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Research Paper

Enhancing Therapeutic Drug Monitoring in Indonesia: An Android-Based Pharmacokinetic Calculator for Amikacin

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ABSTRACT:
Pharmacokinetics employs complex mathematics to study, model, and predict how drugs are absorbed, distributed, metabolized, and excreted by the body. Amikacin, as a model drug with a narrow therapeutic window, requires Therapeutic Drug Monitoring (TDM) to ensure safety. This study developed an Android-based pharmacokinetic calculator, the "Indonesia Pharmacokinetic Calculator" (KFI), to assist clinical practitioners in quickly and accurately calculating pharmacokinetic parameters using patient weight and Amikacin doses as inputs. The application is designed to provide calculations of pharmacokinetic parameters, a pharmacokinetic simulation graph (plasma concentration-time curve), and predictions of individual patient amikacin plasma concentrations to assess therapeutic effectiveness and minimize toxicity risks. The rigorous testing process has demonstrated that KFI reliably produces expected output data, enhancing clinical pharmacy services in Indonesia through the integration of cutting-edge technology. This tool is expected to improve therapeutic outcomes, particularly for sepsis patients, by facilitating accurate and efficient pharmacokinetic calculations.
KEYWORDS: *Amikacin, Android, Pharmacokinetic Calculation*

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I. INTRODUCTION

Pharmacokinetics is the study of how drugs are absorbed, distributed, metabolized, and excreted by the body.[1] The knowledge and application of pharmacokinetic concepts and equations are invaluable tools in designing optimal drug dosing regimens.[2] Clinical practitioners in Indonesia would greatly benefit from pharmacokinetic modeling software that can quickly and accurately calculate pharmacokinetic parameters for patients and analyze experimental data statistically.[3] The COVID-19 pandemic, which began in March 2020, has accelerated the adoption of information and communication technology, including the use of computers, laptops, and smartphones for remote work and study during periods of large-scale social restrictions.[4] This technological shift supports the development and implementation of Android-based pharmacokinetic software in hospitals, aiding clinical practitioners in efficiently determining drug dosages. This research focuses on developing an Android-based pharmacokinetic calculator for amikacin, an antibiotic with a narrow therapeutic window used in the treatment of sepsis. Amikacin poses a high risk of toxicity if not dosed accurately, making Therapeutic Drug Monitoring (TDM) essential.[5]–[8] However, the implementation of TDM in many Indonesian hospitals is hindered by limited human resources and high costs.[3] The application developed in this study aims to help clinical practitioners quickly and easily calculate predicted pharmacokinetic parameter, pharmacokinetic/pharmacodynamic (PK/PD) ratio, and pharmacokinetic simulation graph (plasma concentration-time curve) in individual patient with certain amikacin doses, even in constrained work environments such as hospital wards. The application is expected to improve the accuracy of amikacin therapy dosing, enhance treatment effectiveness, and reduce toxicity risks, esspecialy for sepsis patients.[9], [10]

II. METHODS

The research procedure used to design and test the Android-based pharmacokinetic calculation application uses the Waterfall method which consists of 5 stages[11]:

1. Requirements Analysis and Definition
Services, constraints, and application objectives are determined through consultation with system users. Then, these requirements are specified in detail and serve as system specifications.
2. System and Software Design
The system design process allocates requirements to hardware or software systems. This process establishes the overall system architecture. Software design involves identifying and depicting the fundamental software system abstractions and their relationships.
3. Implementation and Unit Testing
During this stage, the software design is realized as a series of programs or program units. Unit testing involves verifying that each unit meets its specifications.
4. Integration and System Testing
Individual program units or programs are integrated and tested as a complete system to ensure that software requirements have been met. After testing, the software system is delivered to the customer.
5. Operation and Maintenance
This procedure is the longest life cycle phase of the SDLC. The system is installed and put into practical use. Maintenance involves correcting errors not discovered in the early stages of the life cycle, improving the implementation of system units, and improving system services as new requirements are discovered.

III. RESULT

1. Requirements Analysis and Definition

The application is named "Kalkulator Farmakokinetik Indonesia" (KFI) and registered with the Indonesian Directorate General of Intellectual Property with Number: DID2024062227 on July 10, 2024. In English, the name of this application can be translated as Indonesian Pharmacokinetic Calculator. Still, the abbreviation aplication in Indonesian will be used for writing consistency, namely using the "KFI application'. The KFI application's requirements were analyzed by literature studies, and research that obtain the pharmacokinetic parameters of amikacin needed in local clinical conditions. These pharmacokinetic research conclude the amikacin pharmacokinetic parameters ($t_{1/2}$, Vd, and CL) calculated from TDM data on sepsis patients in Indonesia.[12] The bioanalytical method used to measure TDM amikacin is the latest and validated UPLC-MS/MS method.[13]

The calculation of the PK/PD ratio, such as the $AUC_{0\text{-}24h}$/MIC and $C_p$max/MIC ratio, is included in the application because they can be used as data to evaluate the pharmacodynamic effects of dose-dependent antibiotics. Some studies suggest that a $C_p$max/MIC ratio of more than 8 should be achieved to maximize the effect of treatment. $AUC_{0\text{-}24h}$/MIC is not associated with treatment response but can be used as a predictor of amicasin-induced renal toxicity.[14], [15] From the requirements analysis, the KFI application is defined to be able to produce two calculation models, namely:

1. The first calculation model (Calculation with pharmacokinetic research data). This calculation can calculate the calculation of the PK/PD index ($C_p$max/MIC ratio and $AUC_{0\text{-}24h}$/MIC ratio) to see the efficiency of amikacin therapy in sepsis patients and the pharmacokinetic simulation graph (plasma concentration-time curve) to be able to visually predict the amikacin concentration in the blood during therapy and monitor the safety of the amikacin therapy given.
2. The second calculation model (Calculations with input 2 TDM Data). This calculation can produce individual pharmacokinetic data of patients (k, $t_{1/2}$, Vd, and CL) along with the calculation of PK/PD index ($C_p$max/MIC ratio and $AUC_{0\text{-}24h}$/MIC ratio) to see the efficiency of amikacin therapy in sepsis patients and pharmacokinetic simulation graph (plasma concentration-time curve) to be able to visually predict drug levels in the blood during therapy and monitor the safety of the amikacin therapy given.

Detailed required input data and the calculations formula used in the KFI application to give spesific output data as a whole can be seen in table 1.

Table 1. Output Data and Required Input Data

Requirement Output Data	Calculation Formula	Input Data
The First Calculation Mode (Calculation with Pharmacokinetic Research Data)		
Data Output of First Calculation Mode Part 1		
$AUC_{0\text{-}24h}$	$[AUC]_{t_{n-1}}^{t_n} = \frac{C_{n-1}+C_n}{2}(t_n - t_{n-1})$	C_p from time to time for 0-24 hours ; t for 0-24 hours (AUC every 30 minutes interval)
$C_{p\ ss}$ max	$C_{p\ ss}\ max = \frac{MD}{V_d}$ $V_d(L) = BW \times V_d\ (\%)$	Patient MD ; Patient Body Weight (BW) ; V_d (%) study
$C_{p\ ss}$ average	$C_{p\ ss}\ average = \frac{AUC_{0\text{-}24h}}{t_{MDMD}}$	$AUC_{0\text{-}24h}$; Interval time between MD (t_{MDMD})
$C_{p\ ss}$ min	$C_{p\ ss}\ min = C_{p\ ss}\ max \times e^{kt_{MDMD}}$ $k = \frac{0.693}{t_{½}}$	$C_{p\ ss}$ max ; Interval time between MD (t_{MDMD}) ; $t_{½}$ research [12]
t 95% $C_{p\ ss}$	$t\ 95\%\ C_{p\ ss} = t_{½} \times 4.32$	$t_{½}$ research [12]
t 96,87% $C_{p\ ss}$	$t\ 96{,}87\%\ C_{p\ ss} = t_{½} \times 5$	$t_{½}$ research [12]
t 99% $C_{p\ ss}$	$t\ 99\%\ C_{p\ ss} = t_{½} \times 6.65$	$t_{½}$ research [12]
$C_p$max/MIC Ratio	$C_{p\ ss}\ max : MIC$	$C_{p\ ss}$ max ; MIC reference[16]
$AUC_{0\text{-}24h}$/MIC Ratio	$AUC_{0\text{-}24h} : MIC$	$AUC_{0\text{-}24h}$; MIC reference[16]
Data Output of First Calculation Mode Part 2		
Pharmacokinetic simulation graph	plasma concentration-time curve x = t (time from 0 – 120 hours) y = Cp from t $C_p = \frac{LD}{V_d} \times e^{-kt} + \frac{MD_1}{V_d} \times e^{-kt_{..}} + \ldots$	Patient LD ; Patient MD ; Time between LD to MD ; Interval time between MD ; V_d ; t (time 0-120 hours) ; Cp from t ; MIC reference[16] ; MTC-Trough reference[17]
Calculation of predicted Cp at time t	$C_p = \frac{LD}{V_d} \times e^{-kt} + \frac{MD_1}{V_d} \times e^{-kt_{..}} + \ldots$	Patient LD ; Patient MD ; Time between LD to MD ; Interval time between MD ; V_d ; t input between 0-120 hours
The Second Calculation Mode (Calculation with Input 2 TDM Data)		
Data Output of Second Calculation Mode Part 1		
k	$k = \frac{\ln C_p\ TDM\ I - \ln C_p\ TDM\ II}{t\ TDM\ II - t\ TDM\ I}$	t and C_p TDM I ; t and C_p TDM II
$t_{½}$	$t_{½} = \frac{0.693}{k}$	k
V_d (L)	$V_d = (LD \times e^{-kt} + MD \times e^{-k(t-t_{LDMD})} + DP \times e^{-k(t-t_{LDMD}-t_{MDMD})} + DP \times e^{-k(t-t_{LDMD}-2t_{MDMD})}) / C_p\ TDM\ II$	Patient LD ; Patient MD ; Time between LD to MD (t_{LDMD}); Interval time between MD (t_{MDMD}) ; k ; t and Cp TDM II

V_d (%)	$V_d\ (\%) = \frac{V_d\ (L)}{BW}$	V_d (%) ; Patient BW
CL	$CL = V_d \times k$	V_d (L) ; k
$AUC_{0\text{-}24h}$	$[AUC]_{t_{n-1}}^{t_n} = \frac{C_{n-1}+C_n}{2}(t_n - t_{n-1})$	C_p from time to time for 0-24 hours ; t for 0-24 hours (AUC every 30 minutes interval)
$C_{p\ ss}$ max	$C_{p\ ss}\ max = \frac{MD}{V_d}$ $V_d(L) = BW \times V_d\ (\%)$	Patient LD ; Patient MD ; Patient V_d (%)
$C_{p\ ss}$ average	$C_{p\ ss}\ average = \frac{AUC_{0\text{-}24h}}{t_{MDMD}}$	$AUC_{0\text{-}24h}$; Interval time between MD (t_{MDMD});
$C_{p\ ss}$ min	$C_{p\ ss}\ min = C_{p\ ss}\ max \times e^{kt_{MDMD}}$ $k = \frac{0.693}{t_{½}}$	$C_{p\ ss}$ max ; Interval time between MD (t_{MDMD}); Patient $t_{½}$ [12]
t 95% $C_{p\ ss}$	$t\ 95\%\ C_{p\ ss} = t_{½} \times 4.32$	Patient $t_{½}$[12]
t 96,87% $C_{p\ ss}$	$t\ 96{,}87\%\ C_{p\ ss} = t_{½} \times 5$	Patient $t_{½}$[12]
t 99% $C_{p\ ss}$	$t\ 99\%\ C_{p\ ss} = t_{½} \times 6.65$	Patient $t_{½}$[12]
$C_p$max/MIC Ratio	$C_{p\ ss}\ max : MIC$	$C_{p\ ss}$ max ; MIC reference[16]
$AUC_{0\text{-}24h}$/MIC Ratio	$AUC_{0\text{-}24h} : MIC$	$AUC_{0\text{-}24h}$; MIC reference[16]
Data Output of Second Calculation Mode Part 2		
Pharmacokinetic simulation graph	plasma concentration-time curve x = t (time from 0 – 120 hours) y = Cp from t $C_p = \frac{DM}{V_d} \times e^{-kt} + \frac{DP_1}{V_d} \times e^{-kt} + \ldots$	Patient LD ; Patient MD ; Time between LD to MD ; Interval time between MD ; V_d ; t (time 0-120 hours) ; Cp of t ; MIC reference[16] ; MTC-Trough reference[17]
Calculation of predicted Cp at time t	$C_p = \frac{DM}{V_d} \times e^{-kt} + \frac{DP_1}{V_d} \times e^{-kt} + \ldots$	Patient LD ; Patient MD ; Time between LD to MD; Interval time between MD ; V_d ; t input between 0-120 hours

2. System and Software Design

1. Basic Data Design

From the above requirements definition, two basic calculation data designs are made that can produce two calculation models:

1. The First Calculation Model (Calculation with Pharmacokinetic Research Data)

By entering data, such as weight, loading dose (LD) i.v. bolus, maintenance dose (MD) i.v. intermittent, time between LD to MD, time for MD i.v. intermittent, interval time between MD, data on pharmacokinetic parameters of amikacin from the study that have been conducted (k, $t_{1/2}$, V_d, and CL), and pharmacokinetic parameters of the references, namely MIC and MTC Trough of amikacin.

The data output of the first calculation mode part 1: pharmacokinetic parameters without loading dose that can be generated from the input input are $AUC_{0\text{-}24h}$, Cp *steady state* (maximum, average, and minimum), time (t) to reach 95%, 96.87%, and 99% of Css, calculation of PK/PD index ($C_p$max/MIC ratio and $AUC_{0\text{-}24h}$/MIC ratio).

Data output of the first calculation mode part 2: pharmacokinetic simulation graph (plasma concentration-time curve) based on research data and C_p prediction calculation by entering time (t) (0-120 hours).

2. The Second Calculation Mode (Calculation with Input 2 TDM Data)

By entering data, such as weight, LD i.v. bolus, MD i.v. intermittent, time between LD to MD, time for MD i.v. intermittent, interval time between MD, TDM I and II data, TDM I and II retrieval time, and pharmacokinetic parameters of the references, namely MIC and MTC Trough of amikacin.

Data output of the second calculation mode part 1: data on the pharmacokinetic parameters of individual amikacin of patients in the form of (k, $t_{1/2}$, V_d, and CL), and pharmacokinetic parameters without loading dose that can be generated from the input inputs are $AUC_{0\text{-}24h}$, C_pss (maximum, average, and minimum), time (t) to reach 95%, 96.87%, and 99% of C_{ss}, calculation of C_pmax/MIC ratio and $AUC_{0\text{-}24h}$/MIC ratio.

Data output of the second calculation mode part 2: pharmacokinetic simulation graph (plasma concentration-time curve) based on the individual pharmacokinetic values of the patient and cp calculation by entering time (t) (0-120 hours).

2. Interface Design

The interface design is also made to be easy to use by users, in this KFI application uses an interface design between 7 displays of system components with its own specifications.

1. Main Menu Display

The main menu display consists of an image of the Flag of Indonesia Country, the abbreviation of the name of the application, namely KFI, and the full name of the application, namely the Indonesia Pharmacokinetic Calculator. The caption "Pharmacokinetic Calculation IV Amikacin" which explains that the first KFI application uses the initial mode of amikacin drugs with the use of i.v. Caption "Faculty of Pharmacy, Andalas University" and the motto of Andalas University "for the glory of the nation" along with the logo of Andalas University. This main menu has 2 buttons for users to choose from, namely: the first calculation mode with pharmacokinetic data of research that has been carried out: "Calculation with Pharmacokinetic Research Data", and the second calculation mode by entering 2 patient TDM data: "Calculation with Input 2 TDM Data" at the bottom. It looks like in figure 1.

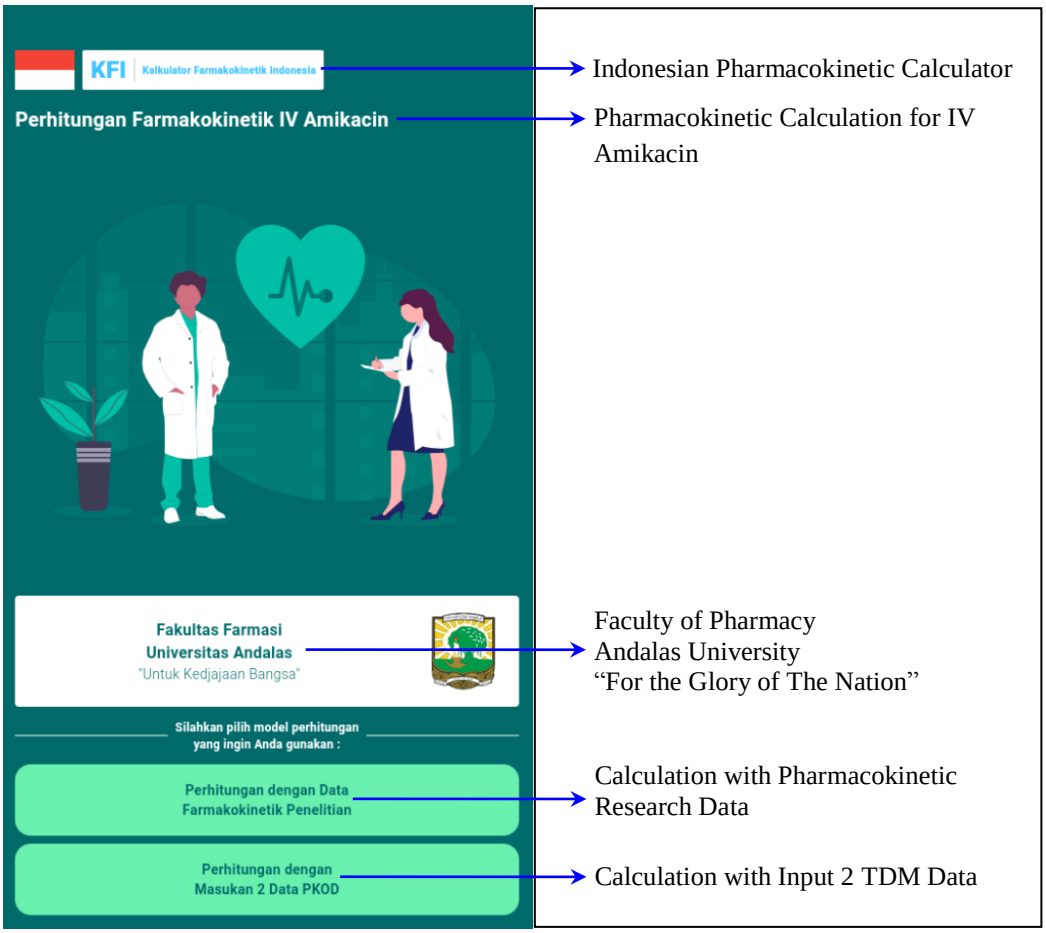

Figure 1. Main menu display on the KFI application with English translation
(Source: Screen shot of the KFI application on Msi App Player, 2024)

2. First Calculation Mode Display

The first calculation mode display with the title “Calculation with Pharmacokinetic Research Data” and consists of 13 sections to enter, the initial part is 6 individual patient data consisting of: weight, LD i.v. bolus, time between LD to MD, MD i.v., time MD i.v. intermittent, and interval time between MD. The middle part is 5 data from the pharmacokinetic parameters of the study, namely: k, $t_{1/2}$, Vd in liters, Vd in %, and CL. The last part is 2 data derived from pharmacokinetic parameters from the references, namely MIC and MTC-Trough. All data has been filled in for the convenience of users unless the patient's weight data is still empty, so to be able to continue the weight data process must be filled in. In this interface there are 3 buttons to choose from, namely: the back button (in the upper left corner in the shape of an arrow to the left) to return to the main menu display, the "Pharmacokinetic Parameters without Loading Dose" button to enter the data output of the first calculation mode part 1 and the "Pharmacokinetic Simulation" button to enter the data output of the first calculation mode part 2. It looks like in figure 2.

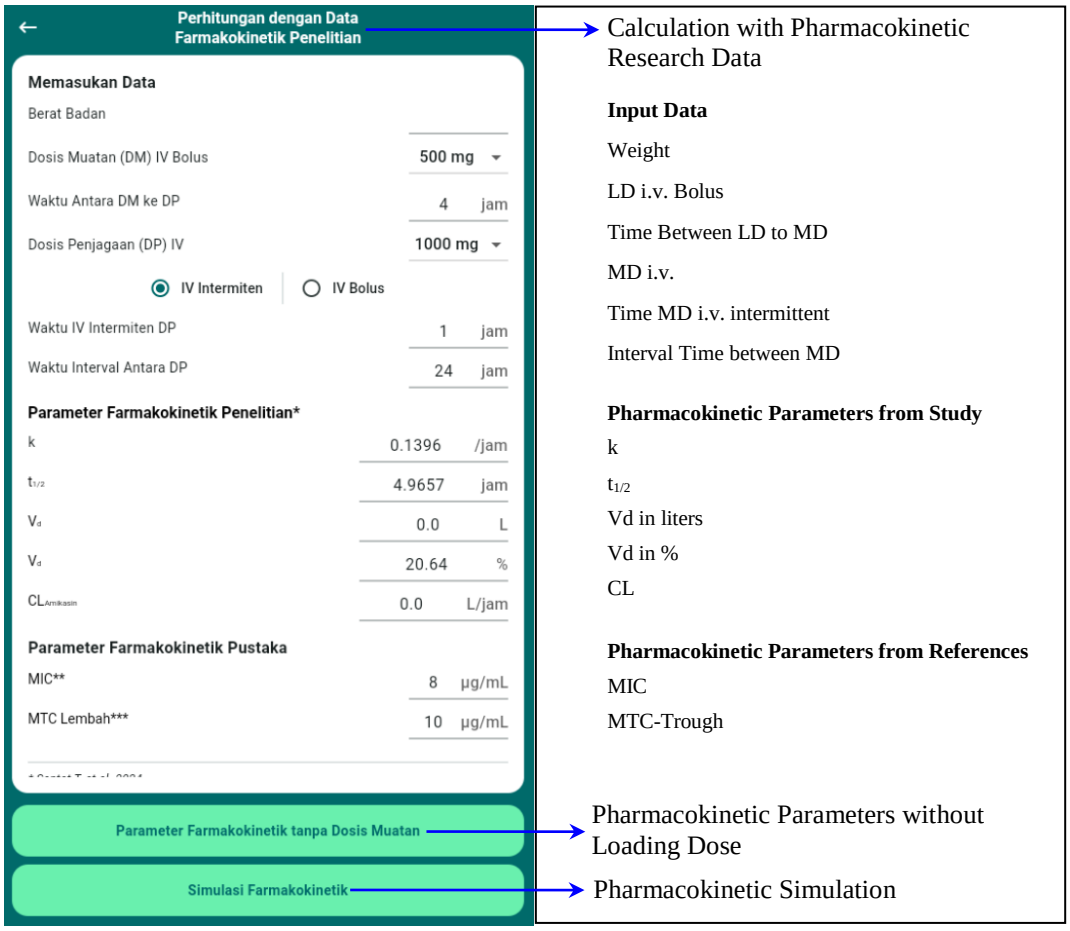

Figure 2. Display of the first calculation mode on the KFI application with English translation (Source: Screen shot of the KFI application on Msi App Player, 2024)

3. Data Output of First Calculation Mode Part 1 Display

Data output of first calculation mode part 1 display consists of 9 data outputs, the first part is in the form of 7 results of the calculation of pharmacokinetic parameters without loading dose: $AUC_{0\text{-}24h}$, C_{ss} max, C_{ss} average, C_{ss} min, t 95% C_{ss}, t 96.87% C_{ss}, and t 99% C_{ss}. The last part is 2 data from the calculation of PK/PD parameters, namely the $C_p$max/MIC ratio and the $AUC_{0\text{-}24h}$/MIC ratio. In this interface there are 2 buttons to choose from, namely: the back button (in the upper left corner in the shape of an arrow to the left) to return to the previous view, and the "Pharmacokinetic Simulation" button to enter the data output of the first calculation mode part 2. It looks like in figure 3.

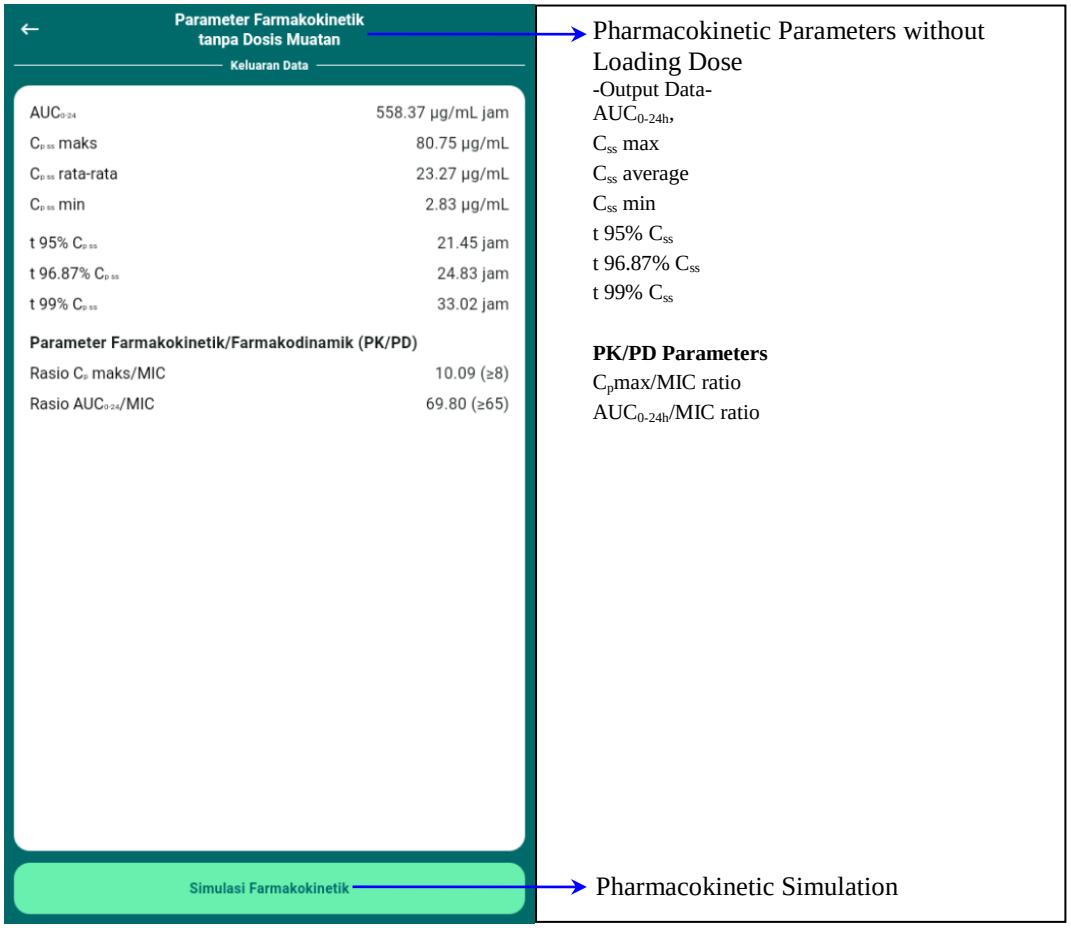

Figure 3. Display of data output of the first calculation mode part 1 in the KFI application with English translation

(Source: Screen shot of the KFI application on Msi App Player, 2024)

4. Data Output Display of First Calculation Mode Part 2
   The data output display of the first calculation mode part 2 consists of a pharmacokinetic simulation graph (plasma concentration-time curve) and C_p calculation by entering a specific time. The curve image will display the drug level in the blood (light blue) from the start time to the end of day 5 (0-120 hours), accompanied by the MIC (gray) and MTC-Trough (red) lines. With the touch screen facility on the light blue curve line on the android screen it is possible to display the coordinates (x,y), where x is the time and y is C_p at the time t. In this interface, there are 3 buttons to choose from, namely: the back button (in the upper left corner in the form of an arrow to the left) to return to the previous view, the "Pharmacokinetic Parameters without Loading Dose" button to enter the data output of the first calculation mode part 1 and the "Calculate" button for the calculation of C_p prediction by entering specific time on input data input, in the range of 0 – 120 hours. It looks like in figure 4.

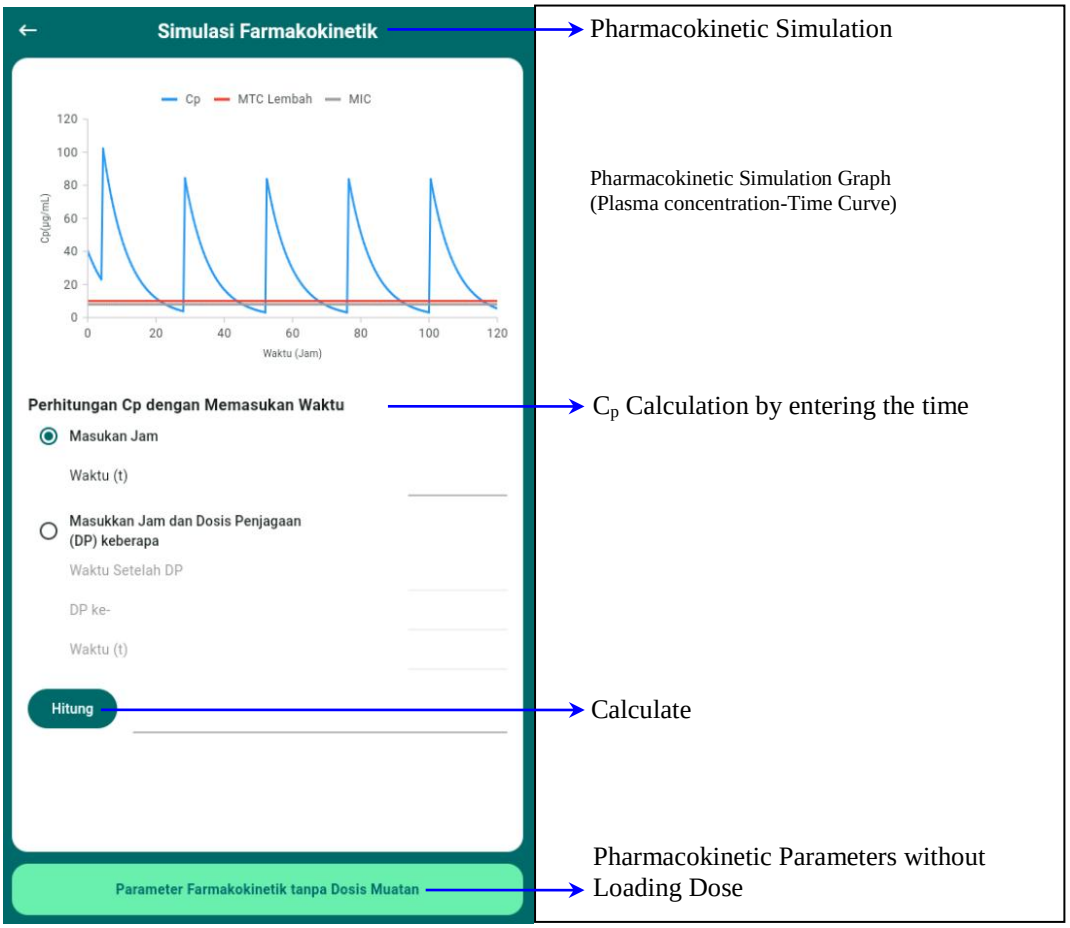

Figure 4. Display of data output of the first calculation mode part 2 on the KFI application with English translation
(Source: Screen shot of the KFI application on Msi App Player, 2024)

5. Second Calculation Mode Display
   The second calculation mode display with the title “Calculation with Input 2 TDM Data” and consist of 12 sections to enter, the first part is 6 individual patient data consisting of: weight, LD i.v. bolus, time between LD to MD, MD i.v., time MD i.v. intermittent, and interval time between MD. The middle part consist 4 TDM data, namely: t TDM I, Cp TDM I, t TDM II, and Cp TDM II. The last part is 2 data derived from pharmacokinetic parameters from the library, namely MIC and MTC-Trough. All data has been filled in for the convenience of users unless the patient's weight data and 4 TDM data are still empty, so to be able to continue all data process must be filled in. In this interface there are 3 buttons to choose from, namely: the back button (in the upper left corner in the form of an arrow to the left) to return to the main menu display, the "Pharmacokinetic Parameters" button to enter the data output of the second calculation mode part 1 and the "Pharmacokinetic Simulation" button to enter the data output of the second calculation mode part 2. It looks like in figure 5.

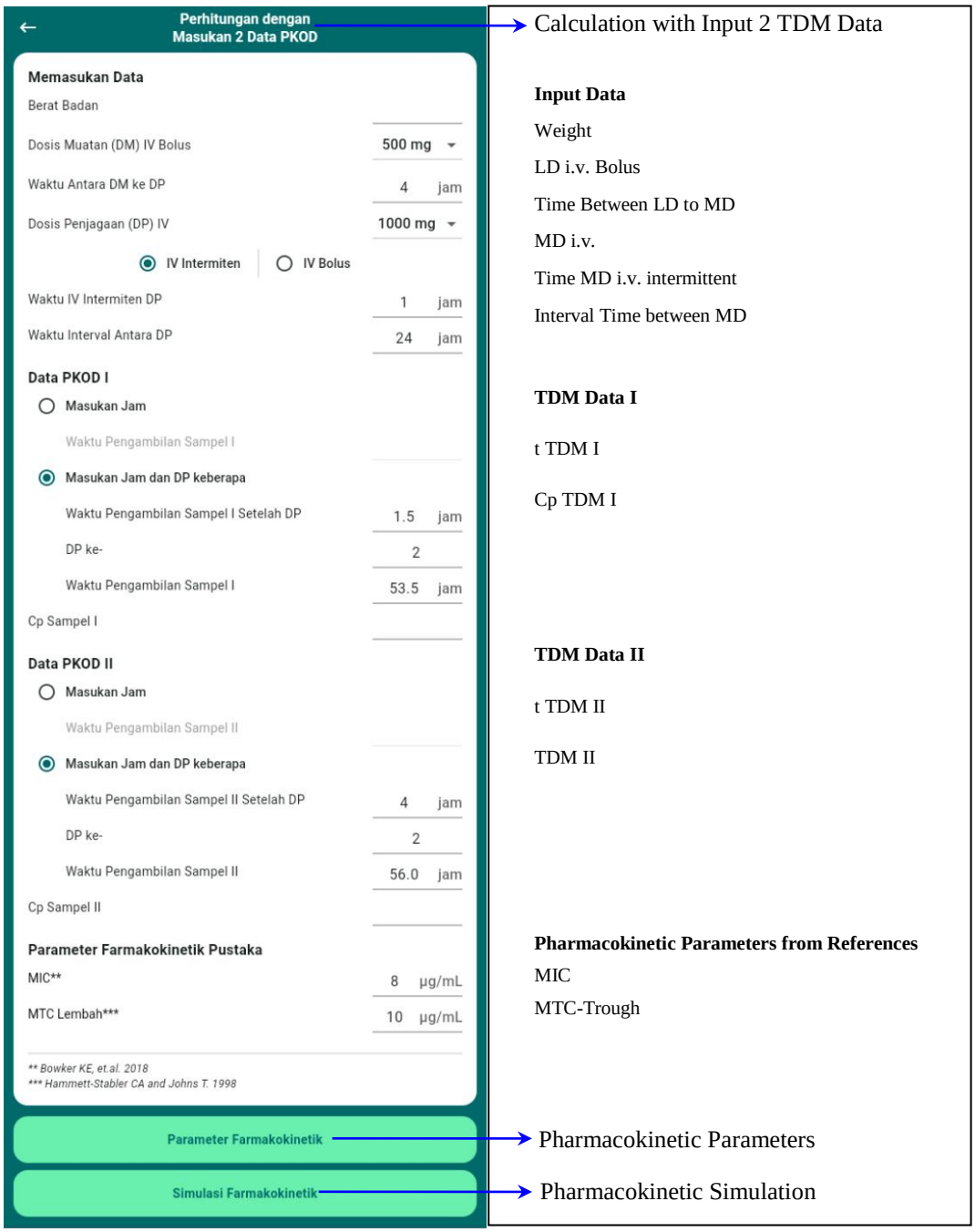

Figure 5. Display of the second calculation mode on the KFI application with English translation (Source: Screen shot of the KFI application on Msi App Player, 2024)

6. Data Output of Second Calculation Mode Part 1 Display
   Data output of second calculation mode part 1 display consists of 14 data outputs, the first part is in the form of 5 results of the calculation of pharmacokinetic parameters from patient, namely: k, t1/2, Vd in liters, Vd in %, and CL. The middle part is in the form of 7 results of the calculation of pharmacokinetic parameters without loading doses: $AUC_{0\text{-}24h}$, C_{ss} max, C_{ss} average, C_{ss} min, t 95% C_{ss}, t 96.87% C_{ss}, and t 99% C_{ss}. The last part is 2 data from the calculation of PK/PD parameters, namely the Cpmax/MIC ratio and the $AUC_{0\text{-}24h}$/MIC ratio. In this interface there are 2 buttons to choose from, namely: the back button (in the upper left corner in the shape of an arrow to the left) to return to the previous view, and the "Pharmacokinetic Simulation" button to enter the data output of the second calculation mode part 2. It looks like in figure 6.

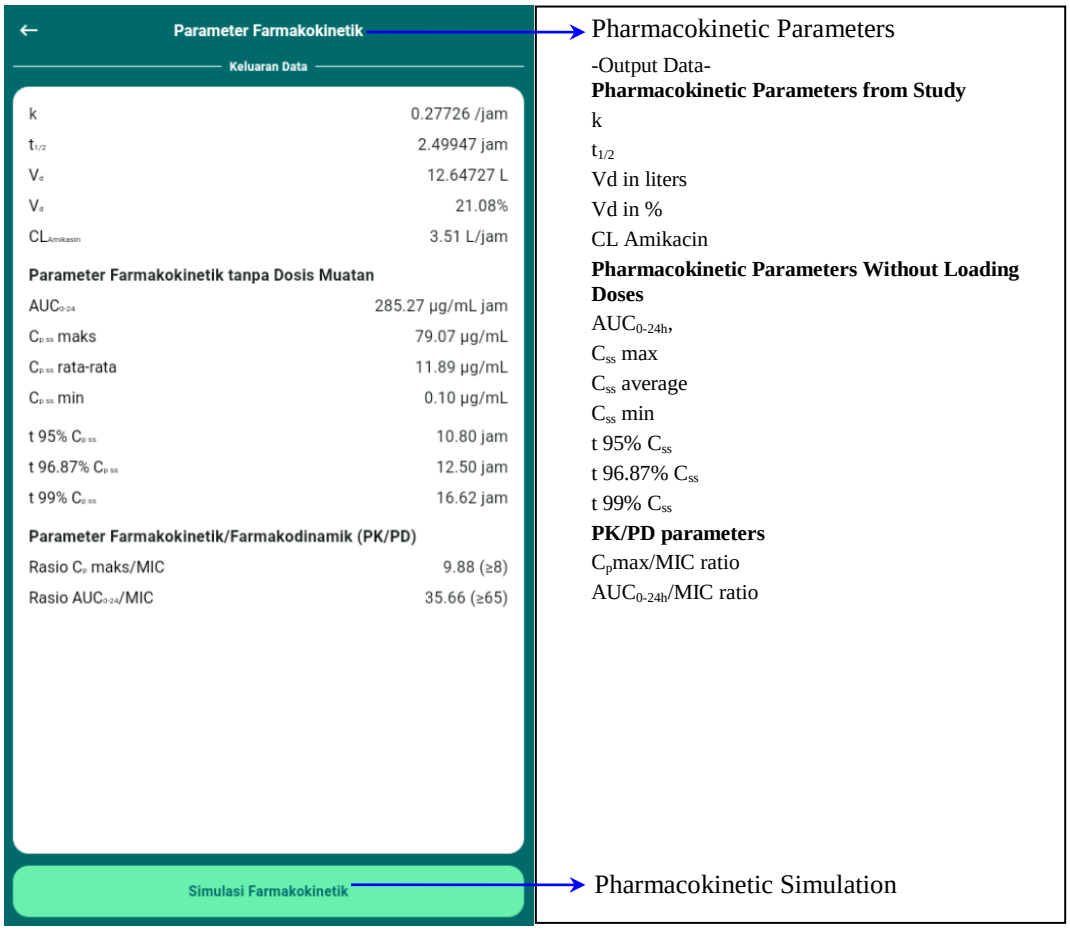

Figure 5.10 Display of data output of the second calculation mode part 1 on the KFI application with English translation
(Source: Screen shot of the KFI application on Msi App Player, 2024)

7. Data Output of Second Calculation Mode Part 2 Display
   The data output display of the second calculation mode part 2 consists of a pharmacokinetic simulation graph (plasma concentration-time curve) and C_p calculation by entering a specific time. The curve image will display the drug level in the blood (light blue) from the start time to the end of day 5 (120 hours), accompanied by the MIC (gray) and MTC-Trough (red) lines. With the touch screen facility on the light blue curve line on the android screen it is possible to display the coordinates (x,y), where x is the time and y is C_p at the time t. In this interface there are 3 buttons to choose from, namely: the back button (in the upper left corner in the form of an arrow to the left) to return to the previous view, the "Pharmacokinetic Parameters " button to enter the data output of the second calculation mode part 1 and the "Calculate" button for the calculation of C_p prediction by entering specific time on input data input, in the range of 0 – 120 hours. It looks like in figure7.

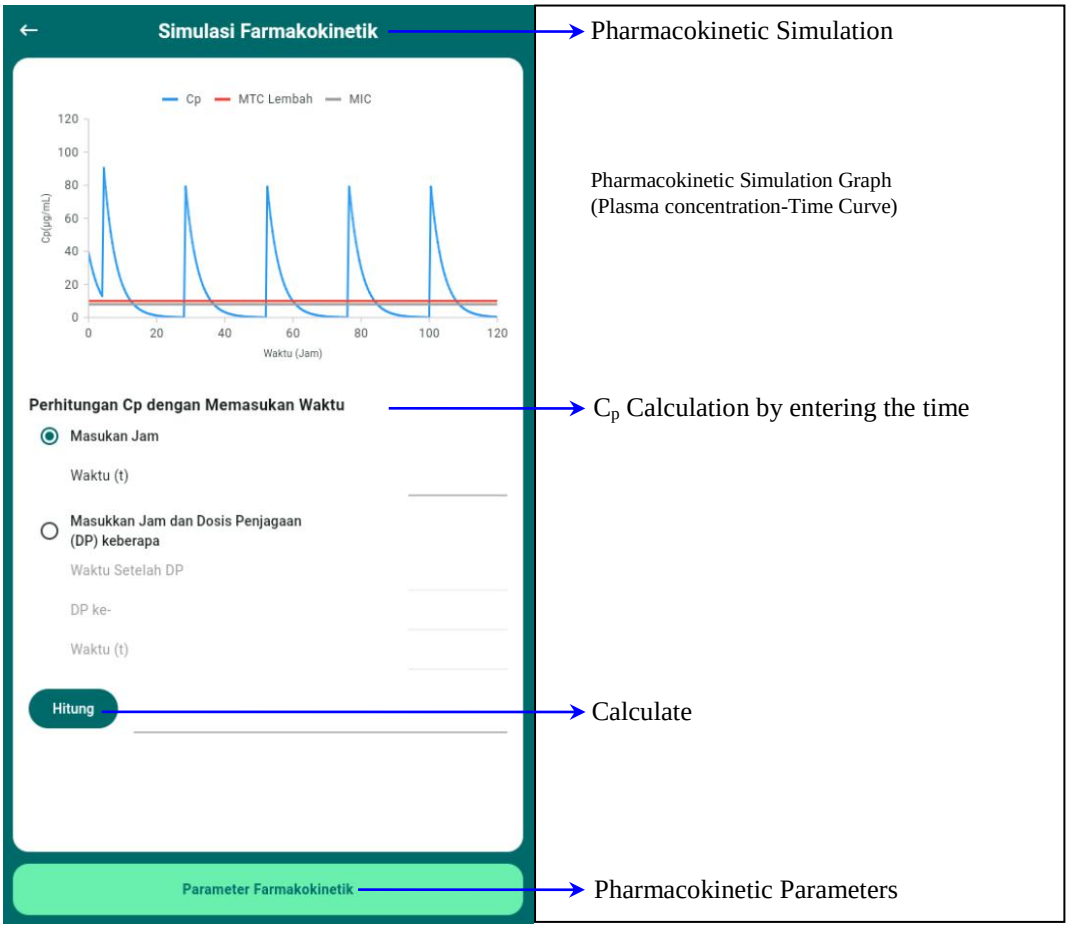

Figure 7. Display of data output of the second calculation mode part 2 on the KFI application with English translation
(Source: Screen shot of the KFI application on Msi App Player, 2024)

3. Architectural Design

The architectural design is created to identify the overall system structure, key components, relationships between components, and how those components are distributed so that the KFI application is easy for users to use. The design of the KFI application architecture can be seen in figure 8.

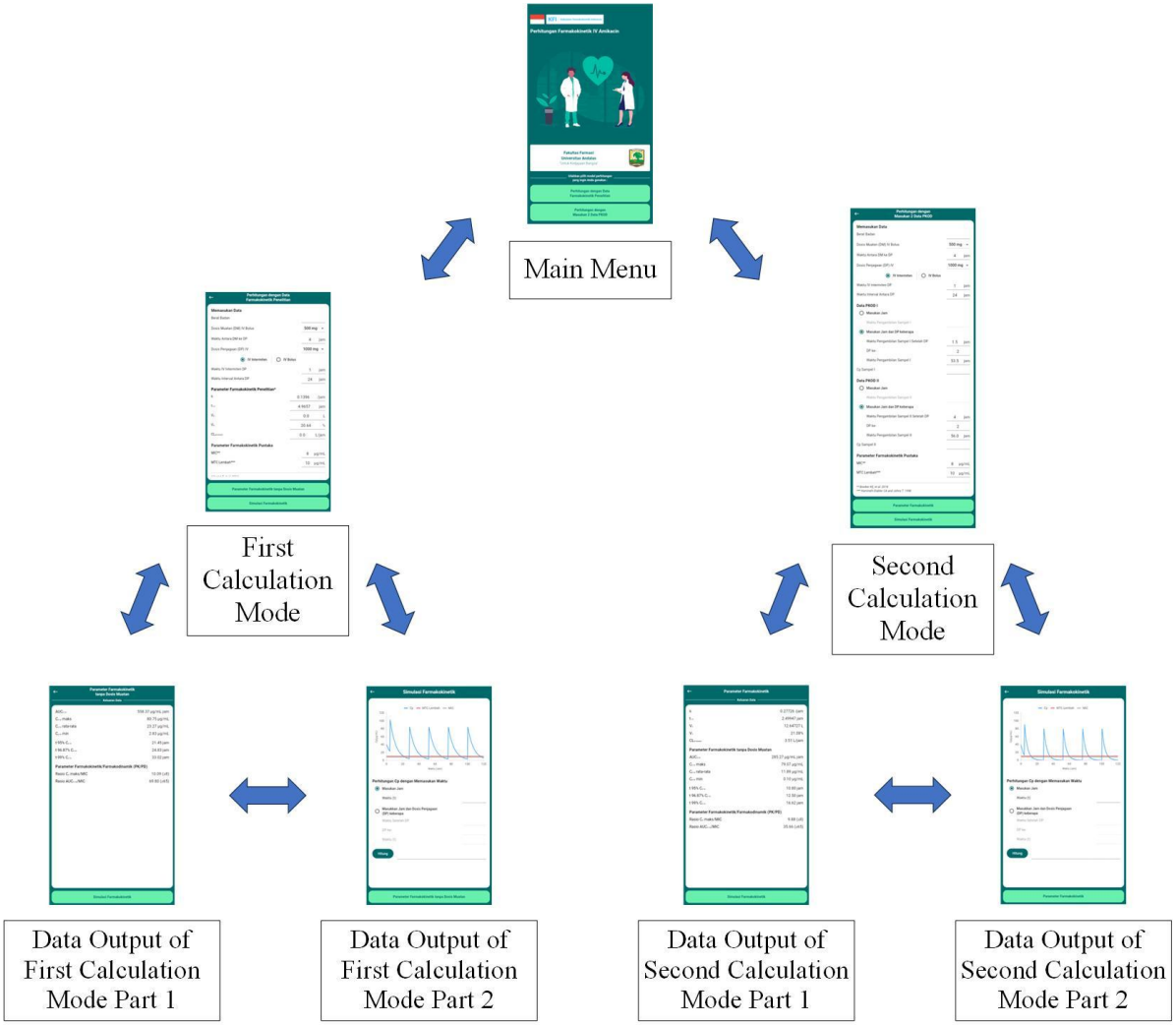

Figure 5.12 Design of KFI application architecture

3. Implementation and Unit Testing

Before the program is implemented, the program must be free of errors. Program errors that may occur include coding errors, process errors, or logic errors. In the implementation stage of the KFI application, the analysis of the needs of supporting devices is very important. This application can run well, if it is able to run smoothly on hardware (android phones). In addition, the need for supporting software must also be available for the smooth implementation of the program.

In the process of implementing this, there are several steps for white box testing that are carried out, namely:

1. Writing program code (coding), this stage is done by an external programmer with the Android Studio application development program. An example of coding can be seen in the appendix.
2. Carry out the packaging process into a "KFI.apk" file using the facilities provided by Android Studio.
3. Test the program using an android phone, as well as debug or improve coding if needed.

The white box testing process has been fulfilled by the ability to install the KFI application into the android mobile phone unit that is checked by external programmers and researchers. This certainty is because the coding process has gone through about 3 times of improvement by external programmers and researchers until the KFI application is able to be operated correctly as planned.

4. Integration and System Testing

1. Test Plan

The testing process used to test the integration and newly built system is to use the black box method in an alpha manner focusing on functional requirements. The menu display test plan can be seen in table 2.

Table 2. Pengujian Tampilan Menu

Tes Item	Test Details	Test Type
Main Menu	• Enter the first calculation mode "Calculation with Pharmacokinetic Research Data" Display • Enter the second calculation mode "Calculation with Input 2 TDM Data" Display	Black box
First Calculation Mode "Calculation with Pharmacokinetic Research Data"	• Back to Main Menu Display • Enter Data Output of First Calculation Mode Part 1 Display • Enter Data Output of First Calculation Mode Part 2 Display	Black box
Data Output of First Calculation Mode Part 1	• Return to Previous Display • Generate appropriate data output • Enter the Data Output of First Calculation Mode Part 2 Display	Black box
Data Output of First Calculation Mode Part 2	• Return to Previous Display • Generate appropriate grafic output • Generate appropriate data output • Enter Data Output of First Calculation Mode Part 1 Display	Black box
Second Calculation Mode "Calculation with Input 2 TDM Data"	• Return to Main Menu Display • Enter Data Output of Second Calculation Mode Part 1 Display • Enter Data Output of Second Calculation Mode Part 2 Display	Black box
Data Output of Second Calculation Mode Part 1	• Return to Previous Display • Generate appropriate data output • Enter Data Output of Second Calculation Mode Part 2 Display	Black box
Data Output of Second Calculation Mode Part 2	• Return to Previous Display • Generate appropriate grafic output • Generate appropriate data output • Enter Data Output of Second Calculation Mode Part 1 Display	Black box

2. Black Box Test Results

Based on the test plan that has been prepared, alpha black box testing can be carried out , which is a test carried out by the researcher himself:

1. Main Menu Testing

Table 3. Main Menu Testing

Cases and Test Results	
Data Input	1. The user selects the first calculation mode "Calculation with Pharmacokinetic Research Data" button. 2. The user selects the second calculation mode "Calculation with Input 2 TDM Data" button.
What to Expect	1. The display show the first calculation mode "Calculation with Pharmacokinetic Research Data" according to the selected mode. 2. The display show the second calculation mode "Calculation with Input 2 TDM Data" according to the selected mode.
Observation	1. The system can enter the calculation mode display the first calculation mode "Calculation with Pharmacokinetic Research Data" according to the mode selected by the user. 2. The system can enter the calculation mode display the second calculation mode " Calculation with Input 2 TDM Data " according to the mode selected by the user.
Conclusion	1. Succeed 2. Succeed

2. First Calculation Mode Testing

Table 4. First Calculation Mode Testing

Cases and Test Results	
Data Input	1. The user selects the arrow image to the left in the upper left corner of the screen. 2. The user enter the weight data input 60 kg, and selects the data output of first calculation mode part 1 "Pharmacokinetic Parameters without Loading Dose" button 3. The user enter the weight data input 60 kg, and selects the data output of first calculation mode part 2 “Pharmacokinetic Simulation” button.
What to Expect	1. The display show the main menu display according to the selected mode. 2. The display show the data output of first calculation mode part 1 "Pharmacokinetic Parameters without Loading Dose" display according to the selected mode. 3. The display show the data output of first calculation mode part 2 “Pharmacokinetic Simulation” display according to the selected mode.
Observation	1. The system can enter the main menu display according to the image selected by the user.

	2. The system can enter the data output of first calculation mode part 1 "Pharmacokinetic Parameters without Loading Dose" according to the mode selected by the user. 3. The system can enter the data output of first calculation mode part 2 "Pharmacokinetic Simulation" according to the mode selected by the user.
Conclusion	1. Succeed 2. Succeed 3. Succeed

3. Data Output of First Calculation Mode Part 1 Testing

Table 5. Data Output of First Calculation Mode Part 1 Testing

Cases and Test Results	
Data Input	1. The user selects the arrow image to the left in the upper left corner of the screen. 2. The user gets the data output of first calculation mode part 1 "Pharmacokinetic Parameters without Loading Dose" correctly. 3. The user selects the data output of first calculation mode part 2 "Pharmacokinetic Simulation" button.
What to Expect	1. The display show the previous display according to the selected image. 2. The display shows the results of the calculation of 9 pharmacokinetic parameters calculation data without loading dose from the previously entered data correctly. $AUC_{0\text{-}24h}$ = 558.37 µg/mLh; C_{ss} max = 80.75 µg/mL, C_{ss} average = 23.27 µg/mL, C_{ss} min = 2.83 µg/mL, t 95% C_{ss} = 21.45 hours, t 96.87% C_{ss} = 24.83 hours, t 99% C_{ss} = 33.02 hours, $C_p$max/MIC ratio = 10.09, and $AUC_{0\text{-}24h}$/MIC ratio = 69.80. 3. The display show the data output of first calculation mode part 2 "Pharmacokinetic Simulation" display according to the selected mode.
Observation	1. The system can enter the previous display according to the image selected by the user. 2. The system can generate precise calculations of the 9 pharmacokinetic parameters calculation data without loading dose and display them all. 3. The system can enter the data output of first calculation mode part 2 "Pharmacokinetic Simulation" according to the mode selected by the user.
Conclusion	1. Succeed 2. Succeed 3. Succeed

4. Data Output of First Calculation Mode Part 2 Testing

Table 6. Data Output of First Calculation Mode Part 2 Testing

Cases and Test Results	
Data Input	1. The user selects the arrow image to the left in the upper left corner of the screen. 2. The user can view the pharmacokinetic simulation graph (plasma concentration-time curve) on the data output of first calculation mode part 2 "Pharmacokinetic Simulation" correctly. 3. The user can view the right C_p calculation by inputing the time with 50 hours and then pressing the "Calculate" button. 4. The user selects the data output of first calculation mode part 1 "Pharmacokinetic Parameters without Loading Dose" button.
What to Expect	1. The display show the previous display according to the selected image. 2. The display shows the pharmacokinetic simulation graph (plasma concentration-time curve) correctly. 3. The display shows the result of the calculation of C_p prediction at 50 hours is 4.1930 µg/mL 4. The display show the data output of first calculation part 1 "Pharmacokinetic Parameters without Loading Dose" display according to the selected mode.
Observation	1. The system can enter the previous display according to the image selected by the user. 2. The system can shows the pharmacokinetic simulation graph (plasma concentration-time curve) correctly. 3. The system can generate precise calculation of C_p prediction on display. 4. The system can enter the data output of first calculation mode part 1 "Pharmacokinetic Parameters without Loading Dose" according to the mode selected by the user.
Conclusion	1. Succeed 2. Succeed 3. Succeed 4. Succeed

5. Second Calculation Mode Testing

Table 7. Second Calculation Mode Testing

Cases and Test Results	
Data Input	1. The user selects the arrow image to the left in the upper left corner of the screen. 2. The user enter the weight data input 60 kg, Cp TDM I data input 60 µg/mL, and Cp TDM II data input 30 µg/mL, and selects the data output of second calculation mode part 1 " Pharmacokinetic Parameters" button 3. The user enter the weight data input 60 kg, Cp TDM I data input 60 µg/mL, and Cp TDM II data input 30 µg/mL, and selects the data output of second calculation mode part 2 "Pharmacokinetic Simulation" button.
What to Expect	1. The display show the main menu display according to the selected mode.

	2. The display show the data output of second calculation mode part 1 "Pharmacokinetic Parameters" display according to the selected mode. 3. The display show the data output of second calculation mode part 2 "Pharmacokinetic Simulation" display according to the selected mode.
Observation	1. The system can enter the main menu display according to the image selected by the user. 2. The system can enter the data output of second calculation mode part 1 "Pharmacokinetic Parameters" according to the mode selected by the user. 3. The system can enter the data output of second calculation mode part 2 "Pharmacokinetic Simulation" according to the mode selected by the user.
Conclusion	1. Succeed 2. Succeed 3. Succeed

6. Data Output of Second Calculation Mode Part 1 Testing

Table 8. Pengujian keluaran data mode perhitungan kedua bagian 1

Cases and Test Results	
Data Input	1. The user selects the arrow image to the left in the upper left corner of the screen. 2. The user gets the data output of second calculation mode part 1 "Pharmacokinetic Parameters" correctly. 3. The user selects the data output of second calculation mode part 2 "Pharmacokinetic Simulation" button.
What to Expect	1. The display show the main menu display according to the selected mode. 2. The display shows the results of the calculation of 14 pharmacokinetic parameters calculation data from the previously entered data correctly. k = 0.27726 /hour, $t_{1/2}$ = 2.49947 hours, V_d = 12.64727 L, V_d = 21.08%, CL = 3.51 L/hour, $AUC_{0\text{-}24h}$ = 558.37 µg/mLh; C_{ss} max = 80.75 µg/mL, C_{ss} average = 23.27 µg/mL, C_{ss} min = 2.83 µg/mL, t 95% C_{ss} = 21.45 hours, t 96.87% C_{ss} = 24.83 hours, t 99% C_{ss} = 33.02 hours, $C_p$max/MIC ratio = 10.09, and $AUC_{0\text{-}24h}$/MIC ratio = 69.80. 3. The display show the data output of second calculation mode part 2 "Pharmacokinetic Simulation" display according to the selected mode.
Observation	1. The system can enter the previous display according to the image selected by the user. 2. The system can generate precise calculations of the 14 pharmacokinetic parameters calculation data without loading dose and display them all. 3. The system can enter the data output of first calculation mode part 2 "Pharmacokinetic Simulation" according to the mode selected by the user.
Conclusion	1. Succeed 2. Succeed 3. Succeed

7. Data Output of Second Calculation Mode Part 2 Testing

Table 9. Data Output of Second Calculation Mode Part 2 Testing

Cases and Test Results	
Data Input	1. The user selects the arrow image to the left in the upper left corner of the screen. 2. The user can view the pharmacokinetic simulation graph (plasma concentration-time curve) on the data output of second calculation mode part 2 "Pharmacokinetic Simulation" correctly. 3. The user can view the right C_p calculation by inputing the time with 50 hours and then pressing the "Calculate" button. 4. The user selects the data output of second calculation mode part 1 "Pharmacokinetic Parameters" button.
What to Expect	1. The display show the previous display according to the selected image. 2. The display shows the pharmacokinetic simulation graph (plasma concentration-time curve) correctly. 3. The display shows the result of the calculation of C_p prediction at 50 hours is 0.2041 µg/mL 4. The display show the data output of second calculation part 1 "Pharmacokinetic Parameters" display according to the selected mode.
Observation	1. The system can enter the previous display according to the image selected by the user. 2. The system can shows the pharmacokinetic simulation graph (plasma concentration-time curve) correctly. 3. The system can generate precise calculation of C_p prediction on display. 4. The system can enter the data output of second calculation mode part 1 "Pharmacokinetic Parameters without Loading Dose" according to the mode selected by the user.
Conclusion	1. Succeed 2. Succeed 3. Succeed 4. Succeed

4. Operation and Maintenance

The KFI application is installed on an Android phone and used practically. Maintenance includes fixing errors that were not identified in the early stages of the lifecycle, enhancing the implementation of system units, and improving system services when new requirements are identified. Analyzing the results of user testing is necessary to ensure the application becomes stable and has a reliable calculation function.

IV. DISCUSSION

The pharmacokinetic calculations have been previously established, however the purpose of the application being designed is to significantly reduce the time required for these calculations. The Indonesian pharmacokinetic calculator abbreviated in Bahasa Indonesia, name as "KFI." The name reflects its function as a tool for calculating pharmacokinetic parameters of drugs with a narrow therapeutic range (initially focusing on amikacin) using pharmacokinetic data from patients in Indonesia.

To address the need for a user-friendly program for pharmacokinetic calculations, an android-based platform was chosen. This choice allows clinical practitioners to use mobile devices, such as phones or tablets, to perform pharmacokinetic calculations conveniently. These devices are portable and can be easily brought to the ward, providing health workers with quick visual explanations of pharmacokinetics through simulation graphs.

The KFI application was tested using black box testing in the alpha phase with various sample cases. The results indicated that the system can functionally produce the expected output data. Testing ensures that the calculation results are valid for use. Ideally, defects in components are identified early in the testing process, while interface issues are discovered during system integration. If defects are found, debugging is necessary, which may require repeating stages of the testing process. Errors in program components can be revealed during system testing, making the process iterative, with feedback from each stage informing the earlier stages. Typically, component testing is part of the normal development process, where programmers create their own test data and test the code incrementally as it is developed. Programmers, being familiar with the components, are best suited to create test cases.

This Android-based pharmacokinetic calculation application is designed for drugs with a narrow therapeutic range, using amikacin TDM. It is expected to predict the effectiveness of therapy by calculating the PK/PD index and anticipate toxicity risks by calculating Cp_{ss} min, particularly in sepsis patients. The results of this dissertation aim to enhance clinical pharmacy services in Indonesia through the application of the latest technology. Analyzing user test results is essential to ensure the application becomes a stable mobile tool with a reliable calculation function.

V. CONCLUSION

The development of the KFI aplication represents a significant advancement in pharmacokinetic calculations by reducing the time required for these processes. Designed as an Android-based application, KFI offers clinical practitioners a user-friendly and portable tool for calculating pharmacokinetic parameters of drugs with a narrow therapeutic range, initially focusing on amikacin. The application facilitates quick visual explanations of pharmacokinetics through simulation graphs, enhancing its utility in clinical settings. The rigorous testing process, including black box testing during the alpha phase, has demonstrated that KFI can reliably produce the expected output data. This iterative testing approach ensures that any defects are identified and addressed early, contributing to the application's stability and reliability. By calculating the PK/PD index and anticipating toxicity risks, KFI aplication is expected to improve therapeutic outcomes, particularly for sepsis patients. Ultimately, this application aims to enhance clinical pharmacy services in Indonesia through the integration of cutting-edge technology, ensuring accurate and efficient pharmacokinetic calculations.

REFERENCES

[1]. L. Shargel and A. B. C. Yu, *Applied Biopharmaceutics and Pharmacokinetics*, 7th ed. New York: The Mc Graw-Hill Companies, 2016.

[2]. Sani, N. Mohamad, O. Chlliah, Y. Azmi, and R. Rusli, *Clinical Pharmacokinetics Pharmacy Handbook*, 2nd ed. Selangor: Clinical Pharmacy Working Committee (Clinical Pharmacokinetics Subspecialty) Pharmacy Practice and Development Division Ministry of Health Malaysia, 2019.

[3]. A. N. Sani, "Implementation of Therapeutic Drug Monitoring in Indonesia," *J. Ayurveda Medistra*, vol. 3, no. 2, Aug. 2021, doi: 10.51690/medistra-jurnal123.v3i2.44.

[4]. R. Komalasari, "Manfaat Teknologi Informasi dan Komunikasi di Masa Pandemi Covid 19," *Tematik*, vol. 7, no. 1, pp. 38–50, Jun. 2020, doi: 10.38204/tematik.v7i1.369.

[5]. H. Kato *et al.*, "Evaluation of Amikacin Pharmacokinetics and Pharmacodynamics for Optimal Initial Dosing Regimen," *Drugs R. D.*, vol. 17, no. 1, pp. 177–187, 2017, doi: 10.1007/s40268-016-0165-5.

[6]. J. S. Pérez-Blanco, E. M. Sáez Fernández, M. V. Calvo, J. M. Lanao, and A. Martín-Suárez, "Evaluation of Current Amikacin Dosing Recommendations and Development of an Interactive Nomogram: The Role of Albumin," *Pharmaceutics*, vol. 13, no. 2, p. 264, 2021, doi: 10.3390/pharmaceutics13020264.

[7]. F. Taccone *et al.*, "Revisiting the Loading Dose of Amikacin for Patients with Severe Sepsis and Septic Shock," *Crit. Care*, vol. 14, no. 2, p. R53, 2010, doi: 10.1186/cc8945.

[8]. W. Duszynska, F. S. Taccone, M. Hurkacz, B. Kowalska-Krochmal, A. Wiela-Hojeńska, and A. Kübler, "Therapeutic drug monitoring of amikacin in septic patients," *Crit. Care*, vol. 17, no. 4, p. R165, 2013, doi: 10.1186/cc12844.

[9]. L. A. Bauer, *Applied Clinical Pharmacokinetics*. New York: The Graw-Hill Companies., 2008.

[10]. A. A. Udy, J. A. Roberts, and J. Lipman, *Antibiotic Pharmacokinetic/Pharmacodynamic Considerations in the Critically Ill*. Singapore: Springer Singapore, 2018.

[11]. I. Sommerville, *Software Engineering*, 10th ed. Boston: Pearson, 2016.

[12]. T. Sentat *et al.*, "Amikacin Dosing Analysis in Sepsis Treatment: A Pharmacokinetic Study Based on Therapeutic Drug

Monitoring," *J. Res. Pharm. Sci.*, vol. 10, no. 8, 2024.
[13]. T. Sentat *et al.*, "Development and Validation of a Bioanalytical Method for Therapeutic Drug Monitoring of Amikacin in Human Plasma Using Ultra-Performance Liquid Chromatography-Tandem Mass Spectrometry," *Int. J. Appl. Pharm.*, pp. 140–144, 2024, doi: 10.22159/ijap.2024.v16s1.30.
[14]. H. Kato *et al.*, "Population pharmacokinetics analysis of amikacin initial dosing regimen in elderly patients," *Antibiotics*, vol. 10, no. 2, pp. 1–13, 2021, doi: 10.3390/antibiotics10020100.
[15]. J. Ruiz *et al.*, "Impact of amikacin pharmacokinetic/pharmacodynamic index on treatment response in critically ill patients," *J. Glob. Antimicrob. Resist.*, vol. 12, pp. 90–95, Mar. 2018, doi: 10.1016/j.jgar.2017.09.019.
[16]. K. E. Bowker, A. R. Noel, S. Tomaselli, M. Attwood, and A. P. MacGowan, "Pharmacodynamics of inhaled amikacin (BAY 41-6551) studied in an in vitro pharmacokinetic model of infection," *J. Antimicrob. Chemother.*, vol. 73, no. 5, pp. 1305–1313, 2018, doi: 10.1093/jac/dky002.
[17]. C. A. Hammett-Stabler and T. Johns, "Laboratory guidelines for monitoring of antimicrobial drugs. National Academy of Clinical Biochemistry.," *Clin. Chem.*, vol. 44, no. 5, pp. 1129–40, 1998.