



Exploratory Study of Digoxin Safety Based on Pharmacokinetic Approach and Drug Interactions in Patients with Congestive Heart Failure

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Abstract: Digoxin has a narrow therapeutic index, requiring close monitoring to prevent toxicity, particularly in patients with heart failure, polypharmacy, and impaired renal function. Due to limitations in therapeutic drug monitoring (TDM), we estimated digoxin serum levels using pharmacokinetic formulas based on creatinine clearance. This retrospective observational study aimed to conduct an initial risk screening by estimating digoxin concentrations, evaluating drug interactions, and assessing heart rate in 17 heart failure patients at a regional general hospital in Jambi (January–August 2025). Descriptive analysis revealed that 76% of patients were within the therapeutic range, while 24% exceeded it, with elevated levels correlating with higher creatinine serum and lower creatinine clearance. Common drug interactions involved furosemide, bisoprolol, and proton pump inhibitors, with spironolactone posing a severe risk. Clinically, bisoprolol combined with hypokalemia appeared associated with lower heart rates in patients with predicted toxic concentrations. While the formula-based pharmacokinetic approach serves as a useful exploratory initial screening tool, these findings require further validation through laboratory-based TDM and larger studies.

Introduction

Congestive heart failure is a complex clinical syndrome arising from various cardiovascular and non-cardiovascular conditions that contribute to increasing morbidity, mortality, and the economic burden on the health system. Although several developed countries report stable prevalence rates, hospitalization and death rates due to congestive heart failure continue to show a high trend (1). Globally, an estimated 64 million individuals are living with congestive heart failure (1). In Asia, prevalence trends show a varied pattern: the Asia Pacific, Central Asia, and East Asia regions experienced declines, while Southeast Asia and South Asia showed increases in cases (2). Based on the 2019 Global Burden of Disease report, Indonesia ranks second in the prevalence of heart failure in Asia, namely 990.90 per 100,000 population, below China (1,032.83) and followed by Malaysia (809.47) (2).

Current management of congestive heart failure is based on left ventricular ejection fraction (LVEF), which is divided into HFrEF (LVEF $\leq$ 40%), HFmrEF (LVEF 41%–49%), and HFpEF (LVEF $\geq$ 50%). In addition to LVEF, the ACC/AHA classifies patients into four clinical stages (A–D) with

specific intervention focuses. Stage A focuses on modifying risk factors to prevent further heart damage. In Stage B patients, the focus is on managing structural risk factors and in several patient can start initiation therapy pharmacology, while in Stage C patients with congestive heart failure classification experiencing reduced ejection fraction (HFrEF, LVEF $\leq$ 40%), the pharmacological approach involves four main therapeutic pillars, namely Angiotensin Converting Enzyme-Inhibitor (ACE-i)/Angiotensin receptor-neprilysin inhibitor (ARNI)/Angiotensin II receptor blockers (ARB), beta-blocker, Mineralocorticoid Receptor Antagonist (MRA), Sodium-Glucose co-transporter-2 (SGLT2) inhibitor, and diuretics are recommended to overcome congestion (3). In patients with stage D or refractory heart failure, interventions are tailored to the clinical condition to reduce symptoms, morbidity, and mortality (4). Additional therapy, such as digoxin, can be considered in patients who remain symptomatic despite receiving standard therapy or for those who show intolerance to the main regimen (4).

Digoxin is a cardiac glycoside with positive inotropic and negative chronotropic effects, increasing cardiac

contractility while decreasing heart rate. This drug is beneficial in reducing symptoms, reducing hospitalization rates, and slowing the progression of congestive heart failure. However, digoxin is not recommended as first-line therapy because it has a narrow therapeutic index. The recommended therapeutic range for patients with congestive heart failure is 0.5–0.9 ng/mL, while patients with atrial fibrillation usually require higher levels (1–2 ng/mL). Dosing beyond this range can increase the risk of toxicity (3, 5). Therefore, regular monitoring of serum digoxin concentrations, at least every six months, is highly recommended to ensure the safety of therapy (6). Digoxin toxicity is nonspecific, including gastrointestinal, neurological, cardiological, and visual disorders, with visual disturbances being one of the most typical manifestations (7). The risk of toxicity increases not only due to overdose, but also due to predisposing factors such as advanced age, hypokalemia, hypomagnesemia, hypercalcemia, impaired renal function, dehydration, hypoxemia, and myocardial ischemia (7). Furthermore, drug interactions, both pharmacokinetic and pharmacodynamic, can increase the potential for toxicity. For example, furosemide can cause hypokalemia, which potentiates the toxic effects of digoxin, characterized by, among other things, sinus bradycardia and ST-segment depression (8).

Digoxin level monitoring is ideally performed through serum testing (therapeutic drug monitoring/TDM) because it is the standard method for directly assessing drug exposure, especially for drugs with a narrow therapeutic index such as digoxin (9). However, in practice, access to TDM remains limited in many healthcare facilities in Indonesia due to limited resources, laboratory facilities, and test availability. This diagnostic gap becomes increasingly dangerous when paired with local epidemiological realities. Data from the studies in a regional setting in Jambi, Indonesia, revealed an alarming trend where analysed digoxin prescriptions in a local hospital setting were categorised as clinically inappropriate, especially to geriatric patients, largely due to a lack of individual risk adjustment, failure to monitor renal function, and unmanaged drug interaction (10). This critical condition raises the need for a more applicable alternative approach to estimate individual digoxin exposure. One approach is mathematical model-based pharmacokinetic estimation, which accounts for patient clinical characteristics such as kidney function, age, and body weight. Several mathematical models have been developed to predict digoxin concentrations, such as the Sheiner, Koup, Jusko, and Jelliffe models. In this study, we used the Sheiner model because its comprehensive approach has been validated in previous studies and shows a good correlation with serum levels in patients with congestive heart failure. This approach is strengthened by the Cockcroft-Gault equation to estimate creatinine clearance and provide a more accurate picture of drug excretion (11).

The Sheiner mathematical model is employed in this study to estimate steady-state digoxin levels, with creatinine clearance serving as the primary predictor of total digoxin clearance. The resulting calculations are not definitive serum concentration values but function as a stratification index for assessing the risk of drug accumulation in healthcare facilities lacking laboratory-based Therapeutic Drug Monitoring (TDM). Previous

studies in Indonesia, including those by Wulandari *et al.* (2021), have used pharmacokinetic equations that combine the Sheiner equation with the Mosadegh and Bafghi formula to estimate steady-state digoxin levels for routine dose adjustments. However, these studies primarily relied on mathematical estimates derived from baseline parameters and did not account for important clinical confounders or complex drug-drug interactions (12).

To address this diagnostic gap, the current study introduces an adjusted Sheiner model that incorporates specific clinical and drug-interaction correction factors, including obesity, thyroid status, and concurrent use of P-glycoprotein inhibitors. This adjusted pharmacokinetic approach offers a low-cost, initial risk-stratification and screening tool to identify patients at elevated risk of drug accumulation and toxicity. It serves as a practical alternative in resource-limited settings where standard Therapeutic Drug Monitoring (TDM) is unavailable. Additionally, this approach provides a more individualized initial estimate of digoxin levels than standard dosing, particularly for patients with impaired renal function or those experiencing drug interactions that may alter digoxin concentrations.

Furthermore, the estimated digoxin levels are correlated with clinical outcomes, specifically signs and symptoms of toxicity such as bradycardia in patients with congestive heart failure. Pulse rate was selected as the primary clinical marker because bradycardia is an objective cardiovascular finding that can be assessed retrospectively from medical records. The objective of this study is to evaluate the relationship between pharmacokinetic-based estimations of digoxin levels and clinical manifestations of toxicity.

Methodology

Study Design

This study is an observational, retrospective design that uses medical record data from patients with congestive heart failure treated at one of the general hospitals in Jambi Province from January to August 2025.

Ethical Clearance

The initial phase of the study involved obtaining administrative permits and ethical approval. The research protocol was approved by the Faculty of Medicine and Health Sciences (No. 2131/UN21.8/PT.01.04/2025) and received authorization from the Head of the Research and Library Division at one of the general hospitals in Jambi Province (No. S.330/RSUD.2.1/VII/2025).

Population and Sample

The study population included all patients with congestive heart failure receiving digoxin therapy during the study period. The sample was determined using a total sampling method based on fulfillment of the inclusion criteria, namely: (1) aged ≥ 18 years; (2) receiving digoxin therapy for at least seven days; and (3) having complete medical records related to treatment. The exclusion criteria in this study were: (1) patients undergoing routine hemodialysis; and (2) patients with Acute Kidney Injury (AKI). The collected data included patient demographic characteristics, laboratory test results, vital signs, and all

information related to the treatment regimen during hospitalization.

Calculation Estimated Digoxin Concentration

The estimated digoxin concentration measurement was obtained using the **Equation 1** (13). Measurement of total digoxin clearance in patients with congestive heart failure is carried out using the Sheiner Formula (**Equation 2**). The patient's creatinine clearance measurement was calculated using the Cockcroft–Gault formula as seen in **Equations 3 and 4**.

This study applied specific correction factors to the calculation of total patient clearance. Conditions such as thyroid disorders (hyper/hypothyroidism) and specific drug interactions were not ignored but instead integrated into the formula by multiplying the patient's clearance value by the relevant adjustment factors (**Table 1**). This allowed the model to remain representative of the patient's digoxin elimination profile despite these confounding factors.

Data Analysis

The estimated digoxin concentrations were categorized into two groups based on the standard therapeutic reference range: therapeutic concentrations (0.5–2 ng/mL) and toxic concentrations (>2 ng/mL). Although the optimal target for congestive heart failure patients is 0.5–0.9 ng/mL, using a 2 ng/mL threshold in this classification aims to identify patients at absolute risk of toxicity based on standard pharmacokinetic parameters. Data analysis was performed descriptively to better describe the clinical profiles of both groups and to avoid interpretation bias arising from limited statistical power in a small sample. Patient demographic data, including age, gender, length of hospitalization, comorbidities, nutritional status, creatinine serum level, creatinine clearance, and electrocardiogram findings, were presented as frequency distributions, percentages, and means with standard

deviations (SD). To provide an accurate hemodynamic picture, the heart rate (pulse) values used were the average of routine measurements (4 times daily) during each patient's hospitalization. A detailed comparison of mean pulse trends is presented across various therapy subgroups, including digoxin alone, digoxin and bisoprolol combination therapy, and comorbidities such as hypokalemia.

Results and Discussion

Characteristics of Congestive Heart Failure Patients

Of the 19 patients with congestive heart failure treated between January and August 2025, two patients were excluded because they received digoxin therapy for less than seven days. As a result, serum drug levels had not yet reached steady state. The limited sample size in this study was due to digoxin not being a first-line therapy, but rather an adjunct therapy for patients who remained symptomatic after receiving the standard regimen. Thus, a total of 17 patients were analyzed. Of this population, a pharmacokinetic evaluation showed that 13 patients (76%) had estimated digoxin concentrations within the therapeutic range (0.5–2 ng/mL), while 4 patients (24%) had concentrations exceeding the toxic limit (>2 ng/mL). In general, the descriptive analysis of demographic characteristics showed no significant differences in age, gender, length of hospitalization, or the accumulation of comorbidities between the therapeutic and toxic concentration groups.

In terms of age, the therapeutic group was dominated by productive-age patients aged 18–59 years (9 patients), whereas in the toxic group, the distribution was balanced between the 18–59 age range (2 patients) and the elderly group (≥60 years; 2 patients). The dominance of the age group <60 years is in line with the latest global epidemiological trends. A study of the global burden of

$$C_{ss} = \frac{F \times D}{CL_{total} \times \tau}$$

(Eq. 1)

$$CL_{digoxin} = [0.33 \text{ mL/min/kg} \times \text{Weight (kg)}] + [0.9 \times CL_{cr} \text{ (mL/min)}]$$

(Eq. 2)

$$CL_{cr \text{ males}} = \frac{(140 - \text{Age}) \times \text{Weight (kg)}}{72 \times \text{Creatinine Serum (mg/dL)}}$$

(Eq. 3)

$$CL_{cr \text{ females}} = \frac{(140 - \text{Age}) \times \text{Weight (kg)}}{72 \times \text{Creatinine Serum (mg/dL)}} \times 0.85$$

(Eq. 4)

Table 1. Factors that can affect digoxin clearance (13).

Factor	Correction Value
Obesity	Ideal Body Weight
Amiodarone	0.5
Quinidine	0.5
Verapamil	0.75
Hyperthyroidism	1.3
Hypothyroidism	0.7

disease reported that from 1990 to 2021, the group of adolescents and young adults aged 15–49 years globally experienced a significant increase in the burden of congestive heart failure and is projected to continue to increase until 2035 (14).

Based on the gender distribution in **Table 2**, male patients accounted for the majority of study subjects overall, both in the therapeutic concentration group (9 of 13 patients; 69.2%) and in the toxic concentration group (3 of 4 patients; 75%). The predominance of male patients in this congestive heart failure (CHF) population aligns with global literature showing significant biological (sex) and sociocultural (gender) differences between men and women. Male patients have a significantly higher predisposition to developing heart failure with reduced ejection fraction (HFrEF). This is driven by the higher incidence of coronary artery disease and myocardial infarction in men, which are the primary etiologies of myocardial structural damage. In contrast, the prevalence of male patients in this study is generally due to aging and non-ischemic comorbidities (15). Therefore, the high proportion of male patients in this study (a total of 12 out of 17 patients) logically correlates with the clinical needs of the male population, which is predominantly a case of

refractory HFrEF, requiring additional inotropic intervention in the form of digoxin.

The length of stay (LOS) of patients in both groups was dominated by short-term hospitalizations (≤ 7 days). In the therapeutic concentration group, 11 of 13 patients (84.6%) were treated for ≤ 7 days, and a similar pattern was observed in the toxic concentration group, where 3 of 4 patients (75%) had the same length of stay. The finding that the majority of congestive heart failure patients in this study had a length of stay ≤ 7 days is consistent with the clinical profile of the efficiency of care for congestive heart failure patients across various hospitals in Indonesia. Based on a study by Laariya *et al.* (2026), the average length of stay for patients with acute and chronic heart failure experiencing acute exacerbations falls within a relatively short and efficient range. This controlled LOS duration generally reflects successful clinical stabilization of the acute phase (e. g., addressing circulatory congestion and shortness of breath) through interventions with primary drug regimens, such as intravenous diuretics combined with appropriate inotropic agents (16).

In the therapeutic concentration group (0.5–2 ng/mL), 84.6% of patients (11 of 13) had normal nutritional status, while 15.4% (2 patients) were overweight. In contrast, all

Table 2. Characteristics of congestive heart failure patients on digoxin therapy.

Parameters	Digoxin Concentration	
	0.5 - 2 ng/mL (N=13)	> 2 ng/mL (N=4)
Age		
18-59 years	9 (69%)	2 (50%)
≥ 60 years	4 (31%)	2 (50%)
Sex		
Men	9 (69%)	3 (75%)
Women	4 (31%)	1 (25%)
Length of Hospitalization		
≤ 7 days	10 (77%)	3 (75%)
> 7 days	3 (23%)	1 (25%)
Nutritional Status		
Normal	11 (85%)	2 (50%)
Overweight	2 (15%)	0 (0%)
Obesity	0 (0%)	2 (50%)
Comorbidities		
≤ 2 comorbidities	12 (92%)	4 (100%)
> 2 comorbidities	1 (8%)	0 (0%)
Creatinine Cerum (mg/dl) (mean $\pm$ SD)	0.96 $\pm$ 0.28	1.35 $\pm$ 0.26
Creatinine Clearance (mean $\pm$ SD)	120.38 $\pm$ 29.73	82.00 $\pm$ 5.35
Electrocardiogram		
AV block present	0 (0%)	3 (75%)
No AV block present	13 (100%)	1 (25%)
Potassium Levels (mEq/L) (mean $\pm$ SD)	3.78 $\pm$ 0.78	3.70 $\pm$ 0.62
Digoxin Daily Dose		
0.25 mg	13 (100%)	4(100%)

obese patients in the study (2 patients; 100%) were in the toxic concentration group (>2 ng/mL). The relationship between nutritional status (body mass index) and accumulated digoxin levels is complex. Digoxin is widely distributed throughout body tissues, especially skeletal muscle and myocardium, but has low affinity for adipose tissue. As a result, the drug's volume of distribution (Vd) is correlated with lean body mass rather than total body weight (17). Regarding comorbidities, most subjects in both groups had 2 or fewer. In the therapeutic concentration group, 92.3% (12 of 13) had ≤ 2 comorbidities; in the toxic concentration group, all patients (4; 100%) had ≤ 2 comorbidities. Congestive heart failure (CHF) rarely presents alone, often occurring alongside chronic disease clusters such as hypertension, diabetes mellitus, coronary heart disease, and chronic kidney disease (18).

Based on laboratory parameter monitoring results, the differences in the mean creatinine and creatinine clearance profiles between patients in the therapeutic and control groups reflect the Sheiner formula's structure, which treats creatinine clearance as the primary predictor variable. The mean creatinine serum level has an inverse linear relationship with the creatinine clearance value (CLCr). Depending on the pharmacokinetic model used, a decrease in renal function will mathematically increase the estimated digoxin level. In the group of patients with digoxin concentrations within the therapeutic range (0.5–2 ng/mL), renal excretory function is in an adequate condition, indicated by a low mean creatinine serum level of 0.96 ± 0.28 mg/dL with a high filtration capacity (CLCr) reaching 120.38 ± 29.73 mL/min. Conversely, significant drug accumulation is projected in the group of patients with toxic concentrations (> 2 ng/mL). This group showed a significant decrease in kidney function, characterized by a high mean serum creatinine of 1.35 ± 0.26 mg/dL, followed by a drastic decrease in creatinine clearance to 82.00 ± 5.35 mL/min.

Therefore, the high estimated steady-state digoxin concentration in patients with poor renal function (high creatinine serum and low CLCr) is a mathematical relationship inherent in the conceptual model and must be recognized as a limitation of its circularity. Pharmacokinetically, digoxin is a hydrophilic compound that is eliminated predominantly by the kidneys (approximately 60–80%) in its intact form through active glomerular filtration and tubular secretion. When the renal filtration rate decreases, as reflected by lower CLCr values in the toxic group, the body's ability to clear digoxin from the systemic circulation also decreases substantially. This decrease in total clearance triggers the progressive accumulation of cardiac glycosides in the serum, which ultimately escalates drug levels beyond the upper limit of the safe therapeutic window and exponentially increases the risk of absolute toxicity in patients with congestive heart failure (19). This approach is not intended to replace direct serum Therapeutic Drug Monitoring (TDM), but rather serves as an initial, clearance-based screening tool to predict the risk of drug accumulation in clinical settings with limited laboratory facilities.

Digoxin toxicity is associated with various electrocardiographic (ECG) abnormalities, including atrioventricular (AV) block. The ECG manifestations of AV block observed in patients with predicted toxic

concentrations are described to assess their correspondence with the molecular pharmacodynamic theory of digoxin action. Given the very limited sample size in the toxic concentration group ($n=4$) and reliance on mathematical estimation, these findings are exploratory and hypothesis-generating rather than definitive. Nevertheless, they highlight the importance of individualized cardiac conduction monitoring in patients with congestive heart failure and reduced renal elimination function. These manifestations result from digoxin's effects on the cardiac conduction system, which are more pronounced at toxic levels. In this study, AV block in patients with congestive heart failure and toxic digoxin concentrations aligns with digoxin's mechanism of action: inhibition of the Na^+/K^+ -ATPase pump increases intracellular sodium, influencing calcium uptake via $\text{Na}^+/\text{Ca}^{2+}$ exchange, thereby prolonging the action potential and increasing vagal tone (20).

Based on the study results, all subjects in both groups (100% in group 0.5–2 ng/mL ($n=13$) and 100% in group >2 ng/mL ($n=4$)) received a uniform daily digoxin dose of 0.25 mg. The 0.25 mg/day dose is a standard maintenance dose often prescribed to adult patients with chronic heart failure or atrial fibrillation to control the ventricular rate.

Potential Drug Interactions in Patients with Congestive Heart Failure

Congestive heart failure is a clinical syndrome that develops due to various etiologies and is often accompanied by complex comorbidities. This condition causes most patients to undergo therapy with multiple medications (polypharmacy), significantly increasing the risk of drug interactions. Digoxin, as a drug with a narrow therapeutic index, is highly susceptible to interactions with various other drugs that can affect its pharmacokinetics and pharmacodynamics.

Based on the medication records of patients with congestive heart failure during their hospitalization, several potential drug interactions were identified, as shown in **Table 3**. Of all the interactions observed, there was one potential severe interaction, namely between digoxin and spironolactone, which was identified in 36% of patients ($n=6$). Based on the literature review, this combination has a pharmacokinetic mechanism that can reduce digoxin clearance and inhibit its elimination. This trend is consistent with a large-scale clinical study by Englund *et al.* (2004) of patients undergoing therapeutic drug monitoring. The study classified spironolactone as one of the main P-glycoprotein (P-gp) inhibitors (Class I P-gp inhibitor), which is significantly associated with increased serum digoxin levels in the body (21).

In terms of moderate interaction, the combination of digoxin and furosemide showed the highest frequency in this study, at 83% ($n=14$). Theoretically, furosemide, as a potent loop diuretic, is known to be associated with a risk of hypokalemia due to increased renal potassium excretion. The literature suggests that hypokalemia can increase myocardial sensitivity to digoxin, potentially increasing the risk of arrhythmias (8). This potential risk of clinical interaction is clearly illustrated in a case report by Patel *et al.* (2022), where the use of furosemide with digoxin was reported to be associated with digoxin toxicity triggered by hypokalemia. In addition to furosemide, hydrochlorothiazide, a thiazide diuretic (identified in 18%

of cases in this study), can also cause hypokalemia, especially at high doses or when combined with loop diuretics (22).

Beta blockers are first-line therapy in patients with congestive heart failure, especially those with reduced ejection fraction. The use of these drugs has been shown to improve ventricular function, improve quality of life, and reduce the incidence of arrhythmias (3). However, the combination of beta blockers, such as bisoprolol, with digoxin (found in 36% of this study) warrants clinical consideration. Several studies have shown that coadministration of digoxin and bisoprolol is associated with an increased risk of major cardiovascular events (MACE) compared with the use of digoxin alone or bisoprolol alone (23).

This study found a potential interaction between digoxin and proton pump inhibitors (PPIs), such as omeprazole (12%) and lansoprazole (24%). According to the literature, PPIs work by increasing gastric pH by suppressing acid secretion and by increasing intercellular permeability in the gastric mucosa. When administered concomitantly with digoxin, these changes in gastric pH may increase digoxin absorption. In contrast, increased mucosal permeability can increase the amount of drug that passes through the gastric lining. The combination of these two mechanisms has been reported to increase

digoxin bioavailability (24). In addition to the effect on gastric pH, a review published by Mar *et al.* (2022) confirmed that the interaction between digoxin and PPIs may also involve the P-glycoprotein (P-gp) transport pathway. Given that digoxin has a narrow therapeutic index and is a P-gp substrate, concomitant use of PPIs that inhibit P-gp may reduce digoxin's gastrointestinal effects, potentially increasing digoxin bioavailability and systemic exposure. The use of sucralfate (6%) should also be considered, as this agent can interfere with digoxin absorption through binding in the gastrointestinal tract, which has been reported to reduce its therapeutic effect (25).

The interaction between nonsteroidal anti-inflammatory drugs (NSAIDs) and digoxin is an important aspect that needs to be considered in clinical practice, especially in patients with cardiovascular disease. In this study, several types of NSAIDs used by patients, including diclofenac sodium (6%), ketorolac (6%), and meloxicam (6%), were identified as interacting with digoxin. Based on pharmacokinetics, the use of NSAIDs together with digoxin is known to increase digoxin concentrations in the blood, primarily through mechanisms such as decreased renal blood flow and impaired excretory function. This risk is potentially higher in patients with impaired renal function, because elimination is further inhibited,

Table 3. Types of digoxin – other drug interactions in patients with congestive heart failure.

Interaction Severity	Types of Drugs	Types of Interaction	Interaction Mechanism	Frequency Occurrence % (n)
Major	Spironolactone	Pharmacokinetics	Spironolactone decreases digoxin clearance and inhibits digoxin elimination.	36% (6)
Moderate	Furosemide	Pharmacodynamics	Furosemide-induced hypokalemia increases the risk of digoxin arrhythmic toxicity.	83% (14)
Moderate	Hydrochlorothiazide	Pharmacodynamics	Hypokalemia and hypomagnesemia-induced hydrochlorothiazide increase the risk of digoxin arrhythmic toxicity.	18% (3)
Moderate	Propylthiouracil	Pharmacodynamics	PTU increases sensitivity to digoxin.	12% (2)
Moderate	Bisoprolol	Pharmacodynamics	The risk of bradycardia and AV block increases.	36% (6)
Moderate	Omeprazole	Pharmacokinetics	Omeprazole increases gastric pH, thereby increasing digoxin absorption.	12% (2)
Moderate	Lansoprazole	Pharmacokinetics	Lansoprazole increases gastric pH, thereby increasing digoxin absorption.	24% (4)
Moderate	Sucralfate	Pharmacokinetics	Decreases digoxin absorption and levels.	6% (1)
Moderate	Diclofenac Sodium	Pharmacokinetics	Decreases digoxin clearance and increases digoxin levels, especially in CKD and the elderly.	6% (1)
Moderate	Ketorolac	Pharmacokinetics	Decreases digoxin clearance and increases digoxin levels, especially in CKD and the elderly.	6% (1)
Moderate	Meloxicam	Pharmacokinetics	Decreases digoxin clearance and increases digoxin levels, especially in CKD and the elderly.	6% (1)

Note: One patient may experience more than one type of drug interaction simultaneously during hospitalization, so that the total cumulative percentage may exceed 100%.

increasing the likelihood of digoxin toxicity (26).

Evaluation of Digoxin Concentration Estimation Based on Patient Hemodynamic Parameters

This study evaluated the relationship between estimated digoxin concentrations (therapeutic and toxic categories) determined through pharmacokinetic calculations and the patient's mean heart rate. It also described the influence of concomitant clinical factors such as bisoprolol use and the presence of hypokalemia. As a drug with a narrow therapeutic index, digoxin has a negative chronotropic effect, meaning fluctuations in plasma concentrations can significantly affect heart rate and rhythm {Formatting Citation}. Research by Gona *et al.* (2023) showed that bradycardia is the most common cardiovascular manifestation of digitalis toxicity. In contrast, other symptoms, such as palpitations, junctional rhythm, and torsades de pointes, have a lower incidence (28). Therefore, evaluating vital parameters such as heart rate is crucial for monitoring the clinical picture of elevated digoxin levels, especially when combined with bisoprolol (a beta-blocker that lowers heart rate) and hypokalemia, which theoretically increases the heart's sensitivity to digoxin. **Table 4** presents a comparison of mean pulse rates by category of estimated digoxin concentration, which serves as a basis for viewing trends in how each comorbid condition contributes to changes in patient hemodynamics.

Based on mean pulse rate, in patients receiving digoxin alone, there was no significant difference between groups with levels within the therapeutic range and those at the toxic threshold (89.7 ± 14.9 vs. 86.4 ± 10.7). These descriptive findings suggest that, within this small cohort, elevated mathematical estimates of digoxin levels above the threshold may not be invariably associated with a significant change in pulse rate when digoxin is administered alone, without other confounding factors. In other words, calculated digoxin levels > 2 ng/mL do not automatically manifest as bradycardia in all patients within this retrospective sample; comorbidities, such as atrial fibrillation, which are common in patients with congestive heart failure taking digoxin, may also help maintain a higher ventricular rate despite elevated estimated digoxin levels. In this study, three of the four congestive heart failure patients with estimated digoxin levels >2 ng/mL were found to have atrial fibrillation. Research conducted by Mousavi and Akbarian (2021) also showed that patients given digoxin had a higher average pulse rate than patients with congestive heart failure without atrial fibrillation (29).

In patients receiving the combination of digoxin and bisoprolol, the mean pulse rate was lower than in those receiving digoxin alone, both at estimated therapeutic

(73.3 ± 9.8 vs. 89.7 ± 14.9 bpm) and estimated toxic digoxin levels (66.2 ± 11.5 vs. 86.4 ± 10.7 bpm). This finding is consistent with the pharmacological mechanism of beta-blockers, which inhibit adrenergic stimulation, resulting in a consistent decrease in pulse rate. Therefore, as an exploratory observation, the combination of digoxin and bisoprolol suggests a trend toward a stronger negative chronotropic effect than digoxin alone, though this requires validation in larger prospective cohorts. Given the retrospective design, reliance on mathematical estimation, very limited subgroup sample sizes, and high interpatient variability, these hemodynamic trends must be interpreted with strict caution as hypothesis-generating rather than definitive clinical conclusions. Furthermore, comorbidities, baseline cardiac rhythm, and individual differences in sensitivity to sympathetic and vagal effects may also influence the magnitude of the decrease in pulse rate.

The mean pulse rate in patients with digoxin and hypokalemia tended to be lower in the estimated toxic group than in the estimated therapeutic group (73.4 ± 11.1 vs. 86.3 ± 5.6 bpm). The mean difference was approximately 13 beats per minute. From a pathophysiological perspective, this descriptive observation is consistent with the literature, which indicates that hypokalemia can increase myocardial sensitivity to digoxin and enhance its effects on the cardiac conduction system. In low potassium conditions, digoxin's affinity for the Na^+/K^+ -ATPase enzyme increases, thereby increasing the degree of inhibition of the ion pump and increasing the risk of bradycardia, atrioventricular block, and other arrhythmias, especially when digoxin levels are toxic (7). The decrease in the mean pulse rate seen in the hypokalemia group provides a preliminary, descriptive glimpse into the potential interaction between mathematically estimated toxic digoxin concentration and low potassium levels. Given the retrospective design, small sample size, and reliance on calculated pharmacokinetic values rather than measured serum assays, these subgroup findings should be considered strictly exploratory. These data provide preliminary descriptive insights into hemodynamic trends that may generate hypotheses for future, well-powered prospective clinical trials.

Conclusion

Evaluation of mathematically estimated digoxin levels based on a pharmacokinetic approach suggests a potential drug accumulation in some patients with congestive heart failure, with higher estimated digoxin exposure observed in patients with lower renal function. Overall, within this small cohort, the majority of patients (76%) were at estimated therapeutic concentrations, while

Table 4. Comparison of mean pulse rate based on therapeutic and toxic digoxin levels.

Patient Groups	Digoxin Concentration	
	0.5 - 2 ng/mL (N=13)	>2 ng/mL (N=4)
Pulse (Digoxin) (mean $\pm$ SD)	89.7 ± 14.9	86.4 ± 10.7
Pulse (Digoxin + Bisoprolol) (mean $\pm$ SD)	73.3 ± 9.8	66.2 ± 11.5
Pulse (Digoxin + Hypokalemia) (mean $\pm$ SD)	86.3 ± 5.6	73.4 ± 11.1

24% had estimated concentrations >2 ng/mL. As an exploratory observation, electrophysiological manifestations, such as atrioventricular block, were more frequently observed in patients with estimated toxic concentrations. The descriptive profile suggests a trend toward lower renal function values in the group with higher estimated concentrations. Furthermore, preliminary observations in this limited subgroup showed a trend toward lower heart rates in patients with combined hypokalemia or bisoprolol use with digoxin. Given the retrospective study design, the very limited sample size, and reliance on mathematical estimation rather than actual serum measurement, these findings regarding concomitant clinical effects, such as hypokalemia, bisoprolol use, and the influence of other medications (such as spironolactone and diuretics), must be interpreted cautiously as strictly preliminary and hypothesis-generating, requiring further confirmation in larger prospective studies. As a standard of care consistent with the literature, monitoring renal function and electrolyte levels (especially potassium), and regularly reviewing drug interactions remain important clinical recommendations for patients receiving digoxin therapy. Overall, this small, retrospective study provides valuable exploratory findings regarding the patient's hemodynamic profile, serving as hypothesis-generating insights rather than definitive clinical conclusions and warranting validation in future prospective studies.

Abbreviations

Css = Concentration at Steady State; F = Bioavailability; D = Dose; CL_{total} = Total Clearance; τ = Dosing Interval; $CL_{digoxin}$ = Digoxin Clearance; CL_{Cr} = Creatinine Clearance

Declaration

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability

The datasets generated and/or analyzed during the current study are available in the article.

Ethics Statement

This study was approved by the Faculty of Medicine and Health Sciences (No.2131/UN21.8/PT.01.04/2025) and received authorization from the Head of the Research and Library Division at one of the general hospitals in Jambi Province (No. S.330/RSUD.2.1/VII/2025).

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Additional Information

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