mortality. Nevertheless, this research represents many strengths as the first endeavour of its sort conducted in Libya. Additionally, the obtained results can serve as a valuable source of information regarding the prevalence of DDIs among patients on HD. Finally, the study presents predictors that are linked to mortality among HD patients as a result of DDIs.

Conclusion

Our retrospective study has identified a significant prevalence of DDIs among HD patients in Libya. We have also identified factors such as hospitalisation duration and polypharmacy, which contribute to the risk of pDDIs. Furthermore, our study has revealed the clinical consequences of DDIs among HD patients, specifically their association with in-hospital mortality in unadjusted analysis.

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Competing interests

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Supplementary material 1

Socio-demographic, clinical characteristics, and laboratory data of patients included in the analysis

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