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Long-term outcomes and prognostic factors in kidney transplant recipients in Jakarta, Indonesia: a cohort study

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ABSTRACT

Objectives To determine the long-term survival rates and prognostic factors in kidney transplant (KT) recipients in Jakarta, Indonesia.

Design Retrospective cohort study.

Setting A KT centre in Jakarta.

Participants We enrolled 754 consecutive adult recipients who underwent KT between 2010 and 2020.

Main outcome measures Rates of 10-year patient, all-cause and death-censored graft survival and their prognostic factors in KT recipients.

Results The 10-year patient survival, all-cause survival and death-censored graft survival rates of KT recipients were 74%, 68% and 81%, respectively. The prognostic factors for poor patient survival were a pretransplant dialysis duration>24 months (HR 1.64, 95% CI, 1.08 to 2.49; p=0.02), cardiovascular disease (HR 1.59, 95% CI, 1.11 to 2.31; p=0.01), delayed graft function (DGF) (HR 4.94, 95% CI, 2.76 to 8.82; p<0.001), post-transplant infection (HR 2.63, 95% CI, 1.56 to 4.43; p<0.001) and acute rejection (HR 2.49, 95% CI, 1.20 to 5.15; p=0.01). All-cause graft survival was prognosticated by a pretransplant dialysis duration>24 months (HR 1.74, 95% CI, 1.15 to 2.47; p=0.007), cardiovascular disease (HR 1.65, 95% CI, 1.18 to 2.33; p=0.004), DGF (HR 5.39, 95% CI, 3.13 to 9.28; p<0.001), post-transplant infection (HR 2.46, 95% CI, 1.05 to 4.02; p<0.001) and acute rejection (HR 4.18, 95% CI, 2.23 to 7.84; p<0.001). Factors associated with poor death-censored graft survival were a pretransplant dialysis duration >24 months (HR 2.19, 95% CI, 1.32 to 3.63; p=0.002), cardiovascular disease (HR 1.65, 95% CI, 1.02 to 2.68; p=0.04) and acute rejection (HR 5.52, 95% CI, 2.80 to 10.83; p<0.001).

Conclusions The survival rates of KT recipients are prognosticated by pretransplant dialysis duration, cardiovascular disease, DGF, post-transplant infection and acute rejection. Stricter eligibility criteria for recipients, more sensitive cross-match testing methods and better infection management strategies may be beneficial for improving the survival rates.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Our study is the first to document the long-term outcomes of kidney transplant recipients in Indonesia as well as the prognostic factors for survival.
⇒ We analysed relevant and practical prognostic factors, which may aid in decision-making.
⇒ The consecutive sampling technique was used to prevent selection bias.
⇒ While our sample size was relatively small as we enrolled participants from only one centre in Jakarta, our participants came from various regions in Indonesia, enhancing our results' applicability to the outcomes of a larger population than initially intended.
⇒ There were missing data in our cohort, which might have interfered with the final results.

INTRODUCTION

Kidney transplantation is considered the best treatment option for end-stage kidney disease. Compared with dialysis, successful kidney transplantation is associated with higher rates of survival and quality of life. Despite these benefits, kidney transplant (KT) recipients are at a risk of allograft nephropathy and subsequent graft failure. They are also predisposed to morbidities such as cardiovascular diseases and infections associated with immunosuppressive medications.[1] These conditions may affect the survival rate of KT recipients. Several other factors, such as dialysis history, comorbidities and time-dependent variables, such as post-transplant infections and rejections, as well as donor characteristics, are known to affect both patient and graft survival after kidney transplantation.[2–4]

In the USA, Canada, Australia and several European countries, the 1-year patient survival rate ranges from 98% to 99%, while the 1-year graft survival rate ranges from 95% to 98%.[5] However, these figures may not accurately reflect the survival rates of KT recipients in developing countries.[6] The lack of transplant centres, strict organ donor policies and economic deprivation may all contribute to poor KT outcomes in developing countries. In Indonesia, the 1-year patient and all-cause graft survival rates are 87% and 82.6%, respectively.[7]

Kidney transplantation has developed rapidly in Indonesia, particularly in the last few years.[8] While a previous study in Indonesia documented the short-term patient survival and graft survival rates, little is known about long-term outcomes. It is important to note that a relatively high short-term survival rate does not guarantee long-term survival.[9] Consequently, it is critical to investigate the long-term outcomes of KT recipients. Therefore, this study aimed to obtain the 10-year patient, all-cause and death-censored graft survival rates of KT recipients as well as to identify the prognostic factors.

METHODS

Design and settings

This single-centre retrospective cohort study was conducted at Cipto Mangunkusumo Hospital (CMH), a KT centre in Jakarta, Indonesia. This study used secondary data obtained by reviewing the participants' medical records.[10] Data collection and analyses were performed from August to September 2021.

Participants

We enrolled all recipients who had undergone living donor KTs in CMH between 2010 and 2020, regardless of the procedure being the first or repeat transplant. Recipients younger than 18 years at the time of transplantation were considered as paediatric recipients and were therefore excluded. The sample size was calculated using the formula for survival analysis. After specifying α=0.05 and β=0.02 (for 80% power), we estimated that a total sample size of 412 would be required. Consecutive sampling was performed using all available data to prevent selection bias.

Follow-Up

The participants were tracked from the time of their transplant until the event of interest or until the end of the follow-up period on 1 August 2021. The minimum follow-up duration was 6 months. In the event that no recent data were available in the medical records, the participants were contacted by phone to determine survival. To prevent serious threats to validity, we concluded that the maximum acceptable proportion of patients lost to follow-up was 20%.

Variables and outcomes

We recorded the clinicodemographic characteristics of the recipients, comorbidities, pretransplant dialysis duration, donor characteristics, pretransplant cross-matching and post-transplant events. All variables were categorised into two groups. The clinicodemographic characteristics of the recipients included age (≤60 or >60 years), sex and body mass index (BMI) (overweight/not overweight). Comorbidities, including diabetes mellitus and cardiovascular disease, were defined as prior diagnosis or treatment before transplantation. Pretransplant dialysis duration was recorded in months (≤24/>24 months), and participants who underwent pre-emptive transplant were included in the 24 months group. The donors' characteristics included age (≤40/>40 years), gender, BMI (overweight/not overweight), pre-donation estimated glomerular filtration rate (eGFR) (>100/100 mL/min/1.73 m^2) and relationship with recipients (biologically related/not biologically related). Pretransplant cross-matching was performed by determining the degree of cell lysis (<30%/≥30%). We also recorded post-transplant events, such as delayed graft function (DGF), acute rejection and post-transplant infections. DGF was defined as the need for dialysis within the first week of transplantation. Acute rejection was defined as an increase in serum creatinine of >20% at 3 months after transplantation, which was not caused by factors other than transplant. Post-transplant infections were defined as hospitalisation due to infectious diseases after transplant, as evidenced by positive culture or PCR for specific pathogens.

The primary outcomes were patient-censored, all-cause-censored and death-censored graft survival rates. Patient survival rate was defined as the proportion of recipients being alive 10 years after transplant. Graft survival rate was defined as the proportion of recipients with a functioning graft, that is, the absence of return to chronic dialysis or repeat transplant after 10 years. In all-cause graft survival analysis, we considered both death and graft failure as events of interest, whereas in death-censored graft survival analysis, only graft failure was considered an event of interest. Participants who were lost to follow-up were excluded.

Statistical analysis

The Kolmogorov-Smirnov test was conducted to determine the data distribution. Numerical data were presented as means and SD for normally distributed data, or medians with first (Q1) and third (Q3) quartiles for non-normally distributed data. Categorical data were presented as frequencies and percentages. The Kaplan-Meier method was used to calculate the survival rates. The proportionality of hazard assumptions was assessed by examining the Kaplan-Meier and ln–ln curves and performing the global test. HRs were estimated using a Cox regression analysis. Time-dependent covariates (post-transplant infections and acute rejection) were analysed using a time-dependent Cox regression analysis. Age and sex were selected for adjustment. The statistical significance was set at $p<0.05$. The interval estimates were based on 95% CIs. Statistical analyses were performed using the IBM SPSS V.20.0.

Patient and public involvement

The patients and/or the public were not involved in the design and conduct of the study, choice of outcome measures or the recruitment process.

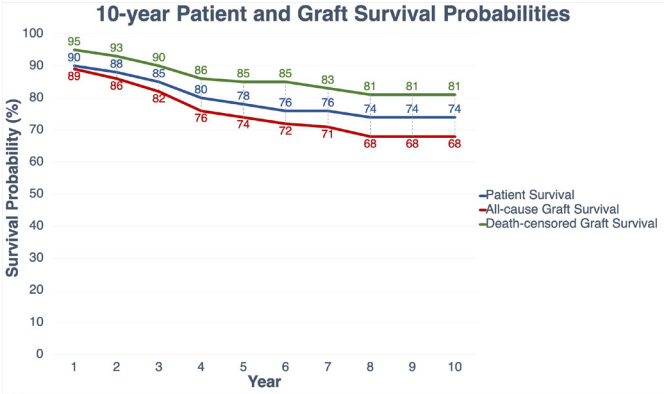

Figure 1 Estimated 10-year patient, all-cause and death-censored graft survival probabilities.

RESULTS

A total of 776 recipients underwent KTs at our centre between 2010 and 2020. Among the recipients, 22 recipients were under 18 years of age at the time of transplantation. After excluding paediatric recipients, 754 recipients were included in the analysis. A total of 132 (17.5%) recipients were lost to follow-up and were therefore censored at the time of their last visit to the KT centre. The median follow-up time was 58 months (range: 31–79 months). figure 1

Characteristics of kidney recipients and donors

The demographic and clinical characteristics of the participants are shown in table 1. Most recipients (82.9%) were under the age of 60 years at the time of transplantation. The recipients were mostly men (71.0%). While our centre is located in Jakarta, only 38.2% of the recipients resided in Jakarta. All recipients and donors were of Malay ethnicity. Most recipients were not overweight (64.0%). The BMI data were missing for 5.2% recipients. The most common primary renal disease in the recipients was hypertension (48.4%), followed by diabetes mellitus (21.6%), glomerulonephritis (8.5%) and other diseases. The primary renal disease was unknown in 11.1% patients. Most recipients (87.8%) underwent haemodialysis prior to receiving kidney grafts. Only 5.8% recipients underwent pre-emptive transplantation. Diabetes mellitus and cardiovascular disease were present in 317 (42.0%) and 266 patients (35.3%), respectively. Post-transplant infections, DGF and acute rejection occurred in 13.0%, 3.1% and 8.1% patients, respectively.

The donors were mostly (61.1%) men. Only 27.9% donors were biologically related to the recipients. Most donors (67.9%) were under the age of 40 years at the time of donation. The majority of donors were not overweight (60.2%). The BMI data were missing for 16.4% donors. Most donors (57.9%) had predonation eGFR over 100 mL/min/1.73 m^2. Predonation eGFR data were missing for 13.8% donors.

Patient and graft survival of kidney recipients

In total, 128 (17.0%) deaths occurred in our study. The proportions of all-cause and death-censored graft failure

Table 1 Characteristics of kidney transplant recipients and donors

Characteristics	n=754
Recipient (n=754)	
Age ≤60, n (%)	625 (82.9)
Men, n (%)	535 (71.0)
Primary renal disease, n (%)	
Hypertension	365 (48.4)
Diabetes mellitus	163 (21.6)
Glomerulonephritis	64 (8.5)
Others	78 (10.3)
Unknown	84 (11.1)
Type of dialysis, n (%)	
Haemodialysis	662 (87.8)
Peritoneal dialysis	17 (2.3)
Pre-emptive transplant	44 (5.8)
Haemodialysis+peritoneal dialysis	16 (2.1)
Missing	15 (2.0)
Dialysis duration (months), median (Q1–Q3)	10 (4–19)
BMI category, n (%)	
Non-overweight	483 (64.0)
Overweight	232 (30.8)
Missing	39 (5.2)
Cross-match, n (%)	
<30%	567 (75.2)
≥30%	75 (9.9)
Unknown	112 (14.9)
Diabetes mellitus, n (%)	317 (42.0)
Cardiovascular disease, n (%)	266 (35.3)
Post-transplant infections, n (%)	98 (13.0)
Delayed graft function, n (%)	23 (3.1)
Acute rejection, n (%)	61 (8.1)
Donor (n=754)	
Age≤40, n (%)	512 (67.9)
Men, n (%)	461 (61.1)
Related to recipients	211 (27.9)
eGFR category	
eGFR>100 mL/min/1.73 m^2, n (%)	437 (57.9)
Missing	104 (13.8)
BMI category, n (%)	
Non-overweight	454 (60.2)
Overweight	176 (23.4)
Missing	124 (16.4)

BMI, body mass index; eFGR, estimated glomerular filtration rate.

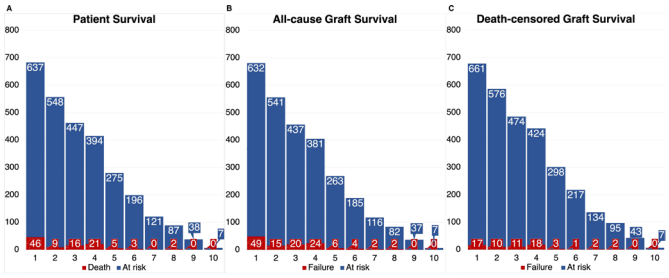

Figure 2 Population at risk at each landmark timepoint for death (A), all-cause graft failure (B), death-censored graft failure (C).

were 154 (20.4%) and 86 (11.4%), respectively. Figure 1 shows the probabilities of patient and graft survival, both of which tended to decline over time. Figure 2 shows the population at risk.

Prognostic factors for patient survival

Table 2 summarises the estimates of the HR and the 95% CI of all prognostic factors for patient survival in kidney recipients. The results implied that recipients on dialysis for more than 24 months and who were diagnosed with cardiovascular diseases prior to transplantation were at a greater risk of mortality. Moreover, DGF, post-transplant infection and acute rejection were associated with poor patient survival. All variables remained statistically significant after the adjustment. Conversely, being diabetic or overweight did not increase the risk of mortality in kidney recipients. No donor characteristics were associated with a greater risk of mortality.

Table 3 summarises the prognostic factors for all-cause graft survival in kidney recipients. All-cause graft failure was associated with dialysis for more than 24 months prior to transplant, cardiovascular disease, DGF, post-transplant infection and acute rejection. Our results imply that patient survival and all-cause graft survival were prognosticated by the same variables. Similarly, donor characteristics were not associated with all-cause graft failure.

Similar to all-cause graft survival, death-censored graft survival was associated with dialysis duration, cardiovascular disease and acute rejection. However, we found no association between DGF and post-transplant infection with death-censored graft failure in kidney recipients after transplant. Table 4 summarises the estimates of the HR of prognostic factors for death-censored graft survival.

DISCUSSION

Principal findings

This single-centre retrospective cohort study established the rates of 10-year patient, all-cause and death-censored graft survival of KT recipients as 74%, 68% and 81%, respectively. Moreover, a pretransplant dialysis duration>24 months, cardiovascular disease, DGF, post-transplant infections and acute rejection are associated with poor patient and all-cause graft survival. Meanwhile, the prognostic factors for death-censored graft failure were a duration of pretransplant dialysis>24 months, cardiovascular disease and acute rejection. However, diabetes mellitus and being overweight were not associated with either patient or graft survival. We also found

Table 2 HRs of prognostic factors for patient survival

	HR (95% CI)	P value	Adjusted HR (95% CI)	P value
Time-independent covariates				
Recipient				
Overweight	1.14 (0.79 to 1.67)	0.26		
>24 months on dialysis	1.56 (1.04 to 2.34)	0.03	1.64 (1.08 to 2.49)	0.02
Diabetes mellitus	1.30 (0.92 to 1.84)	0.14		
Cardiovascular disease	1.71 (1.19 to 2.47)	0.004	1.59 (1.11 to 2.31)	0.01
Delayed graft function	5.20 (2.98 to 9.07)	<0.001	4.94 (2.76 to 8.82)	<0.001
Cross-match>30%	1.03 (0.59 to 1.79)	0.93		
Donors				
Related to recipients	1.21 (0.83 to 1.74)	0.33		
Age>40 years	1.22 (0.84 to 1.77)	0.30		
Female	1.03 (0.72 to 1.47)	0.87		
Overweight	0.88 (0.58 to 1.32)	0.53		
eGFR<100 mL/min/1.73 m^2	1.19 (0.80 to 1.78)	0.37		
Time-dependent covariates				
Post-transplant infection	2.55 (1.51 to 4.29)	<0.001	2.63 (1.56 to 4.43)	<0.001
Acute rejection	2.29 (1.11 to 4.73)	0.02	2.49 (1.20 to 5.15)	0.01

eGFR, estimated glomerular filtration rate.

Table 3 HRs of prognostic factors for all-cause graft survival

	HR (95% CI)	P value	Adjusted HR (95% CI)	P value
Time-independent covariates				
Recipient				
Overweight	1.32 (0.94 to 1.87)	0.11		
>24 months on dialysis	1.83 (1.27 to 2.62)	0.002	1.74 (1.15 to 2.47)	0.007
Diabetes mellitus	1.17 (0.85 to 1.60)	0.34		
Cardiovascular disease	1.68 (1.21 to 2.34)	0.002	1.65 (1.18 to 2.33)	0.004
Delayed graft function	3.37 (1.71 to 6.61)	<0.001	5.39 (3.13 to 9.28)	<0.001
Cross-match>30%	1.03 (0.59 to 1.79)	0.93		
Donors				
Related to recipients	1.21 (0.83 to 1.74)	0.33		
Age>40 years	1.22 (0.84 to 1.77)	0.30		
Female	1.03 (0.72 to 1.47)	0.87		
Overweight	0.88 (0.58 to 1.32)	0.53		
eGFR<100 mL/min/1.73 m^2	1.19 (0.80 to 1.78)	0.37		
Time-dependent covariates				
Post-transplant infection	2.42 (1.48 to 3.94)	<0.001	2.46 (1.05 to 4.02)	<0.001
Acute rejection	3.83 (2.05 to 7.13)	<0.001	4.18 (2.23 to 7.84)	<0.001

eGFR, estimated glomerular filtration rate.

Table 4 HRs of prognostic factors for death-censored graft survival

	HR (95% CI)	P value	Adjusted HR (95% CI)	P value
Time-independent covariates				
Recipient				
Overweight	1.41 (1.08 to 3.04)	0.14		
>24 months on dialysis	2.16 (1.37 to 3.40)	0.001	2.19 (1.32 to 3.63)	0.002
Diabetes mellitus	1.08 (0.71 to 1.65)	0.71		
Cardiovascular disease	1.58 (1.02 to 2.45)	0.04	1.65 (1.02 to 2.68)	0.04
Delayed graft function				
Cross-match>30%	1.07 (0.53 to 2.14)	0.85		
Donors				
Related to recipients	0.95 (0.59 to 1.52)	0.83		
Age>40 years	1.06 (0.67 to 1.69)	0.79		
Female	1.05 (0.67 to 1.62)	0.84		
Overweight	1.00 (0.61 to 1.64)	0.99		
eGFR<100 mL/min/1.73 m^2	1.48 (0.92 to 2.39)	0.10		
Time-dependent covariates				
Post-transplant infection	1.70 (0.87 to 3.33)	0.12		
Acute rejection	5.51 (2.81 to 10.81)	<0.001	5.52 (2.80 to 10.83)	<0.001

eGFR, estimated glomerular filtration rate.

no association between the donor characteristics and recipient survival.

Strengths and weaknesses of our study

To our knowledge, this study is the first to document the long-term outcomes of KT recipients in Indonesia. Our study focused on relevant and practical prognostic factors that may aid in determining whether transplant candidates would benefit from receiving kidney grafts. While we enrolled participants from one centre located in Jakarta, our participants came from various regions in Indonesia because of the lack of KT centres in other regions. Thus, our results reflect the outcomes of a larger population than was initially intended. Nevertheless, our study had several limitations. First, our study was conducted in a retrospective manner. Second, there were missing data in our cohort, which may have interfered with the validity of our results. Third, there were insufficient data on malignancy, immunosuppressive treatments and adherence. Therefore, we could not estimate the influence of these factors on patient and graft survival.

Difference in relation to other studies

Compared with those of similar studies, our sample size was relatively small. This may be partly associated with the lower recognition of organ transplantation, which might explain the lower transplant rate in Indonesia compared with other countries, including neighbouring Southeast Asian countries. Kidney transplantation from living donors only has been performed in Indonesia. Therefore, we could not estimate its influence on patient outcomes. However, in comparison with other studies, we have provided an analysis of rather wide-ranging variables. We simultaneously evaluated relevant variables related to recipients and donors.

That the 10-year patient survival rate at our centre was lower than that reported in a previous study in a neighbouring country, Singapore (74% vs 84.7%).[4] We suggest several factors, which may contribute to the lower 10-year patient survival rates compared with those in other centres. First, the eligibility criteria for receiving a kidney graft in Indonesia are relatively lenient. In Singapore, only patients with no prior history of cardiovascular and cerebrovascular disease are eligible to receive kidney grafts. However, cardiovascular disease was present in 266 (35.3%) recipients at our centre and was significantly associated with increased mortality and graft failure. Second, all KT recipients in Singapore were followed up by nephrologists in a tertiary hospital with subsidised immunosuppressive agents, while in Indonesia, there were limited centres available, which may result in poorer medication compliance.[4]

Our findings regarding the prognostic factors for patient and graft survival may be explained by several factors. Poorer outcomes in recipients with longer pretransplant dialysis durations may result from longer exposure to the uraemic state, which leads to vascular calcification, a well-known risk factor for cardiovascular disease. Longer pretransplant dialysis is also associated with anaemia, which consequently impairs the circulation and causes ventricular hypertrophy and congestive heart failure.[3] Cardiovascular disease is the leading cause of death and all-cause graft failure in kidney recipients. However, we found that cardiovascular diseases were also associated with death-censored graft failure.

Our results suggest that DGF is associated with both patient and graft survival. DGF manifests as a result of ischaemia–reperfusion injury (IRI), which damages cells by promoting microvascular dysfunction. IRI may also alter immunogenicity, promoting alloantibody production and, ultimately, resulting in acute rejection.[11] Nevertheless, we found no significant association between DGF and death-censored graft survival, possibly because of a disparity in the DGF duration in our patients. A previous study found that only a DGF duration>14 days was associated with an increased risk of graft failure. Although we did not record the DGF duration of recipients in our centre, we hypothesise that although some recipients fail to recover from DGF and eventually die, others may recover rather quickly and continue to have functioning grafts.

In our study, post-transplant infection was significantly associated with a greater risk of mortality and all-cause graft failure. This finding was in accordance with a previous study in which post-transplant infection was listed as the second most common cause of death with functioning grafts in kidney recipients, owing to the prolonged use of immunosuppressive agents in this population. Although infection may cause graft failure through renal scarring and immunological imbalance,[12] we found no association between postoperative infection and death-censored graft failure in this study.

Acute rejection episodes, particularly within the first year after transplantation, result in a prolonged alloimmune response, leading to progressive fibrosis and chronic antibody-mediated injury, which may endanger both patient survival and long-term graft survival.[13] It is important to note that the degree of cell lysis based on cross-match testing performed before transplantation did not affect either patient survival or graft survival rates. This finding may indicate that the current procedure is inadequate for assessing the risk of rejection.

Possible explanations and implications for clinicians and policy-makers

Considering our findings, several points should be considered by clinicians and policy-makers. First, patients with end-stage kidney disease may benefit from stricter eligibility criteria for transplant recipients. Clinicians should carefully consider the eligibility of transplant candidates and whether the candidates would benefit from receiving kidney grafts, particularly taking into account the pretransplant duration of dialysis, as well as the presence of cardiovascular diseases. Second, we suggest the use of a more sensitive cross-match test using the analysis

of donor-specific antibodies to assess the risk of and prevent acute rejection in kidney recipients. Third, we emphasise the importance of better management and prevention of DGF as well as post-transplant infection in KT recipients.

Unanswered questions for future research

As we are the first to document the long-term outcomes of KT recipients in Indonesia, we would like to encourage future studies to advance research of the long-term outcomes of KT recipients. A national KT registry may assist in the advances made in future studies on KT recipients.

CONCLUSIONS

The survival rates of KT recipients are prognosticated by age, pretransplant dialysis duration, cardiovascular disease, post-transplant infections, acute rejection and DGF. Stricter eligibility criteria for recipients, more sensitive cross-match testing methods and better infection management strategies may be beneficial for improving the survival rates.

Contributors Study concept and design were provided by MM, ES and US. Data collection was performed by US and TA. Analysis of data was done by MM, US and TA. Drafting of the manuscript was done by MM and TA. MM, ES, US and TA provided final approval of the manuscript. MM is the guarantor of the article.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants. This study has been approved by the Ethical Committee of Faculty of Medicine Universitas Indonesia on 19 May 2021 (reference number: KET-498/UN2.F1/ETIK/PPM.00.02/2021).Data were collected retrospectively by reviewing medical records.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available in a public, open access repository. Dataset available from the Dryad repository, DOI: https://orcid.org/0000-0001-7505-0289.

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