Abstract—Digoxin continues to be an important drug in long-term heart failure patient management. Digoxin serum levels monitoring is aimed to optimise therapy, whereas the concentration required for optimal efficacy without risking toxicity remains not clearly defined. Objectives: This study was aimed to assess how frequently occur the so-called toxic digoxin levels in elderly patients being treated in faculty hospitals. Methods: Retrospective search for serum digoxin trough levels record as determined throughout the period of two years (2007-2008) was conducted in two independent hospital facilities. Only digoxin levels > 2ng/mL in patients older than 65 year were included. Potassium and serum creatinine levels were also evaluated if available with consecutive digoxin levels. Data from 301 hospitalised patients (91 males, 210 females) were valid for the purpose of this study. Results: Total of 427 trough levels (sampled shortly before the next doses) from patients within age 66-100 years were found to be above the upper therapeutic limits post Digitalis Investigation Group study recommendations. Serum digoxin levels recorded showed: Max. 6.19, Mean 3.129± 0.70, Mode 2.8, and Median 3 ng/mL values, respectively. Women were found to have high digoxin levels more frequently than men on similar oral doses of 0.125 - 0.250 on chronic basis. In conclusion, this retrospective study demonstrated that significant number of elderly patients live with potentially toxic levels of digoxin most probably for long time, before being discovered.

Keywords— Digitalis effect, elderly patients, digoxin toxicity

1.INTRODUCTION

Digitalis found in nature from several plant sources (Fig. 1) has been widely used in the treatment of several disorders in the olden days and continues today on evidence basis. Their use as treatment for cardiac disease for more than two centuries starts from the observation Sir William Withering (1741-1799), who introduced power of curing as well as killing of the foxgloves Component, [1] whereas new perspective on its beneficia use is also recently published. [2]. Withering published, in 1785, his testimony on the use of foxglove believing that digitalis had a diuretic effect in patients with a weak and irregular pulse who had edema. He had probably first learned the value of foxglove, from which digitalis can be extracted, from an old woman who had reportedly „cured„ some cases after the more regular practitioners had failed to do so. [3] Since then, the product of digitalis Janata, identified as a drug digoxin(Fig. 2) with functional structures (Fig. 3) remains one of the most prescribed cardiac drugs. [4]
polypharmacy and possible drug interactions with the increasing age and how concomitant disease states or drug interactions including over the counters and herbals maybe containing digitalis affecting the pharmacokinetics of digoxin. The main aim of this study was to assess how frequently occur the so-called toxic digoxin levels in elderly patients in two independent teaching hospitals.

2. Patients and Methods

The search for serum digoxin trough levels record as determined throughout the period of two years (2007-2008) was conducted in two independent hospital facilities. Only digoxin levels > 2ng/mL in patients older than 65 years were included. Potassium and serum creatinine levels were also evaluated if available with digoxin levels. Records of serum digoxin levels from 301 hospitalised patients (91 male, 210 female) were included for the retrospective evaluation in terms of potential toxicity. The blood samples are drawn into the tube with accelerator of hemocoagulation. Then centrifuged 10 minutes at 4000 rpm and temperature 8 °C for obtaining serum immediately after reaching the laboratory. Serum samples were stored at temperature 4 to 8 ± 3 °C in fridge and were frozen at -20 ± 5 °C if long-term storage is required. It isn’t allowed to freeze serum after thawing again. We needed 100–200 µl of nonhemolytic serum for valid analyses. The levels of digoxin in patients' samples were determined by Cobas Integra 400 (Roche) analyzer utilizing Kinetic Interaction of Microparticles in Solution (KIMS). The method is principally based on measuring of absorbance of microparticles aggregate. The reagent cassette for determination of digoxin includes 2 reagents, where one of them contains anti-digoxin monoclonal mouse antibody and the other contains microparticles coated with digoxin. The microparticles interact with anti-digoxin antibody very fastly and that results in formation of aggregate. If the patient’s sample possesses digoxin, inhibition of aggregation takes place due to interaction of antibody with drug in patients’ sample. However, the ability of formation of aggregate between microparticles and antibodies slows down with growing concentration of digoxin in sample. That’s why measured absorbance of sample slopes also decreases. The value of digoxin concentration is taken from the calibrating curve.

3. Results

Total of 427 trough levels (sampled shortly before the next doses) from patients within age 66-100 years were found to be above the upper therapeutic limits of the older dates or post DIG study recommendations (Fig. 4 and 5). However, 44 samples were excluded due to uncertainty of information on dosing regimen, whereas, 383 samples were valid for final analysis. Serum digoxin levels recorded showed values, Max. 6.19, Mean 3.129±0, 70, Mode 2.8, and Median 3 ng/mL,
The highest recorded value of trough serum digoxin concentration was in male gender, although the number of males in the study was less compared to women. Women were found to have high digoxin levels more than twice frequently as men on the same oral doses of 0.125 - 0.250 mg per day in this study as showed in summary statistics. Although elevated in some individuals, analyses like plasma potassium and serum creatinine did not show clear relation with serum digoxin concentrations.

This is particularly true mainly because adverse effects are more often prevalent and pronounced in this population. Over the years, it has been documented, that digoxin is a frequently prescribed medication in elderly populations. Although this drug can be beneficial when used in the appropriate setting, recent data would suggest that inappropriate administration of digoxin is common and not without potentially serious consequences. It is likely that the excessive use of digoxin in elderly populations as discussed in this presentation is perhaps based on the prevalence of diastolic heart failure in the elderly as well as other co-morbid conditions that may mimic heart failure signs and symptoms. Since the elderly appear to be at high risk for digoxin toxicity, the inappropriate use of this medication to treat these conditions could result in significant and unnecessary morbidity. Although it is probable that the indications for digoxin use to treat congestive heart failure will continue to evolve, at the present time most would recommend using this agent in symptomatic heart failure related to a reduction in left ventricular systolic function or when associated with atrial fibrillation. Problem with interference of endogenous substances may challenge interpretation. However, Lackner et al. [11], who studied the effect of digoxin-like immunoreactive substance (DLIS) on serum digoxin determinations in elderly patients with normal serum creatinine concentrations concluded that there was no significant increase in the difference between the Immophase results with decreasing creatinine clearance. In the elderly patients with normal serum creatinine concentrations, there was no evidence that measurement of serum digoxin concentration using Immophase assays was compromised by DLIS. Hanratty et al. [12] expressed that application of basic pharmacological principles may be helpful in anticipating these problems. Many hospital admissions of elderly patients for drug toxicity occur after administration of a drug known to cause drug-drug interactions, where many of these interactions could have been avoided [13].

Despite the common knowledge that the elderly are at an increased risk of digoxin toxicity, awareness seems anadequate as the levels recorded in our retrospective analysis demonstrate. Low dosages of digoxin bearing lower levels appear to be effective in the treatment of heart failure due to systolic dysfunction and may reduce the incidence of digitalis toxicity in these patients [14].

Although not well documented clinical manifestation of toxicity as often published (Table 4) in patients enrolled in our retrospective analysis, it is evident that the drug levels we recorded were far higher than the latest recommendations, especially post DIG conclusions (Fig. 4). The relationship between dynamic effect of digoxin and its serum concentrations are still vague and a matter.

### Table 1
Illustrates descriptive statistical summary of serum digoxin concentrations in both genders (F and M)

<table>
<thead>
<tr>
<th></th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>3.297261</td>
</tr>
<tr>
<td>+/- SD</td>
<td>0.702788</td>
</tr>
<tr>
<td>Max</td>
<td>6.19</td>
</tr>
<tr>
<td>Min</td>
<td>2</td>
</tr>
<tr>
<td>Mode</td>
<td>2.8</td>
</tr>
<tr>
<td>Median</td>
<td>3</td>
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</table>

### Table 2
Illustrates descriptive statistical summary of serum digoxin concentrations in elderly females.

<table>
<thead>
<tr>
<th></th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>2.638414</td>
</tr>
<tr>
<td>Minimum</td>
<td>2.100000</td>
</tr>
<tr>
<td>Maximum</td>
<td>4.900000</td>
</tr>
<tr>
<td>Std. Dev.</td>
<td>0.570186</td>
</tr>
</tbody>
</table>

### Table 3
Illustrates descriptive statistical summary of serum digoxin concentrations in elderly males.

<table>
<thead>
<tr>
<th></th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>3.305577</td>
</tr>
<tr>
<td>Minimum</td>
<td>2.080000</td>
</tr>
<tr>
<td>Maximum</td>
<td>6.190000</td>
</tr>
<tr>
<td>Std. Dev.</td>
<td>0.673167</td>
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</table>

### 4. DISCUSSION
Stults [9] stated that time extensive use of digoxin in elderly patients with left ventricular failure and sinus rhythm may not be clinically justifiable; in a significant proportion of these patients the frequency of digitalis toxicity may outweigh the therapeutic benefits of the drug. To add to the challenge, older patients are also more likely to develop toxicity and diagnosis of digoxin toxicity can be difficult in this group. It is important to understand how the pharmacokinetics of digoxin may be altered in the older population, so that the specific geriatric pharmacology of the drug must be considered, when digoxin is used in elderly patients. Clinical benefit should also be documented before proceeding to long-term maintenance therapy. In selected elderly patients, withdrawal of digoxin with careful follow-up may be a worthwhile procedure. Due age related polymorbidity, the elderly population requires treatment with multiple types of medications including cardiovascular pharmacotherapeutic regimen, where the risk versus the benefit of each medication must be strongly considered.
of controversy, however our past reports also indicates that people can do well even with undetectable concentrations on chronic regular doses [15] However, the fact that many patients taking digoxin on chronic basis are incidentally detected to have unacceptably higher serum drug concentrations carrying potential hazards warrants more attention. Thus, besides knowing the underlying pathophysiology in the elderly patient population and the drug itself better, therapeutic drug monitoring with very qualified interpretation my help to reduce toxicity risk at the same time avoiding subtherapeutic levels [16] Similar to ours and other previous studies, a recently published two center retrospective study findings also demonstrated that elderly patients and women are at higher risk of digoxin toxicity with potentially worse outcomes [17] A recent prospective Turkish study that included 800 patients aged 70 or over also showed that nearly 40% of elderly patients receive digoxin with inappropriate indications and 75% of these patients take digoxin at higher doses than the recommended doses for this age group [18] Similar results were published in late 19th, showing that the prevalence of digoxin use was 19% in older patients at the time of admission to the nursing home and almost half of patients (47%) receiving digoxin at the time of admission had an inappropriate indication for digoxin use at that time [19] Approximately one-third of long-term care facility residents with heart failure received digoxin where atrial fibrillation was the most important determinant of use and at least 26% of these residents were exposed to an increased risk of digoxin toxicity [20] In general, available reports indicate that as for any pharmacologically active problematic agent, therapeutic drug monitoring of digoxin is considered of vital importance due to both significant pharmacokinetic variability and strong clinically relevant exposure-effect relationships. Digoxin may exhibit marked variability in plasma drug concentration as a result of inconsistent absorption (oral form), and elimination, or interaction with concomitantly used medications in polymorbid elderly population, where many other age related changes make the situation even more complicated.

Table 4. Common symptoms expected during acute versus chronic digitalis/digoxin toxicity

<table>
<thead>
<tr>
<th>Acute toxicity</th>
<th>Chronic toxicity</th>
</tr>
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<tbody>
<tr>
<td>Asymptomatic for several hours</td>
<td>Elderly on digoxin and diuretics</td>
</tr>
<tr>
<td>GI symptoms often occur first</td>
<td>May mimic influenza or gastroenteritis</td>
</tr>
<tr>
<td>Bradycardias or supraventricular with AV block</td>
<td>Mental status change</td>
</tr>
<tr>
<td>Severity correlates with K+ not with digoxin level</td>
<td>Many dysrhythmias, but ventricular more common than in acute</td>
</tr>
<tr>
<td>High digoxin level</td>
<td>K+ often low and digoxin is a poor predictor</td>
</tr>
</tbody>
</table>

Fig. 4. The digoxin levels in patients older than 65 year included in the retrospective study reveals that all were within potentially toxic ranges and do not comply with the recommended leves (trogh levels below 0.9 ng/mL). Inspite of the introduction of quantity of new drugs classes for the management of heart failure, digoxin continues to have an important role in long-term patient management. A wide variety of placebo-controlled clinical trials have unequivocally shown that treatment with digoxin can improve symptoms, quality of life, and exercise tolerance in patients with mild, moderate, or severe heart failure. [21] The Digitalis Investigation Group (DIG) trial reported that digoxin provided no overall mortality benefit and only a modest reduction in hospitalizations among patients with heart failure and depressed left ventricular systolic function. [7] However, the clinical outcomes associated with digoxin therapy at different serum concentrations in the DIG trial have not been assessed. Later findings demonstrated that higher serum digoxin concentrations (SDC) were associated with increased mortality and suggest that the effectiveness of digoxin therapy in men with heart failure and a left ventricular ejection fraction of 45% or less may be optimized in the SDC range of 0.5 to 0.8 ng/mL. [22] In heart failure, digoxin at low SDC reduces all-cause mortality and hospitalizations. However, the effects of digoxin on other cause-specific outcomes have not been studied in a propensity-matched, while evidence based on more sophisticated analysis showes that digoxin at low SDC significantly reduced mortality and hospitalizations in ambulatory chronic systolic and diastolic heart failure. [23] Post hoc analyses of the Digitalis Investigation Group trial indicate that digoxin at low (0.5 to 0.9 ng/ml) serum digoxin concentration reduces mortality, which is eliminated at higher (>or=1 ng/ml), and that low-dose digoxin (<or=0.125 mg/day) predicts low digoxin serum level. [24] In patients with ambulatory chronic systolic and diastolic heart failure with normal sinus rhythm receiving angiotensin-
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Data from post hoc analyses of the DIG trial suggest that digoxin reduces mortality at low (0.5–0.9 ng/ml) serum digoxin concentrations, but had no effect at higher (≥1 ng/ml) SDC. [25], [24], [26] Examenation of DIG trial reveals an early mortality reduction in the digoxin group, followed by later virtual overlap of the plots, suggesting that while the early survival benefit was eliminated in later years, there was no increase in mortality, indicating that lack of a long-term effect of digoxin on mortality may be due to use of open-labeled digoxin in the placebo group, and a cumulative effect of the use of high-dose digoxin. [27] In the DIG trial, serum digoxin level of 0.8–2.5 ng/ml was considered therapeutic and was used as a basis for dose adjustment [7,8]. However, over 80% of the DIG participants were receiving ≥0.25 mg of digoxin, which was higher than the currently recommended daily dosage of digoxin and the continued use of high-dose digoxin in patients who grew older with deteriorating kidney function may have resulted in higher digoxin levels. [28] Today, the clinical efficacy of digoxin can no longer be doubted and its safety at certain doses has been verified by the multicenter DIG trial. The lower dose is advised to be used in patients with advanced age, those with impaired renal function, or those with a low lean body mass. In patients with congestive heart failure, Majumdar et al. [29] examined whether treatment with high dose-ACE inhibitors, beta-blockers, and digoxin would each provide incremental benefits over that achieved with usual care and whether concurrent use of high-dose ACE inhibitors, beta-blockers, and digoxin would provide maximal benefits and found that compared with usual care for patients with CHF, incorporating high-dose ACE inhibitors plus beta-blockers plus digoxin was associated with incrementally greater reductions in morbidity and mortality. [29] Physiologic changes and disease associated with aging have an impact on pharmacokinetics and pharmacodynamics of medications. Altered drug response and increased adverse reactions are common amongst the elderly. The narrow therapeutic index of digoxin and pharmacokinetic changes associated with aging increases the risk of toxicity. In the aging population, a number of factors combine to increase the risk, severity and likelihood of hospitalisation or death due to adverse drug effects: changes to absorption, distribution, metabolism and excretion, increased susceptibility to drug sensitivity, co-existing pathology, polypharmacy. A thorough understanding of digoxin pharmacokinetics in the older person is essential for improved therapeutic outcomes, improved compliance, reduced morbidity and improved quality of life. [30] Digoxin has been reported to improve symptoms and reduce hospitalization in patients with heart failure as well as to control rapid ventricular rate in patients with atrial fibrillation. Both of these are high-prevalence diseases in the elderly, and yet studies have indicated that digoxin may not be used appropriately in this population. Clinical trials evaluating digoxin use specifically in the elderly are scarce. In recent review article, Cheng and Rybak [31] stated that the elderly population appears to gain comparable benefits as does a younger population from the use of digoxin for heart failure management in terms of symptom improvement and reduction of hospitalization, however the elderly have reduced elimination of digoxin, so if digoxin is to be used, the dosing strategy must be conservative and therapeutic monitoring is needed. Further clinical studies are needed to confirm the pharmacokinetic parameters of digoxin in elderly patients with heart failure and/or atrial fibrillation. Digoxin is often used in long-term care residents with heart failure despite a high risk of toxicity associated with increased age, comorbidities and polypharmacy. This toxicity may occur at serum digoxin concentrations that are as low as 1.54 nmol/L. A Cross-sectional survey result in Canada published by Misiaszek et al. [32] indicates that approximately one-third of residents with heart failure received digoxin mostly for atrial fibrillation and at least 26% of these residents were exposed to an increased risk of digoxin toxicity. Adverse drug events are an important cause of preventable hospitalizations among elderly individuals taking high-risk medications. In a prospective cohort study to identify health care system factors that affect the risk of digoxin toxicity for older adults on digoxin, Haynes et al. [33] observed that the risk of digoxin toxicity-related hospitalization is higher in the post-hospital period, where digoxin toxicity is commonly associated with serum levels >2 ng/mL but may occur with lower digoxin levels if hypokalemia, hypomagnesemia, or hypothyroidism coexist. Lee et al. [34] published a case of digoxin toxicity in the context of dehydration, renal dysfunction and concomitant use of the macrolide antibiotic, clarithromycin a known inhibitor of P-glycoprotein mediated efflux mechanisms of digoxin indicating a need to be vigilant of this mechanism of drug-drug interaction, which is also relevant to other commonly used cardiovascular drugs. A retrospective population-based case–control study also provides evidence that digoxin–clarithromycin interactions do increase the risk of hospitalization for digoxin intoxication in HF patients and that this risk could reach as high as 55.4-fold strongly recommending that the combined use of
digoxin with clarithromycin should be avoided and that digoxin concentrations should be monitored closely in situations where the combination can not be avoided. [35] The major early side effect associated with amiodarone, bradyarrhythmia, frequently requires discontinuation of digoxin due to considerable unfavorable interaction. [36] In the population-based, nested case-control study, Gomes et al. [37] investigated the association between hospitalization for digoxin toxicity and recent exposure to individual macrolide antibiotics revealing that Clarithromycin was associated with the highest risk of digoxin toxicity. Concomitant use of agents such as quinidine, verapamil, and spironolactone among others can increase serum digoxin levels and risk of digoxin toxicity. Lin et al. [38] reported an outbreak of foxglove leaf poisoning following the use of alleged "comfrey" (herbal tea with leaves resembling those of foxglove (Digitalis purpurea), where exposed patients presented with nausea, vomiting, diarrhea and dizziness, mild hyperkalemia with peak serum digoxin concentration ranging from 4.4 ng/mL to 139.5 ng/mL. Natural sources of digitalis may also cause significant health problems as Rajapakse et al. [39] recently reported poisoning due to deliberate self-harm with the seeds of yellow oleander (Thevetia peruviana) results in significant morbidity and mortality each year in South Asia since oleander seeds contain highly toxic cardiac glycosides including thevetins A and B and neriifolin causing a wide variety of bradycardias and tachyarrhythmias. Thus patients on regular digoxin dose may be in greater danger if exposed to natural sources accidentally. From biomarkers, in contrast to patients with acute digoxin overdose, the prognostic utility of the serum potassium concentration for patients with chronic digoxin toxicity is unclear. In such patients, Lin et al. [40] evaluated the relationship between pre-treatment serum potassium and surfoval in patients with chronic digoxin toxicity and revealed that elevated serum potassium was associated with mortality. From the fact that digoxin is an inhibitor of the sodium-potassium ATPase, overdose, may cause hyperkalemia often treated with intravenous calcium, which is traditionally contraindicated in digoxin toxicity. According to recent findings, among digoxin-intoxicated humans, intravenous calcium does not seem to cause malignant dysrhythmias or increase mortality showing no support for the historical belief that calcium administration is contraindicated in digoxin-toxic patients. [41]

5. Conclusions
This retrospective study demonstrated that significant number of elderly patients live with toxic levels of digoxin most probably for long time, before being discovered. The levels are far from the range recommended post DIG study and warrant special attention to this patients. More knowledge about the causes and prevention of digoxin toxicity should further reduce the morbidity and mortality arising from digoxin toxicity, especially in the elderly patient population.

Acknowledgments
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Reference
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