

## DAFTAR PUSTAKA

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## LAMPIRAN

### Lampiran A. Referensi Data Demografi Pasien Transplantasi Hati

#### 1. Z. Hamim (2005)

**TABLE 1. Demographic and Biochemical Data of Study Population (n = 67)**

Variables	Value	Range
Gender (% male)	67.2	—
Age (yr)	46.2 ± 12.7#	17.4–67.5
Weight (kg)	77.8 ± 17.4#	50.0–137.3
Time posttransplant (d)	40.2 ± 17.3#	14–94
Observations per patient	10.3 ± 5.8#	1–35
Dose of tacrolimus (mg/d)	7.6 ± 4.8#	1–24
Tacrolimus blood concentration (ng/mL)	11.1 ± 5.6#	1.5–29.5
Sample time (time after dose, h)	9.8 ± 1.5	6–13
Hematocrit (%)	41*	25–46
Albumin (g/dL)	4.3*	2.3–5.2
Total cholesterol (mmol/L)	4.8*	3.6–6.6
ALT (U/L)	149*	14–5450
AST (U/L)	51*	8–4830
GGT (U/L)	298*	13–6382
Bilirubin (μmol/L)	39*	5–614
Creatinine (μmol/L)	74.5*	18–803

#Mean ± SD, \*median.

#### 2. Ju Yeun Lee (2006)

**Table 1. Characteristics of the Study Patients**

Characteristic	Model-Building Group (n=35)	Validation Group (n=16)
	Median (range)	
Age (yrs)	46 (24–66)	53 (39–59)
	No. of Patients	
Sex		
Male	25	12
Female	10	4
Transplant type		
Cadaveric	11	4
Living donor	24	12
	Mean ± SD (range)	
Body weight (kg)	59.68 ± 10.87 (37–101)	59.21 ± 8.77 (43–79)
Grafted hepatic weight (g)	877.31 ± 364.88 (420–1714)	809.95 ± 265.52 (398–1400)
Graft:recipient weight ratio (%)	1.50 ± 0.62 (0.54–2.97)	1.43 ± 0.54 (0.74–2.55)
No. of postoperative days	133.03 ± 74.08 (24–308)	230.06 ± 61.24 (95–306)
Total bilirubin level (mg/dL)	3.61 ± 5.13 (0.2–44.3)	1.72 ± 4.86 (0.3–10.9)
Alanine aminotransferase level (U/L)	78.73 ± 66.87 (4–1141)	84.45 ± 116.82 (2–1314)
International normalized ratio	1.25 ± 0.35 (0.87–4.97)	1.17 ± 0.27 (0.89–3.45)
Serum albumin level (g/dL)	3.33 ± 0.41 (2.2–4.8)	3.48 ± 0.48 (2.2–4.5)
Hematocrit (%)	26.60 ± 5.53 (15.2–48.6)	29.45 ± 6.12 (15.3–27.9)
Alkaline phosphatase level (U/L)	140.22 ± 199.94 (3–3000)	72.32 ± 36.75 (20–393)
Corticosteroid dosage (mg/day)	39.54 ± 71.12 (0–625)	26.54 ± 37.35 (0–250)
Tacrolimus dosage (mg/dose q12h)	2.77 ± 1.41 (0.2–8.0)	2.82 ± 1.31 (0.5–6.0)
Blood tacrolimus concentration (ng/mL)	11.53 ± 4.09 (0.7–30.0)	10.80 ± 0.59 (3.1–24.9)
No. of blood samples/patient*	35.77 ± 7.16 (24–51)	34.31 ± 7.25 (23–51)
Sampling time after dose (hr)	10.05 ± 0.46 (3–14)	10.08 ± 0.59 (7–14)

\*Total number of samples obtained for blood tacrolimus concentrations was 1251 in the model-building group and 524 in the validation group.

### 3. D. Li (2007)

**Table 1.** Characteristics of liver transplant recipients

Variables	Full population (n = 104)			Subpopulation (n = 73)
	Index dataset <sup>a</sup> (n = 72)	Validation dataset (n = 32)	Whole dataset (n = 104)	Pharmacogenetics dataset
<b>Demography</b>				
Age (years)	49 (19–66)	51 (38–66)	49 (19–66)	48 (19–66)
Gender (male : female)	60 : 12	30 : 2	90 : 14	63 : 10
Body weight (kg)	65 (41–115)	65 (50–91)	65 (41–115)	65 (41–115)
Post-transplantation days	13.5 (1–88.5)	17.5 (1–175)	14.5 (1–175)	14.0 (1–175)
Hematocrit (%)	31.0 (19.6–45.0)	30.4 (16.0–52.3)	31.0 (16.0–52.3)	31.0 (16.0–52.3)
International normalized ratio (IU)	1.066 (0.840–2.182)	1.071 (0.883–1.931)	1.071 (0.840–2.182)	1.072 (0.840–2.182)
Alanine aminotransferase (U/L)	92 (9–1621)	63 (5–563)	81 (5–1621)	79 (5–1621)
Aspartate aminotransferase (U/L)	42 (14–2713)	32 (10–236)	39 (10–2713)	39 (10–2713)
Total protein (g/L)	63.4 (38.5–88.0)	63.6 (41.8–83.3)	63.6 (38.5–88.0)	63.9 (38.5–88.0)
Albumin (g/L)	38.5 (10.0–51.7)	39.3 (27.1–54.8)	38.8 (10.0–54.8)	38.7 (10.0–54.8)
Total bilirubin (μmol/L)	43.2 (4.4–545.5)	36.1 (8.6–268.6)	40.7 (4.4–545.5)	42.2 (9.7–545.5)
Serum creatinine (μmol/L)	77.0 (8.7–692.0)	80.0 (25.7–355)	78.0 (8.7–692.0)	80.0 (8.7–692.0)
<b>Pharmacokinetics of tacrolimus</b>				
Observations	703	403	1106	766
Observations per patient	10 (2–38)	13 (4–37)	11 (2–38)	10 (4–37)
Dose (mg/day)	6 (1.0–12)	6 (0.8–12)	6 (0.8–12)	6 (0.8–12)
Blood concentration (ng/mL)	8.4 (1.2–28.4)	8.2 (1.2–20.9)	8.3 (1.2–28.4)	8.4 (1.2–22.0)

Data are shown as median (range).  
<sup>a</sup>Model-building dataset.

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### 4. Z. Chen-Yan (2015)

**Table 2**

Demographics of external dataset

Characteristics	Mean ± SD	Median (Range)
Number of recipients (Samples) <sup>a</sup>	52(509)	/
by Male/Female <sup>a</sup>	32/17 (44/1168)	/
Age (years)	38.9 ± 8.6	39.4 (21.9–61.2)
Height (cm)	168.3 ± 6.6	170.0 (150.0–180.0)
Total body weight (kg)	59.7 ± 9.5	59.5 (39.5–86.3)
Fat-free mass (kg)	45.8 ± 8.7	49.3 (28.9–63.3)
Postoperative time (days)	37.6 ± 25.7	32.0 (0.0–90.0)
Tacrolimus daily dose (mg day <sup>-1</sup> )	4.6 ± 1.8	5.0 (1.0–6.0)
Tacrolimus daily dose (mg kg <sup>-1</sup> day <sup>-1</sup> )	0.078 ± 0.032	0.078 (0.017–0.200)
Trough concentration (ng ml <sup>-1</sup> )	6.6 ± 2.9	6.3 (2.1–26.1)
Haemoglobin (g l <sup>-1</sup> )	114.6 ± 20.5	115.0 (57.0–155.0)
Haematocrit (%)	34.7 ± 6.1	34.9 (17.6–47.6)
Albumin (g l <sup>-1</sup> )	41.3 ± 6.0	42.0 (22.0–52.0)
Globulin (g l <sup>-1</sup> )	25.2 ± 3.8	25.0 (11.0–37.0)
Aspartate transferase (U l <sup>-1</sup> )	22.5 ± 17.5	18.0 (7.0–187.0)
Total protein (g l <sup>-1</sup> )	66.5 ± 7.6	68.0 (38.0–81.0)
Total bilirubin (μmol l <sup>-1</sup> )	8.8 ± 4.4	7.9 (2.0–38.8)
Serum creatinine (μmol l <sup>-1</sup> )	109.7 ± 43.9	105.0 (47.0–481.0)
Creatinine clearance (ml min <sup>-1</sup> )†	69.7 ± 17.4	69.4 (10.9–115.8)
Blood uric nitrogen (mmol l <sup>-1</sup> )	8.9 ± 4.5	7.8 (3.2–42.2)
Oral prednisone daily dose (mg day <sup>-1</sup> )	21.6 ± 14.3	20.0 (0.0–80.0)
Concomitant calcium channel blocker <sup>a</sup>	50 (5/3)	/
Nicardipine <sup>a</sup>	14 (2/4)	/
Diltiazem <sup>a</sup>	0	/
Diabetes mellitus <sup>a</sup>	4 (1/8)	/

<sup>a</sup>Data are expressed as number of recipients (Samples). †Using Cockcroft-Gault formula:  $CL_{cr} = \frac{140 - \text{Age (years)}}{72} \times \frac{\text{Total body weight (kg)}}{72} \times S_{cr}$  (μmol l<sup>-1</sup>) × 0.85, if female

**Table 3**

Allele frequencies of genetic polymorphisms in CYP3A4, CYP3A5 and ABCB1 genes of external dataset

Genotypes	Number of recipients	Percentage (%)
<b>CYP3A4*1G (G20230A, rs2282480)</b>		
GG (**/**)	27	51.92
GA (**/*G)	22	42.31
AA (*G/**G)	3	5.77
<b>CYP3A5*3 (A6996G, rs776746)</b>		
AA (**/**)	4	7.69
GA (**/*3)	19	36.54
GG (*3/**3)	29	55.77
<b>ABCB1-C1236T (rs1128503)</b>		
CC	6	11.54
CT	19	36.54
TT	27	51.92
<b>ABCB1-C3435T (rs1045642)</b>		
CC	25	48.08
CT	24	46.15
TT	3	5.77
<b>ABCB1-G2677T/A (rs2032582)</b>		
GG	14	26.92
GT	19	36.54
GA	4	7.69
TT	6	11.54
TA	8	15.38
AA	1	1.92

All frequencies were in agreement with those predicted by the Hardy-Weinberg equation ( $P > 0.05$ )

5. J. Eunhee (2018)

**Table 1** Characteristics of the study population

Characteristics	Mean $\pm$ SD (range)
Age (years)	49.2 $\pm$ 8.7 (19–65)
Male, n (%)	46 (79.3)
Graft-to-recipient body weight ratio (%)	1.07 $\pm$ 0.24 (0.59–1.60)
Hematocrit (%)	26.7 $\pm$ 4.5 (15.8–40.9)
Total bilirubin (mg/dL)	2.4 $\pm$ 1.9 (0.4–12.0)
ALT (IU/L)	141 $\pm$ 113 (7–570)
Albumin (g/dL)	3.0 $\pm$ 0.3 (1.7–3.9)
Tacrolimus dosage (mg/dose)	1.9 $\pm$ 1.2 (0.1–6)
Body weight (kg)	61.4 $\pm$ 10.1 (40.1–85.5)
Number of blood samples/patient	10.4 $\pm$ 2.5 (3–13)
Tacrolimus concentration (ng/mL)	9.7 $\pm$ 3.9 (1.6–21.4)

**Abbreviation:** ALT, alanine transaminase.

6. C. Xiojung (2020)

**Table 2** Characteristics of external evaluation dataset

Characteristics	Number or mean $\pm$ SD	Median (range)
No. of patients (Male/Female)	84 (69/15)	/
No. of samples	572	/
Primary disease		
virus related cirrhosis		
hepatitis B virus *	61	/
hepatitis C virus *	3	/
hepatitis E virus *	1	/
hepatocellular carcinoma *	13	/
alcohol cirrhosis *	4	/
autoimmune hepatitis *	2	/
Age (years)	51 $\pm$ 9.97	51(17-74)
Body weight, WT (kg)	63.24 $\pm$ 11.14	62(40-100)
Body height (m)	1.69 $\pm$ 0.07	1.70(1.54-1.80)
Grafted hepatic weight, GHW (g)	1299.25 $\pm$ 218.51	1300(603-2100)
Graft: recipient weight ratio, GRWR (%)	2.14 $\pm$ 0.51	2.03(1.04-3.58)
Tacrolimus daily dose (mg day <sup>-1</sup> )	3.13 $\pm$ 1.61	3.00(0.25-8.00)
Tacrolimus trough concentration (ng ml <sup>-1</sup> )	6.78 $\pm$ 2.94	6.59(1.00-23.11)
Postoperative days, POD (day)	13.8 $\pm$ 8.5	12(4-50)
Haemoglobin, HB (g l <sup>-1</sup> )	104.64 $\pm$ 16.7	104(61-159)
Haematocrit, HCT (%)	31.28 $\pm$ 4.99	31(16.6-53.6)

## Lampiran B. Perhitungan Parameter Farmakokinetika Tacrolimus

### 1. Area Under Curva (AUC)

$$AUC = Dosis \cdot \frac{F_{oral}}{Cl}$$

$$AUC_1 = 7,6 \text{ mg/d} \cdot \frac{(0,25 \cdot 1000 \mu\text{g/mg})}{4,67 \text{ L/h}} = 406,83 \mu\text{g} \cdot \text{h} \cdot \text{L}^{-1}$$

$$AUC_2 = 2,77 \text{ mg/d} \cdot \frac{(0,25 \cdot 1000 \mu\text{g/mg})}{3,58 \text{ L/h}} = 189,24 \mu\text{g} \cdot \text{h} \cdot \text{L}^{-1}$$

$$AUC_3 = 6 \text{ mg/d} \cdot \frac{(0,25 \cdot 1000 \mu\text{g/mg})}{3,9 \text{ L/h}} = 384,6 \mu\text{g} \cdot \text{h} \cdot \text{L}^{-1}$$

$$AUC_4 = 4,6 \text{ mg/d} \cdot \frac{(0,25 \cdot 1000 \mu\text{g/mg})}{3,582 \text{ L/h}} = 321,03 \mu\text{g} \cdot \text{h} \cdot \text{L}^{-1}$$

$$AUC_5 = 1,9 \text{ mg/d} \cdot \frac{(0,25 \cdot 1000 \mu\text{g/mg})}{3,68 \text{ L/h}} = 129,07 \mu\text{g} \cdot \text{h} \cdot \text{L}^{-1}$$

$$AUC_6 = 3,13 \text{ mg/d} \cdot \frac{(0,25 \cdot 1000 \mu\text{g/mg})}{3,79 \text{ L/h}} = 206,45 \mu\text{g} \cdot \text{h} \cdot \text{L}^{-1}$$

### 2. Klirens

$$Cl = 0,06 \text{ L/h/kg} \times \text{BB}$$

$$Cl_1 = 0,06 \text{ L/h/kg} \times 77,8 \text{ kg} = 4,67 \text{ L/h}$$

$$Cl_2 = 0,06 \text{ L/h/kg} \times 59,68 \text{ kg} = 3,59 \text{ L/h}$$

$$Cl_3 = 0,06 \text{ L/h/kg} \times 65 \text{ kg} = 3,9 \text{ L/h}$$

$$Cl_4 = 0,06 \text{ L/h/kg} \times 59,7 \text{ kg} = 3,582 \text{ L/h}$$

$$Cl_5 = 0,06 \text{ L/h/kg} \times 61,4 \text{ kg} = 3,68 \text{ L/h}$$

$$Cl_6 = 0,06 \text{ L/h/kg} \times 63,24 \text{ kg} = 3,79 \text{ L/h}$$

### 3. Volume Distribusi

$$Vd = \frac{D_0}{C_0}$$

$$Vd_1 = \frac{7,6 \text{ mg/d}}{11,1 \times 10^{-3} \text{ mg/L}} = 684,68 \text{ L}$$

$$Vd_2 = \frac{2,77 \text{ mg/d}}{11,53 \times 10^{-3} \text{ mg/L}} = 240,24 \text{ L}$$

$$Vd_3 = \frac{6 \text{ mg/d}}{8,4 \times 10^{-3} \text{ mg/L}} = 714,28 \text{ L}$$

$$Vd_4 = \frac{4,6 \text{ mg/d}}{6,6 \times 10^{-3} \text{ mg/L}} = 696,96 \text{ L}$$

$$Vd_5 = \frac{1,9 \text{ mg/d}}{9,7 \times 10^{-3} \text{ mg/L}} = 195,87 \text{ L}$$

$$Vd_6 = \frac{3,13 \text{ mg/d}}{6,78 \times 10^{-3} \text{ mg/L}} = 461,65 \text{ L}$$

#### 4. Waktu Paruh

$$t_{1/2} = \frac{0,693}{k}$$

$$\text{Laju eliminasi} = \frac{dD_t}{dt} = C_t \cdot Cl$$

$$k_1 = (11,1 \times 10^{-3}) \times 4,67 = 5,14 \times 10^{-2} \text{ mg/h}$$

$$k_2 = (11,53 \times 10^{-3}) \times 3,58 = 4,13 \times 10^{-2} \text{ mg/h}$$

$$k_3 = (8,4 \times 10^{-3}) \times 3,9 = 3,28 \times 10^{-2} \text{ mg/h}$$

$$k_4 = (6,6 \times 10^{-3}) \times 3,582 = 2,36 \times 10^{-2} \text{ mg/h}$$

$$k_5 = (9,7 \times 10^{-3}) \times 3,68 = 3,57 \times 10^{-2} \text{ mg/h}$$

$$k_6 = (6,78 \times 10^{-3}) \times 3,79 = 2,57 \times 10^{-2} \text{ mg/h}$$

$$t_{1/2} = \frac{0,693}{5,14 \times 10^{-2}} = 13,48$$

$$t_{1/2} = \frac{0,693}{4,13 \times 10^{-2}} = 16,78$$

$$t_{1/2} = \frac{0,693}{3,28 \times 10^{-2}} = 21,13$$

$$t_{1/2} = \frac{0,693}{2,36 \times 10^{-2}} = 29,36$$

$$t_{1/2} = \frac{0,693}{3,57 \times 10^{-2}} = 19,41$$

$$t_{1/2} = \frac{0,693}{2,57 \times 10^{-2}} = 26,96$$



## Lampiran C. Hasil Pengolahan Data

Tabel 1. Pengolahan Data Model Farmakkokinetika Linier

C1	D1	C2	D2	C3	D3	C4	D4	C5	D5	C6	D6
11,1	3,695	11,53	2,85	8,4	2,518	6,6	1,829	9,7	2,221	6,78	1,752
22,2	7,389	23,06	5,7	16,8	5,056	13,2	3,659	19,4	4,442	13,56	3,505
33,3	11,085	34,59	8,55	25,2	7,584	19,8	5,488	29,1	6,663	20,34	5,257
44,4	14,779	46,12	11,4	33,6	10,112	26,4	7,318	38,8	8,884	27,12	7,009
55,5	18,475	57,65	14,251	42	12,64	33	9,148	48,5	11,105	33,9	8,762
66,6	22,169	69,18	17,101	50,4	15,168	39,6	10,977	58,2	13,325	40,68	10,515
77,7	25,865	80,71	19,95	58,8	17,696	46,2	12,806	67,9	15,546	47,46	12,267
88,8	29,559	92,24	22,8	67,2	20,224	52,8	14,639	77,6	17,767	54,24	14,019
99,9	33,255	103,77	25,65	75,6	22,753	59,4	16,466	87,3	19,988	61,02	15,772
111	36,95	115,3	28,5	84	25,28	66	18,295	97	22,209	67,8	17,525
122,1	40,645	126,83	31,35	92,4	27,809	72,6	20,125	106,7	24,43	74,58	19,277
133,2	44,339	138,36	34,2	100,8	30,337	79,2	21,954	116,4	26,651	81,36	21,029
144,3	48,035	149,89	37,05	109,2	32,865	85,8	23,784	126,1	28,87	88,14	22,782
155,4	51,729	161,42	39,9	117,6	35,393	92,4	25,613	135,8	31,093	94,92	24,535
166,5	55,425	172,95	42,75	126	37,921	99	27,443	145,5	33,314	101,7	26,287

Tabel 2. Pengolahan Data Model Farmakkokinetika Nonlinier MM Awal

C1	MMP1	C2	MMP2	C3	MMP3	C4	MMP4	C5	MMP5	C6	MMP6
11,1	1,629	11,53	1,639	8,4	1,553	6,6	1,477	9,7	1,594	6,78	1,486
22,2	1,763	23,06	1,768	16,8	1,717	13,2	1,67	19,4	1,742	13,56	1,675
33,3	1,812	34,59	1,816	25,2	1,78	19,8	1,745	29,1	1,797	20,34	1,749
44,4	1,838	46,12	1,841	33,6	1,813	26,4	1,786	38,8	1,826	27,12	1,789
55,5	1,854	57,65	1,856	42	1,833	33	1,811	48,5	1,844	33,9	1,814
66,6	1,864	69,18	1,867	50,4	1,847	39,6	1,829	58,2	1,856	40,68	1,83
77,7	1,872	80,71	1,874	58,8	1,857	46,2	1,841	67,9	1,865	47,46	1,843
88,8	1,878	92,24	1,88	67,2	1,865	52,8	1,851	77,6	1,872	54,24	1,852
99,9	1,882	103,77	1,884	75,6	1,871	59,4	1,858	87,3	1,877	61,02	1,859
111	1,886	115,3	1,888	84	1,875	66	1,864	97	1,88	67,8	1,865
122,1	1,889	126,83	1,89	92,4	1,879	72,6	1,869	106,7	1,885	74,58	1,87
133,2	1,891	138,36	1,893	100,8	1,883	79,2	1,873	116,4	1,887	81,36	1,873
144,3	1,894	149,89	1,895	109,2	1,885	85,8	1,877	126,1	1,89	88,14	1,877
155,4	1,895	161,42	1,897	117,6	1,888	92,4	1,879	135,8	1,892	94,92	1,881
166,5	1,897	172,95	1,898	126	1,89	99	1,882	145,5	1,89	101,7	1,883

Tabel 3. Pengolahan Data Model Farmakkokinetika Nonlinier MM Akhir

C1	MMP1	C2	MMP2	C3	MMP3	C4	MMP4	C5	MMP5	C6	MMP6
11,1	2,709	11,53	2,441	8,4	2,336	6,6	2,099	9,7	2,372	6,78	2,163
22,2	3,099	23,06	2,739	16,8	2,727	13,2	2,511	19,4	2,714	13,56	2,589
33,3	3,255	34,59	2,856	25,2	2,888	19,8	2,687	29,1	2,851	20,34	2,771
44,4	3,339	46,12	2,918	33,6	2,976	26,4	2,784	38,8	2,925	27,12	2,872
55,5	3,392	57,65	2,957	42	3,031	33	2,846	48,5	2,972	33,9	2,936
66,6	3,428	69,18	2,983	50,4	3,069	39,6	2,889	58,2	3,003	40,68	2,98
77,7	3,454	80,71	3,002	58,8	3,097	46,2	2,902	67,9	3,026	47,46	3,013
88,8	3,474	92,24	3,017	67,2	3,118	52,8	2,944	77,6	3,043	54,24	3,038
99,9	3,489	103,77	3,028	75,6	3,135	59,4	2,949	87,3	3,057	61,02	3,057
111	3,502	115,3	3,037	84	3,148	66	2,979	97	3,069	67,8	3,073
122,1	3,513	126,83	3,045	92,4	3,159	72,6	2,991	106,7	3,078	74,58	3,086
133,2	3,521	138,36	3,051	100,8	3,169	79,2	3,002	116,4	3,085	81,36	3,097
144,3	3,529	149,89	3,056	109,2	3,177	85,8	3,011	126,1	3,092	88,14	3,107
155,4	3,535	161,42	3,061	117,6	3,184	92,4	3,019	135,8	3,097	94,92	3,115
166,5	3,541	172,95	3,065	126	3,189	99	3,026	145,5	3,102	101,7	3,122