Annals of Hepatology
The Official Journal of the Mexican Association of Hepatology, the Latin-American Association for Study of the Liver and the Canadian Association for the Study of the Liver

ORIGINAL ARTICLE

Drug-Drug Interactions in Hepatitis Patients: Do these Interactions Matter in Clinical Perspectives?

Sidra Noor,* Mohammad Ismail,* Iqbal Haider,** Faiza Khadim*

* Department of Pharmacy, University of Peshawar, Khyber Pakhtunkhwa, Pakistan.
** Department of Medicine, Medical Teaching Institute, Khyber Teaching Hospital, Peshawar, Pakistan.

ABSTRACT

Introduction and aim. Hepatitis patients usually present with comorbidities and polypharmacy which increases risk of potential drug-drug interactions (pDDIs). We explored frequency, levels, predictors, and clinical relevance of pDDIs in hospitalized hepatitis patients. **Material and methods.** Retrospective cohort study was used. Clinical profiles of 413 hepatitis patients were reviewed for pDDIs using Micromedex-DrugReax. Frequency, levels and clinical relevance of pDDIs were reported. Logistic regression analysis was used to calculate odds-ratios for predictors. **Results.** Of total 413 patients, pDDIs were reported in 55.2%. Major-pDDIs were found in 35% patients. Total 660 pDDIs were identified, of which, 304 (46%) were of major-severity and 299 (45%) of moderate-severity. Patient's profiles of top-10 major-pDDIs were presented with signs/symptoms such as fever, hepatomegaly, anorexia, jaundice, hypertension, tachycardia, bradycardia, & pedal edema; and abnormalities in labs such as electrolytes-level, alanine aminotransferase, blood urea nitrogen, bilirubin-level, & serum creatinine. Significant association was observed for the presence of pDDIs with > 9 prescribed medicines ($p < 0.001$), hospitalization of > 5 days ($p = 0.03$), and stroke as comorbidity ($p = 0.05$). Moreover, odds of exposure to major-pDDIs were significantly higher in patients taking > 9 prescribed medicines ($p < 0.001$), hospitalization of > 5 days ($p = 0.002$), and stroke as comorbidity ($p = 0.002$). **Conclusion.** We observed hepatitis patients presented with a considerable number of clinically relevant pDDIs. Attention should be given to widespread major-pDDIs and their potential adverse outcomes. Clinically relevant parameters, such as labs and signs/symptoms should be monitored particularly in high risk patients having polypharmacy, prolong hospitalization, and stroke as comorbidity.

Key words. Potential drug-drug interactions. Patient safety. Polypharmacy. Clinical pharmacist. Drug interaction screening.

INTRODUCTION

Viral hepatitis refers to inflammation of the liver caused by one of the several types of viruses. Liver plays a vital role in the metabolism of endogenous and exogenous substances.[1] Chronic hepatitis can gradually lead to complications such as hepatocellular carcinoma, liver cirrhosis, and decompensated chronic liver disease.[2] Impaired liver function may cause change in pharmacokinetics of drugs used in patients with hepatitis.[3] There is alteration of absorption process, increase in bioavailability due to portosystemic shunting,[4] increase in free fraction of highly protein bound drugs in patients with hypoalbuminemia,[3] decrease in hepatic drug clearance due to lower hepatic blood flow,[5] and decreased activity of phase I enzymes.[6] Pharmacodynamic alterations are also prevalent such as cardio-toxicity by QT interval prolonging drugs[7] and nephrotoxicity associated with non-steroidal anti-inflammatory drugs.[8]

Hepatitis patients usually present with comorbid illnesses and taking medications that have potential for drug-drug interactions (DDIs).[9,10] Development of new anti-viral agents causes significant improvements in efficacy and declines toxicity paralleled to earlier interferon-based treatments. Nonetheless, judicious use of these agents necessitates strict attention to DDIs because all hepatitis combination regimens interact with drug transporters, drug metabolizing enzymes, or both.[11] All of these factors can potentially influence the effectiveness of a drug and/or the probability that a drug is causing adverse reac-

Manuscript received: October 20, 2017. **Manuscript accepted:** March 01, 2018.

DOI:10.5604/01.3001.0012.2238

tions. Adverse drug reactions (ADRs) may further increase morbidity and mortality in hepatitis patients.[12] Knowledge of DDIs is important for appropriate clinical management, which usually requires dose adjustments, monitoring for adverse effects, or discontinuation of contraindicated medications.[13]

Some pharmacoepidemiological studies have investigated potential DDIs (pDDIs) in patients with hepatitis.[9,10,14,15] These studies have a number of limitations such as inclusion of patients only with hepatitis C,[9,10,14] investigation of pDDIs involving only anti-viral and anti-retroviral drugs in HIV/HCV co-infected patients,[15] work on only contraindicated interactions,[9] and use of a specific online drug interaction screening tool.[10,14,15] Furthermore, pDDIs among drugs (other than anti-viral agents) given for the management of various comorbidities are purely neglected. Such interactions must be reported in order to help health professionals in their clinical practice because they can affect patient outcome. Apart from this, the above studies are lacking information about the overall prevalence of pDDIs in patients with all types of hepatitis, scientific evidence (documentation levels) supporting the occurrence of pDDIs, predictors of pDDIs, contribution of comorbidities towards exposure to pDDIs, and more importantly clinical relevance of the identified pDDIs. Studies are needed to explore all such areas. Moreover, all of these studies have been conducted in developed countries. Therefore, there is need of explicit work in developing countries like Pakistan because literature is least reported from these regions.

We aimed to explore frequency, levels, predictors, and clinical relevance of pDDIs in hospitalized patients with hepatitis at tertiary care hospitals. The secondary objective was to develop a list of widespread major-pDDIs along with their potential adverse outcomes and monitoring/management guidelines.

MATERIAL AND METHODS

Study setting and design

This was a retrospective cohort study, carried out in medicine wards of two tertiary care hospitals at Peshawar, Khyber Pakhtunkhwa, Pakistan, Hayatabad Medical Complex (HMC) and Khyber Teaching Hospital (KTH). HMC is a 1,280-bed hospital. It is located in Hayatabad Town of Peshawar city and is second largest hospital in the city. Apart from the western parts of Peshawar, the hospital also serves patients coming from adjacent areas and neighboring Afghanistan for treatment. KTH is a 1,200-bed hospital. It is located on main university road in Peshawar city, providing healthcare coverage to population residing at university road and surrounding regions. As far as pharmacy services are concerned, there is no proper clinical pharmacy coverage at ward level in both the hospitals. Patient's profiles are developed in hand written format and records are maintained manually. Moreover, there is no computerized drug interaction screening programs available in these hospitals.

Ethical approval

Ethical approval was obtained from Institutional Research and Ethics Board of Postgraduate Medical Institute, Peshawar.

Inclusion and exclusion criteria

Following were the inclusion criteria:

- Consecutive patient's profiles with viral hepatitis of any type, admitted to medicine wards during a one-year period, from July 2015 to June 2016.
- Patient's profiles of all age.
- Both gender either male or female patient's profiles.
- All medication, regular and PRN (pro-re-nata, means as required), were included in analysis which were prescribed during the whole hospital-stay of the patient (from the time of admission till discharge).

Patient's profiles were excluded if their medications profiles were incomplete with respect to relevant data needed for study.

Data source

On the basis of inclusion and exclusion criteria, we included 413 patients' clinical profiles. Permission from administration of both of the hospitals was obtained in order to access patients' clinical records. Data were collected regarding hospital admissions, patients' demographics, diagnoses, comorbidities/complications, medications therapy, sign/symptoms, and labs tests. All diagnoses and comorbidities/complications were reported as documented in the patients' profiles maintained in the hospital settings.

Screening of medications profiles for pDDIs

Different software are available for DDIs screening but we selected Micromedex Drug-Reax® (Truven Health Analytics, Greenwood Village, Colorado, USA).[16] Because it has been reported to have highest score in term of sensitivity, specificity and completeness.[17,18] Micromedex

Drug-Reax®, classify drug interactions on the basis of severity-levels and documentation-levels as follows:[16]

Severity-levels:

- **Contraindicated.** The drugs are contraindicated for concurrent use.
- **Major.** The interaction may be life threatening and/or require medical intervention to minimize or prevent adverse effects.
- **Moderate.** The interaction may result in exacerbation of the patient condition and/or require an alteration in therapy.
- **Minor.** The interaction would have limited clinical effects. Manifestations may include an increase in the frequency or severity of the side effects but generally would not require a major alteration in therapy.

Documentation-levels:

- **Excellent.** Controlled studies have clearly established the existence of the interaction.
- **Good.** Documentation strongly suggests the interaction exists, but well-controlled studies are lacking.
- **Fair.** Available documentation is poor, but pharmacologic considerations lead clinicians to suspect the interaction exists; or documentation is good for a pharmacologically similar drug.

Frequency of pDDIs as well as frequencies of severity-levels (contraindicated, major, moderate and minor) were identified. Clinical relevance of top-10 major interactions was reported by correlating them with patients' signs, symptoms and lab tests results. Monitoring/management guidelines were described for these interactions. Widespread list of major-pDDIs was developed along with their potential adverse outcomes.

Statistical analysis

Descriptive statistics were used for presenting data in the form of frequencies and percentages or median (interquartile range, IQR), where appropriate. Logistic regression analysis was applied in order to identify association of the presence of one or more pDDIs with patients' gender, age, number of prescribed medicines, hospital stay, number of comorbidities/complications, and comorbidities/complications. Moreover, association of the presence of major-pDDIs with above mentioned variables was also identified. Exposure to pDDIs of any severity, or, exposures to major-pDDIs were the dependent variables in the model. Patients' characteristics that were taken as independent variables in the model were gender, age, number of prescribed medicines, hospital stay, number of comorbidities/complications, and comorbidities/complications. For each independent variable odds ratios (OR) and 95% confidence intervals (CI) were determined. Initially, univariate logistic regression analysis was carried out. Then, for variables with significant univariate p-values, multivariate analyses were performed. In this study, p-value of 0.05 or less was considered statistically significant. SPSS-v23 was used for statistical analyses of the data.

RESULTS

General characteristics and exposure to interactions

Patients' characteristics and comorbidities/complications of hepatitis were presented in table 1. Of the total 413 studied patients, majority were females (n = 220; 53.3%). The median age was 50 years (IQR = 40-60), median hospital stay was 5 days (IQR = 3-7), and median drugs prescribed was 9 (IQR = 7-11). The most frequent types of hepatitis in this study were hepatitis C infection (n = 319; 77.2%) and hepatitis B infection (n = 69; 16.7%). The most frequent comorbidities/complications were diabetes mellitus (n = 113), chronic liver disease (100), decompensated chronic liver disease (99), and hepatic encephalopathy (97).

Table 1 also lists exposure to all types of pDDIs and pDDIs of major-severity stratified with respect to patient's characteristics. In females pDDIs of all types of severity and major-pDDIs were more frequent as compared to males. Similarly, all types of pDDIs and pDDIs of major severity were more frequently observed in patients aged ≤ 50 years, taking > 9 medicines, hospital stay of > 5 days, and in hepatitis C infected patients. While, in patients with 1-2 comorbid illnesses/complications, all types of pDDIs and pDDIs of major severity were more when compared with ≥ 3 comorbid illnesses/complications or no comorbid illness/complications. Moreover, in diabetes mellitus and hepatic encephalopathy all types of pDDIs and pDDIs of major-severity were mostly observed. In sub group analysis of pDDIs exposure in various types of hepatitis, it was observed that among patients with hepatitis C infection (n = 319), pDDIs of all types were found in 57% patients, while, major-pDDIs were recorded in 34%. Similarly, in patients with hepatitis B infection (n = 69), all types- and major-pDDIs were observed in 44% and 32% patients, respectively. Of total 17 patients infected with hepatitis A, 47% patients encountered all types of pDDIs and 41% major-pDDIs. Hepatitis E infected patients were 8 in number, of which, 50% each were observed with all types- and major-pDDIs.

Table 1. General characteristics of study subjects and exposure to all pDDIs and major-pDDIs.

Patient's characteristics	Patients: n (%)	Exposure to pDDIs [Patients: n (%)]	
		All types of pDDIs	Major-pDDIs
Gender			
Male	193 (46.7)	96 (23.2)	68 (16.5)
Female	220 (53.3)	132 (31.9)	75 (18.2)
Age (years)			
≤ 30	56 (13.6)	28 (6.8)	20 (4.8)
31-45	94 (22.8)	47 (11.3)	31 (7.5)
46-60	177 (42.9)	108 (26.1)	64 (15.5)
> 60	86 (20.8)	45 (10.9)	28 (6.8)
Median (interquartile range)	50 (40-60)		
Hospital stay (days)			
≤ 3	113 (27.4)	51 (12.3)	22 (5.3)
4-6	173 (41.9)	86 (20.8)	51 (12.3)
> 6	127 (30.8)	91 (22)	70 (16.9)
Median (interquartile range)	5 (3-7)		
Drugs prescribed per patient			
≤ 4	27 (6.5)	3 (0.7)	1 (0.2)
5-8	167 (40.4)	67 (16.2)	31 (7.5)
9-12	146 (35.4)	93 (22.5)	61 (14.8)
> 12	73 (17.7)	65 (15.7)	50 (12.1)
Median (interquartile range)	9 (7-11)		
Number of comorbidities/complications			
No comorbidities	27 (6.5)	11 (2.7)	8 (1.9)
1-2	264 (63.9)	137 (33.2)	87 (21.1)
≥ 3	122 (29.5)	80 (19.4)	48 (11.6)
Types of hepatitis			
Hepatitis C infection	319 (77.2)	185 (44.8)	110 (26.6)
Hepatitis B infection	69 (16.7)	31 (7.5)	22 (5.3)
Hepatitis A infection	17 (4.1)	8 (1.9)	7 (1.7)
Hepatitis E infection	8 (1.9)	4 (0.9)	4 (1)
Comorbidities/complications			
Diabetes mellitus	113 (27.4)	73 (17.7)	41 (9.9)
Chronic liver disease	100 (24.2)	56 (13.5)	31 (7.5)
Decompensated chronic liver disease	99 (24)	53 (12.8)	31 (7.5)
Hepatic encephalopathy	97 (23.5)	57 (13.8)	36 (8.7)
Hypertension	71 (17.2)	49 (11.9)	30 (7.3)
Liver cirrhosis	28 (6.8)	17 (4.1)	8 (1.9)
Urinary tract infection	24 (5.8)	16 (3.9)	8 (1.9)
Spontaneous bacterial peritonitis	20 (4.8)	11 (2.7)	9 (2.2)
Tuberculosis	17 (4.1)	11 (2.7)	10 (2.4)
Hepatocellular carcinoma	14 (3.4)	6 (1.5)	3 (0.7)
Hepatoma	14 (3.4)	11 (2.7)	7 (1.7)
Malaria	14 (3.4)	6 (1.5)	1 (0.2)
Stroke	14 (3.4)	12 (2.9)	10 (2.4)
Acute gastroenteritis	13 (3.1)	6 (1.5)	4 (1)
Chronic kidney disease	12 (2.9)	9 (2.2)	3 (0.7)
Pneumonia	10 (2.4)	5 (1.2)	4 (1)
Pyrexia of unknown origin	10 (2.4)	2 (0.5)	1 (0.2)
Chronic obstructive pulmonary disease	9 (2.2)	4 (1)	4 (1)
Pleural effusion	7 (1.7)	3 (0.7)	1 (0.2)
Porto-systemic encephalopathy	7 (1.7)	4 (1)	4 (1)
Anemia	6 (1.5)	1 (0.2)	0 (0)
Asthma	6 (1.5)	5 (1.2)	3 (0.7)
Congestive cardiac failure	5 (1.2)	2 (0.5)	1 (0.2)
Hepatorenal syndrome	5 (1.2)	4 (1)	3 (0.7)
Ischemic heart disease	5 (1.2)	5 (1.2)	2 (0.5)
Human immune virus syndrome	4 (1)	3 (0.7)	3 (0.7)
Left ventricular failure	4 (1)	4 (1)	3 (0.7)
Pancytopenia	4 (1)	0 (0)	0 (0)
Rheumatoid arthritis	4 (1)	3 (0.7)	2 (0.5)

pDDIs: potential drug-drug interactions.

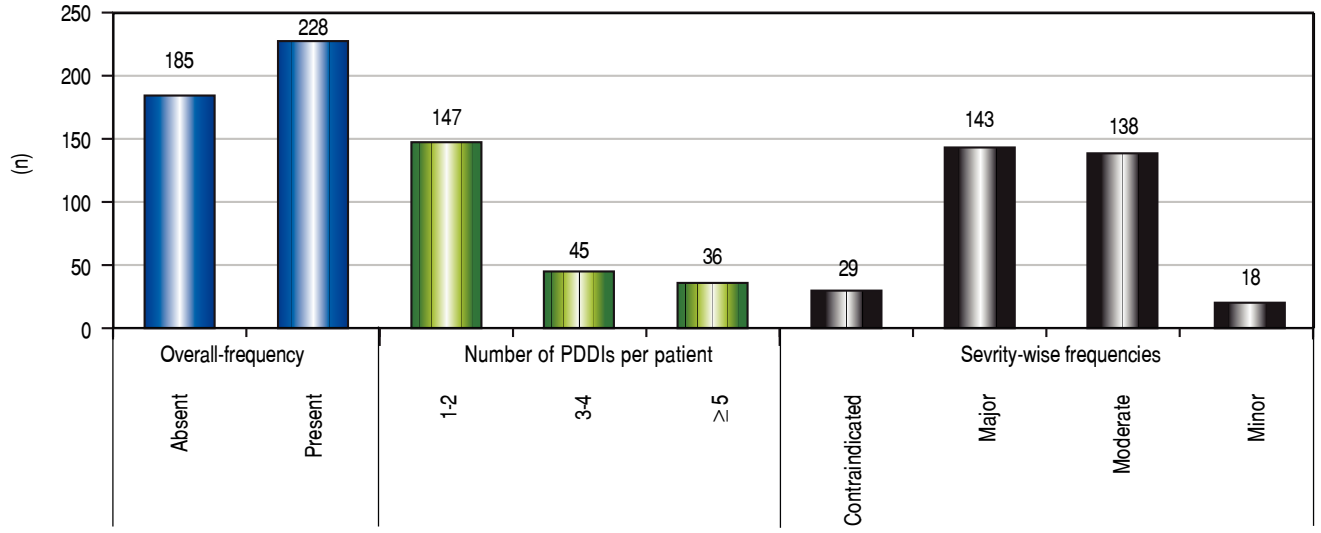

Figure 1. *Frequencies of potential drug-drug interactions. Overall-frequency is the occurrence of at least one pDDIs irrespective of severity type. Total number of hepatitis patients were 413, therefore overall-frequency was 55.2%. Severity-wise frequencies do not add up to 228 (55.2%) because many study subjects were exposed to interactions of different severity-levels. pDDIs: potential drug-drug interactions.*

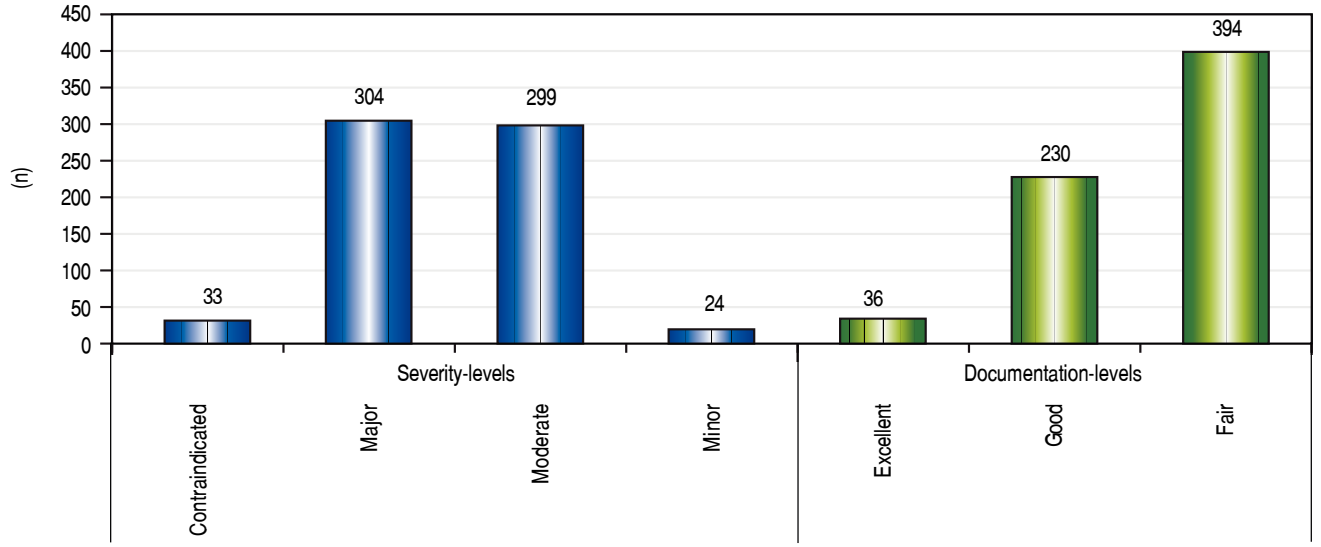

Figure 2. *Levels of the identified potential drug-drug interactions. Levels were identified out of 660 i.e., total number of potential drug-drug interactions. Total interactions: 660.*

Frequencies of potential drug-drug interactions

Figure 1 illustrates that out of total 413 patients, 228 (55.2%) encountered at least one pDDIs. In 8.7% patients, ≥ 5 pDDIs were identified. Frequencies of at least one major-pDDIs were recorded most frequently (n = 143; 35%) followed by moderate-pDDIs (n = 138; 33.4%). While, a limited number of at least one contraindicated-pDDIs and minor-pDDIs were observed.

Levels of potential drug-drug interactions

The recorded pDDIs were categorized on the basis of severity types and documentation types. Total 660 interactions were identified, of which 46% were of major-severity and 45% of moderate-severity; whereas, 60% and 35% were of fair and good scientific-evidence, respectively (Figure 2).

Table 2. Logistic regression analysis based on exposure to all types of pDDIs and major-pDDIs.

Variables	All types of pDDIs				Major-pDDIs			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Gender								
Male	Reference		Reference		Reference		-	
Female	1.5 (1-2.2)	0.04	1.4 (0.9-2.1)	0.2	0.9 (0.6-1.4)	0.8	-	-
Age (Years)								
≤ 50	Reference		-		Reference	-		
> 50	1 (0.7-1.5)	0.9	-	-	0.9 (0.6-1.3)	0.5	-	-
Drugs prescribed								
≤ 9	Reference		Reference		Reference		Reference	
> 9	5 (3.3-7.8)	< 0.001	4.3 (3-7)	< 0.001	6 (3.7-9)	< 0.001	5.1 (3.2-8.2)	< 0.001
Hospital stay (days)								
≤ 5	Reference		Reference		Reference		Reference	
> 5	2.2 (1.5-3.3)	< 0.001	1.6 (1-2.6)	0.03	3 (2-4.4)	< 0.001	2.1 (1.3-3.3)	0.002
Number of comorbidities/complications								
No comorbidities	Reference		Reference		Reference	-		
1-2	1.7 (0.7-3.5)	0.3	1.5 (0.6-3.7)	0.3	1.2 (0.5-2.8)	0.7	-	-
≥ 3	2.8 (1.2-6.5)	0.02	1.6 (0.6-4.5)	0.3	1.5 (0.6-3.8)	0.3	-	-
Comorbidities/complications								
Diabetes mellitus	1.7 (1.1-2.7)	0.02	1.5 (0.9-2.6)	0.1	1.1 (0.7-1.7)	0.7	-	-
Chronic liver disease	1 (0.7-1.6)	0.9	-	-	0.8 (0.5-1.3)	0.4	-	-
Decompensated chronic liver disease	0.9 (0.6-1.4)	0.7	-	-	0.8 (0.5-1.3)	0.4	-	-
Hepatic encephalopathy	1.2 (0.8-1.9)	0.4	-	-	1.2 (0.7-1.9)	0.6	-	-
Hypertension	2 (1.2-3.5)	0.01	1.2 (0.6-2.5)	0.5	1.5 (0.8-2.5)	0.1	-	-
Liver cirrhosis	1.3 (0.6-2.8)	0.5	-	-	0.7 (0.3-1.7)	0.5	-	-
Urinary tract infection	1.7 (0.7-4)	0.2	-	-	0.9 (0.4-2.3)	0.9	-	-
Spontaneous bacterial peritonitis	0.9 (0.4-2.4)	0.9	-	-	1.6 (0.6-4)	0.3	-	-
Tuberculosis	1.5 (0.5-4.2)	0.4		-	2.8 (1.1-7.6)	0.04	1.9 (0.6-5.7)	0.2
Hepatocellular carcinoma	0.6 (0.2-1.8)	0.3	-	-	0.5 (0.1-1.8)	0.3	-	-
Hepatoma	3.1 (0.8-11.2)	0.08	-	-	1.9 (0.7-5.6)	0.2	-	-
Malaria	0.6 (0.2-1.8)	0.3	-	-	0.1 (0.01-1.1)	0.05	0.1 (0.02-1.2)	0.07
Stroke	5.1 (1.1-23)	0.03	5 (1-26)	0.05	5 (1.5-16)	0.007	7.7 (2.1-27.6)	0.002
Acute gastroenteritis	0.7 (0.2-2.1)	0.5	-	-	0.8 (0.3-2.8)	0.8	-	-
Chronic kidney disease	2.5 (0.7-9.3)	0.2	-	-	0.6 (0.2-2.3)	0.5	-	-
Pneumonia	0.8 (.2-2.8)	0.7	-	-	1.3 (0.4-4.6)	0.7	-	-
Pyrexia of unknown origin	0.2 (0.04-0.9)	0.04	0.2 (0.05-1.2)	0.08	0.2 (0.03-1.6)	0.1	-	-
Chronic obstructive pulmonary disease	0.6 (0.2-2.4)	0.5	-	-	1.5 (0.4-5.8)	0.5	-	-
Pleural effusion	0.6 (0.1-2.7)	0.5	-	-	0.3 (0.03-2.6)	0.3	-	-
Porto-systemic encephalopathy	1.1 (0.2-5)	0.9	-	-	2.6 (0.6-12)	0.2	-	-

pDDIs: potential drug-drug interactions. OR: odds ratio. CI: confidence interval.

Predictors of potential drug-drug interactions

Results of univariate logistic regression analysis for exposure to all types of pDDIs are presented in table 2. This analysis showed that association for the presence of all types of pDDIs with patient's age was not significant (95% CI = 0.7-1.5; p = 0.9). However, significant association was observed for the presence of all types of pDDIs with female gender (95% CI = 1-2.2; p = 0.04), > 9 prescribed medicines (95% CI = 3.3-7.8; p < 0.001), hospital stay of >5 days (95% CI = 1.5-3.3; p < 0.001), ≥ 3 number of comorbidities/complications (95% CI = 1.2-6.5; p = 0.02), comorbidities such as diabetes mellitus (95% CI = 1.1-2.7; p = 0.02), hypertension (95% CI = 1.2-3.5; p = 0.01), & stroke (95% CI = 1.1-23; p = 0.03), and absence of pyrexia of unknown origin (95% CI = 0.04-0.9; p = 0.04).

Results of multivariate logistic regression analysis for exposure to all types of pDDIs (Table 2) showed that association for the presence of all types of pDDIs was not significant with patient's gender (95% CI = 0.9-2.1; p = 0.2), ≥ 3 number of comorbidities/complications (95% CI = 0.6-4.5; p = 0.3), comorbidities such as diabetes mellitus (95% CI = 0.9-2.6; p = 0.1) & hypertension (95% CI = 0.6-2.5; p = 0.5), and absence of pyrexia of unknown origin (95% CI = 0.05-1.2; p = 0.08). However, significant association was observed for the presence of all types of pDDIs with > 9 prescribed medicines (95% CI = 3-7; p < 0.001), hospital stay of > 5 days (95% CI = 1-2.6; p = 0.03), and stroke as comorbidity (95% CI = 1-26; p = 0.05).

Results of univariate logistic regression analysis for exposure to one or more major-pDDIs are also presented in table 2. The univariate logistic regression analysis showed that association for presence of major-pDDIs was not significant with patient's gender (95% CI = 0.6-1.4; p = 0.8), age (95% CI = 0.6-1.3; p = 0.5), and number of comorbidities/complications such as 1-2 (95% CI = 0.5-2.8; p = 0.7) & ≥ 3 (95% CI = 0.6-3.8; p = 0.3). While, association was significant with > 9 prescribed medicines (95% CI = 3.7-9; p < 0.001), hospital stay of > 5 days (95% CI = 2-4.4; p < 0.001), comorbidities such as tuberculosis (95% CI = 1.1-7.6; p = 0.04) & stroke (95% CI = 1.5-16; p = 0.007), and absence of malaria (95% CI = 0.01-1.1; p = 0.05).

The multivariate logistic regression analysis is presented in table 2 from which it is observed that association for presence of major-pDDIs was not significant with comorbidity as tuberculosis (95% CI = 0.6-5.7; p = 0.2) and absence of malaria (95% CI = 0.02-1.2; p = 0.07). While, significant association was observed for presence of major-pDDIs with > 9 prescribed medicines (95% CI = 3.2-8.2; p < 0.001), hospital stay of >5 days (95% CI = 1.3-3.3; p = 0.002), and stroke as comorbidity (95% CI = 2.1-27.6; p = 0.002).

Clinical relevance

In Table 3 relevant clinical findings (pertinent signs/symptoms and laboratory test results) and monitoring/management guidelines[16,19,20] for top-10 widespread major interactions have been presented. Patients with the interaction, metronidazole + Sodium Phosphate/Sodium Biphosphate, metronidazole + norfloxacin, metronidazole + octreotide, ciprofloxacin + metronidazole, and domperidone + ranitidine presented with tachycardia, bradycardia, and abnormal potassium levels. Clinical features indicating poor response and nephrotoxicity were detected in patients with interactions such as aspirin + furosemide and diclofenac + spironolactone. In patients with the interaction isoniazid + rifampin and pyrazinamide + rifampin, signs/symptoms of hepatotoxicity were observed such as abdominal distension, anorexia, ascites, constipation, fever, hepatomegaly, hepatospleenomegaly, pedal edema, weight loss, and abnormality in labs such as increase Alanine Aminotransferase, increase Alkaline Phosphatase, increase serum bilirubin, and decrease serum albumin. Patients with the interaction ramipril + spironolactone, presented with tachycardia, orthopnea, fatigue, nausea, vomiting, abnormal potassium level, hyponatremia, increase serum creatinine, and increase blood urea nitrogen.

DISCUSSION

DDIs remains one of the challenges in pharmacotherapy of patients with hepatitis.[9,14] This report presents the frequency and categorization of pDDIs in hospitalized hepatitis patients. Up to our knowledge prevalence based pDDIs studies, which are related to drugs prescribed to hospitalized patients with hepatitis remains poorly addressed. The overall prevalence of pDDIs in our study was high (55.2%) when compared with a study conducted in New York on hepatitis C infected patients.[9] The study reports 16.7% prevalence of pDDIs and considers only contraindicated type of pDDIs.[9] Moreover, this inconsistency may be due to variability in study population, study design, drug prescribing pattern, and drug interaction screening software. Similarly, prevalence of major-pDDIs in our study was high when compared with a study conducted on hepatitis C infected patients. The study reports 30%-44% of clinically significant pDDIs. The aforementioned study only considers interactions of anti-viral agents with the drugs used in hepatitis.[14] Furthermore, comparing studies related to medicine wards, our prevalence of pDDIs remains within range i.e., 43% to 56.2%.[21-23] Regardless of variations in the study design, study population, and drug interaction screening programs, these published reports indicate a high prevalence of pDDIs in hospitalized patients that support our findings. Taking in to

Table 3. Clinical relevance and monitoring/management guidelines of top ten major potential drug-drug interactions in patients with hepatitis.

Interaction*	Signs and symptoms*	Labs results*	Monitoring/management guidelines[16,19,20]	Documentation[16]
Metronidazole-Sodium Phosphate/ Sodium Biphosphate (35)	Tachycardia (15) Bradycardia (1)	Hyperkalemia (3) Hypokalemia (2)	Monitoring of ECG and signs and symptoms of QT interval prolongation, especially in high riskpatients. Avoidance of medications known to cause QT interval prolongation in such patients is suggested.	Fair
Aspirin – Furosemide (13)	Leg edema (2) High blood pressure (5)	Hyponatremia (6) Hypokalemia (4) Hypochloremia (3) Increase BUN (10) Increase serum creatinine (7)	Patients should be monitored for signs of renal toxicity and salicylate toxicity. Diuretic effectiveness should be assured including its effects on blood pressure. Avoid high dose of salicylates in those taking loop diuretics, an alternative analgesic should be given.	Good
Metronidazole-Norfloxacin (11)	Tachycardia (1)	Hypokalemia (1)	Monitoring of ECG and signs and symptoms of QT interval prolongation, especially in high risk patients. Avoidance of medications known to cause QT interval prolongation in such patients is suggested.	Fair
Metronidazole-Octreotide (9)	Tachycardia (1)	Hyperkalemia (2)	Monitoring of ECG and signs and symptoms of QT interval prolongation, especially in high risk patients. Avoidance of medications known to cause QT interval prolongation in such patients is suggested.	Fair
Ciprofloxacin-Metronidazole (8)	Tachycardia (4)	Hyperkalemia (1) Hypokalemia (2)	Monitoring of ECG and signs and symptoms of QT interval prolongation, especially in high risk patients. Avoidance of medications known to cause QT interval prolongation in such patients is suggested.	Fair
Isoniazid-Rifampin (8)	Abdominal distension (3) Anorexia (3) Ascites (2) Constipation (1) Fever (5) Hepatomegaly (2) Hepatospleenomegaly (1) Pedal edema (2) Weight loss (3)	Increase ALT (3) Increase ALP (1) Increase serum Bilirubin (2) Decrease serum Albumin (1)	Patients should be monitored for signs and symptoms of liver toxicity including fever, anorexia, vomiting and jaundice. Baseline and periodic LFTs monitoring is suggested.	Good
Diclofenac Spironolactone (6)	Tachycardia (1) Bradycardia (3)	Hyponatremia (2) Hypokalemia (1) Hyperkalemia (2) Hyperchloremia (2) Increase BUN (2)	Patients should be monitored for hyperkalemia and signs of renal toxicity. Diuretic effectiveness should be assured including its effects on blood pressure.	Good

Pyrazinamide-Rifampin (6)	Abdominal distension (2) Anorexia (3) Ascites (2) Constipation (1) Fever (3) Hepatomegaly (2) Hepatospleenomegaly (1) Pedal edema (2) Weight loss (3)	Increase ALT (1) Increase ALP (1) Increase serum Bilirubin (1)	Monitoring of LFTs at baseline and at 2, 4, 6, and 8 weeks of treatment. Patient education about reporting symptoms of liver injury.	Good
Domperidone-Ranitidine (6)	Tachycardia (1) Bradycardia(1)	Hypokalemia (1)	Monitor patients for signs and symptoms of domperidone toxicity. Initiate domperidone at lowest possible dose and titrate with caution. Domperidone should be discontinued if patient experiences dizziness, palpitations, syncope, or seizure.	Fair
Ramipril-Spironolactone (5)	Tachycardia (1) Orthopnea (4) Fatigue (2) Nausea (1) Vomiting (1)	Hypokalemia (1) Hyperkalemia (1) Hyponatremia (4) Increase serum Creatinine (3) Increase BUN (5)	The hyperkalemia associated with this combination is of special concern in patients with renal impairment or diabetes, those with a risk for dehydration, and in the elderly. Renal function and serum potassium levels should be monitored in patients receiving this combination. Daily doses of 12.5 mg to 25 mg of spironolactone co-administered with conventional therapy of angiotensin converting enzyme inhibitors, loop diuretics, and digitalis are relatively safe, provided that serum potassium levels are monitored.	Good

*BUN: blood urea nitrogen. ALT: alanine aminotransferase. ALP: alkaline phosphatase. LFTs: liver function tests. Doc: Documentation. *Frequencies are given in parenthesis and calculated among patients with respective interaction.*

consideration the findings of this study, Pakistani population are more at risk to pDDIs because there is neither clinical pharmacy departments nor DDIs screening systems available in hospitals.[24] Evidence based strategies should be recommended in hospitals in order to manage DDIs such as clinical pharmacist participation in evaluating patient medications profiles for pDDIs,[25] screening of medications profiles for pDDIs by the use of computerized screening programs,[26] assessment of pertinent laboratory tests for clinical relevance of interactions,[27] and procedure for structured assessment of pDDIs.[28]

Considering levels of identified interactions healthcare providers are responsible for management of adverse effects caused by pDDIs. In this report, major-pDDIs were frequently identified followed by moderate-pDDIs and concerning scientific evidence, fair type were more common followed by good type of scientific evidence. These findings are inconsistent with other studies conducted in hospitalized patients in which moderate-pDDIs and good type of scientific evidence pDDIs were more frequently observed.[23,29] Our findings threaten that hepatitis patients are at risk for adverse outcomes related to pDDIs. Therefore, it is essential for health care providers to properly identify the type of pDDIs. As, it is vital for clinical management of pDDIs, designing prophylactic measures for prevention, and reducing the associated risk.

Polypharmacy has become an important issue among patients with hepatitis. These patients receive multiple therapy for treating comorbidities or associated complications.[30] A positive relationship is seen for risk of pDDIs with polypharmacy, longer hospitalization, and stroke.[31,32] We also observed significant association for presence of pDDIs with polypharmacy, longer hospitalization, and stroke as comorbidity. These findings are in accordance with other published reports, in which polypharmacy, longer hospitalization, and stroke are predictors for pDDIs.[9,23,29,32] In this regard, hepatitis patients are more likely to be at risk to pDDIs, particularly to major-pDDIs. On the other hand, our findings i.e., absence of significant association of older age with pDDIs was not in accordance with other published reports.[23,29,33] One of the reason may be related to survival, whereby hepatitis is usually acquired at adult or middle age and these patients are less liable to live to an older age. Furthermore, we have

calculated odds of exposure to major-pDDIs separately. Significant results for association of major-pDDIs with polypharmacy, longer hospitalization, and stroke are consistent with other studies.[24,32] Health care professionals should be informed about all possible risk factors for pDDIs, so that patients at risk should be carefully individualized in order to optimize therapy and to avoid or minimize pDDIs.

All identified pDDIs are not clinically important. Therefore, there is an immense need to develop list of clinically significant interactions that are observed in hospitalized hepatitis patients. This list will be used by health care professionals for selective identification and management of pDDIs and to develop clinical guidelines. Every healthcare provider cannot differentiate pDDIs from ADRs, and take corrective measures accordingly.[34] A clinician's knowledge and understanding of DDIs can decrease the likelihood of ADR, able to provide better quality care to such patients, adjust therapeutic regimen of high risk patients, and avoid associated medico legal issues. Clinical relevance of clinically significant interactions present potential outcomes of interactions on clinical manifestations and laboratory tests results, which additional emphasizes the significance of medications profiles screening for DDIs, also enlightens by published studies.[24,29] The clinical relevance of pDDIs is frequently classified into two aspects, the predicted severity of patient's reaction to a pDDIs and the documentation i.e., the quality and amount of research that intends whether a specific DDIs will certainly occur in individuals.[35] The clinical consequences of any DDI, nevertheless of how well recorded, do not appear in every patient or to the same extent of intensity.[36] These depend on patient associated aspects that usually necessitate individual consideration. Future research can evaluate the clinical relevance of a pDDIs actually. Monitoring parameters for interactions and management guidelines will be helpful for physicians and clinical pharmacists to evaluate and manage DDIs in hepatitis patients.

Following is the potential limitation of our study. We conducted this study in tertiary care hospitals where hepatitis patients are mainly admitted for the management of various complications of hepatitis and/comorbid illnesses. The pDDIs that we have identified are mainly related to use of drugs for the management of such problems. Therefore, our results may not be generalizable to outpatient settings where the disease and drug interaction pattern possibly will be different.

CONCLUSION

Patients with hepatitis present with a considerable number of clinically relevant pDDIs. Attention should be given to widespread major-pDDIs and their potential adverse outcomes. Clinically relevant parameters, such as labs and signs/symptoms should be monitored particularly in high risk patients having polypharmacy, prolong hospitalization, and stroke as comorbidity. Software based screening of pDDIs is recommended in order to identify, prevent/reduce, and manage pDDIs in hepatitis patients. Moreover, hepatologists should not only be aware of the principles of dose adjustment in patients with hepatitis, but also the clinically significant DDIs of the drugs used to treat hepatitis and comorbid illnesses in this population.

ABBREVIATIONS

- **ADRs:** adverse drug reactions.
- **DDIs:** drug-drug interactions.
- **IQR:** interquartile range.
- **pDDIs:** potential drug-drug interactions.

CONFLICT OF INTEREST

The authors declares that there is no conflict of interest regarding the publication of this article.

REFERENCES

1. Sembulingam K, Sembulingam P. (eds.) Essentials of Medical Phsyiology. 2nd Ed. New Dehli, India: Jaypee Brothers Medical Publishers, 2012; pp. 179-88.
2. Perz JF, Armstrong GL, Farrington LA, Hutin YJ, Bell BP. The contributions of hepatitis B virus and hepatitis C virus infections to cirrhosis and primary liver cancer worldwide. *J Hepatol* 2006; 45: 529-38.
3. Delco F, Tchambaz L, Schlienger R, Drewe J, Krähenbühl S. Dose adjustment in patients with liver disease. *Drug Saf 2005*; 28: 529-45.
4. Blaschke TF, Rubin PC. Hepatic first-pass metabolism in liver disease. *Clin Pharmacokinet* 1979; 4: 423-32.
5. Vyas K, Gala B, Sawant P, Das HS, Kulhalli PM, Mahajan SS. Assessment of portal hemodynamics by ultrasound color Doppler and laser Doppler velocimetry in liver cirrhosis. *Indian J Gastroenterol* 2001; 21: 176-8.
6. Adedoyin A, Arns PA, Richards WO, Wilkinson GR, Branch RA. Selective effect of liver disease on the activities of specific metabolizing enzymes: Investigation of cytochromes P450 2C19 and 2D6. *Clin Pharmacol Ther* 1998; 64: 8-17.
7. Wœniowska B, Tylutki Z, Wyszogrodzka G, Polak S. Drug-drug interactions and QT prolongation as a commonly assessed cardiac effect-comprehensive overview of clinical trials. *BMC Pharmacol Toxicol* 2016; 17: 12.
8. Ginès P, Arrovo V, Rodés J. Pharmacotherapy of ascites associated with cirrhosis. *Drugs* 1992; 43: 316-32.
9. Patel N, Nasiri M, Koroglu A, Bliss S, Davis M, McNutt L-A, Miller C. A cross-sectional study comparing the frequency of drug interactions after adding simeprevir-or sofosbuvir-containing therapy to medication profiles of hepatitis C monoinfected patients. *Infect Dis Ther* 2015; 4: 67-78.
10. Lauffenburger JC, Mayer CL, Hawke RL, Brouwer KL, Fried MW, Farley JF. Medication use and medical comorbidity in patients with chronic hepatitis C from a US commercial

claims database: high utilization of drugs with interaction potential. *Eur J Gastroenterol Hepatol* 2014; 26: 1073-82.
11. Burger D, Back D, Buggisch P, Buti M, Craxí A, Foster G, Klinker H, et al. Clinical management of drug-drug interactions in HCV therapy: Challenges and solutions. *J Hepatol* 2013; 58: 792-800.
12. Franz CC, Egger S, Born C, Bravo AER, Krähenbühl S. Potential drug-drug interactions and adverse drug reactions in patients with liver cirrhosis. *Eur J Clin Pharmacol* 2012; 68: 179-88.
13. Back D, Else L. The importance of drug–drug interactions in the DAA era. *Dig Liver Dis* 2013; 45: S343-S348.
14. Kondili LA, Gaeta GB, Ieluzzi D, Zignego AL, Monti M, Gori A, Soria A, et al. Real-life data on potential drug-drug interactions in patients with chronic hepatitis C viral infection undergoing antiviral therapy with interferon-free DAAs in the PITER Cohort Study. *PLoS One* 2017; 12: e0172159.
15. Poizot-Martin I, Naqvi A, Obry-Roguet V, Valantin M-A, Cuzin L, Billaud E, Cheret A, et al. Potential for drug-drug interactions between antiretrovirals and HCV direct acting antivirals in a large cohort of HIV/HCV coinfected patients. *PLoS One* 2015; 10: e0141164.
16. Micromedex Drug-Reax®, Greenwood Village, CO: Truven Health Analytics. Available at: https://www.micromedexsolutions.com/micromedex2/librarian/ssl/true. Accessed February 10 2017.
17. Patel RI, Beckett RD. Evaluation of resources for analyzing drug interactions. *J Med Libr Assoc* 2016; 104: 290-5.
18. Kheshti R, Aalipour M, Namazi S. A comparison of five common drug–drug interaction software programs regarding accuracy and comprehensiveness. *J Res Pharm Pract* 2016; 5: 257-63.
19. Tatro DS. (ed.) Drug Interaction Facts: Facts and Comparisons. St. Louis, Missouri: Wolters Kluwer Health, 2008; pp. 901-1358.
20. Baxter K. (ed.) Stockley's Drug Interactions. 9th ed. London, Chicago: Pharmaceutical Press; 2010; pp.349-1123.
21. Vonbach P, Dubied A, Krähenbühl S, Beer JH. Prevalence of drug-drug interactions at hospital entry and during hospital stay of patients in internal medicine. *Eur J Intern Med* 2008; 19: 413-20.
22. Ibáñez A, Alcalá M, García J, Puche E. Drug-drug interactions in patients from an internal medicine service. F*arm Hosp* 2008; 32: 293-297.
23. Ismail M, Iqbal Z, Khattak MB, Khan MI, Arsalan H, Javaid A, Gul Q, et al. Potential drug–drug interactions in internal medicine wards in hospital setting in Pakistan. *Int J Clin Pharm* 2013; 35: 455-62.
24. Ismail M, Aziz S, Noor S, Haider I, Shams F, Haq I, Khadim F, et al. Potential drug-drug interactions in pediatric patients admitted to intensive care unit of Khyber Teaching Hospital, Peshawar, Pakistan: A cross-sectional study. *J Crit Care* 2017; 40: 243-50.
25. Langness JA, Nguyen M, Wieland A, Everson GT, Kiser JJ. Optimizing hepatitis C virus treatment through pharmacist interventions: Identification and management of drug-drug interactions. *World J Gastroenterol* 2017; 23: 1618-26.
26. Moura CS, Prado NM, Belo NO, Acurcio FA. Evaluation of drug–drug interaction screening software combined with pharmacist intervention. *Int J Clin Pharm* 2012; 34: 547-52.
27. Geerts AF, De Koning FH, De Smet PA, Van Solinge WW, Egberts TC. Laboratory tests in the clinical risk management of potential drug-drug interactions. *Drug Saf* 2009; 32: 1189-97.
28. van Roon EN, Flikweert S, le Comte M, Langendijk PN, Kwee-Zuiderwijk WJ, Smits P, Brouwers JR. Clinical relevance of drug-drug interactions. *Drug Saf* 2005; 28: 1131-9.
29. Egger SS, Drewe J, Schlienger RG. Potential drug–drug interactions in the medication of medical patients at hospital discharge. *Eur J Clin Pharmacol* 2003; 58: 773-8.
30. Boccaccio V, Bruno S. Optimal management of patients with chronic hepatitis C and comorbidities. *Liver Int* 2015; 35: 35-43.
31. Moura CSd, Acurcio FdA, Belo NdO. Drug-drug interactions associated with length of stay and cost of hospitalization. *J Pharm Pharmaceut Sci* 2009; 12: 266-72.
32. Caratozzolo S, Gipponi S, Marengoni A, Pari E, Scalvini A, Pasina L, Magoni M, et al. Potentially Serious Drug-Drug Interactions in Older Patients Hospitalized for Acute Ischemic and Hemorrhagic Stroke. *Eur Neurol* 2016; 76: 161-6.
33. Gagne J, Maio V, Rabinowitz C. Prevalence and predictors of potential drug-drug interactions in Regione Emilia-Romagna, Italy. *J Clin Pharm Ther* 2008; 33: 141-51.
34. Glassman PA, Simon B, Belperio P, Lanto A. Improving recognition of drug interactions: benefits and barriers to using automated drug alerts. *Med Care* 2002; 40: 1161-71.
35. Roberts JS, Watrous ML, Schulz RM, Mauch RP, Nightengale BS. Quantifying the Clinical Significance of Drug—Drug Interactions: Scaling Pharmacists' Perceptions of a Common Interaction Classification Scheme. *Ann Pharmacother* 1996; 30: 926-34.
36. Jankel CA, Fitterman LK. Epidemiology of drug-drug interactions as a cause of hospital admissions. *Drug Saf* 1993; 9: 51-9.

Correspondence and reprint request:
Mohammad Ismail, Ph.D.
Assistant Professor, Department of Pharmacy, University of Peshawar, Peshawar, Khyber Pakhtunkhwa, Pakistan.
Tel.: +92-91-9216750, Fax: +92-91-9218131
ORCID ID: http://orcid.org/0000-0001-7227-3399
E-mail: ismailrph@upesh.edu.pk