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Research article

A survey of post-transplant direct non-medical and indirect costs for recipients and caregivers at five transplant centers in Thailand

Pannapa Sangmala[1,*], Udomsak Bunworasate[2], Pimjai Niparuck[3], Chagriya Kitiyakara[3], Cholatip Pongskul[4], Natavudh Townamchai[2], Sirima Jaroenpatarapesaj[5]

[1]Division of Health Economics Research, Department of Research Innovation and International Relations, HRH Princess Chulabhorn College of Medical Science, Chulabhorn Royal Academy, Bangkok, Thailand
[2]Department of Medicine, King Chulalongkorn Memorial Hospital, Chulalongkorn University, Bangkok, Thailand
[3]Department of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand
[4]Department of Medicine, Srinagarind Hospital, Khon Kaen University, Khon Kaen, Thailand
[5]Nursing Department, Chulabhorn Hospital, HRH Princess Chulabhorn College of Medical Science, Chulabhorn Royal Academy, Bangkok, Thailand

*Corresponding author: Pannapa Sangmala (pannapa.san@pccms.ac.th)

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Abstract

Background: A previous study in Thailand examined the cost-effectiveness model of an oral form of anti-cytomegalovirus drug, valganciclovir, versus intravenous ganciclovir in post-transplant care for national policy decision. Due to valganciclovir gave lower costs for hospital visits, but higher drug costs than ganciclovir. This study therefore presented the direct non-medical and indirect costs from the same study, to enable a fuller description how these cost parameters simulated in the model came from. **Methods:** A total of 87 kidney and 67 bone marrow transplant recipients in Thailand were followed-up 1 year after transplantation at three kidney and two bone marrow transplant centers. They were surveyed to identify the direct non-medical costs arising from their transplant. These included out-of-pocket payments for traveling to centers, food during visits, and hotel stays. Patient and caregiver productivity losses were included as indirect costs using the human capital approach and estimated from Thai Gross National Income per capita. Mean and standard error (SE) were used to estimate all costs. **Results:** The mean daily traveling costs were 400.4286 Thai baht (THB) (SE = 28.1833). The incidental daily costs for food were 162.7792 THB (SE = 13.6701). The annual accommodation cost was 402.2727 THB (SE = 200.2631), and the individual daily productivity loss was estimated as 390.7139 THB for patients and 189.0142 THB for caregivers. **Conclusions:** This study identified the unit costs for patients visiting hospitals during 1 year of post-transplant care. These costs can be used to supplement information about the management patterns for valganciclovir or ganciclovir modelling, and may also be useful in economic evaluation of other post-transplant care for future decision-making in Thailand.

Keywords: Direct non-medical costs, Indirect costs, Transplantation, Kidney, Bone marrow

Introduction

Transplantation is a medically sophisticated therapy with a lifetime duration. In Thailand, the direct medical costs of post-transplant care are covered by national insurances of social security benefits, and the civil servant medical benefit scheme.[1,2] Kidney transplantation is one of the optional treatments for end-stage renal failure patients.[3] The registered service units or transplant centers provide service activity codes to the national data center to receive payment for their services, in line with the protocol from the Thai Transplantation Society.[4] The costs covered for post-transplant care include treatment and monitoring for clinical outcomes such as drug prescriptions, laboratory and urine testing, and therapeutic monitoring of immunosuppressive drugs. They are reimbursed by monthly lump sums, as a flat rate of 30,000 and 25,000 Thai baht (THB) for months 1–6 and 7–12 after transplantation. The reimbursement system for drugs only covers those on the National List of Essential Medicines (NLEMs).[1] For bone marrow transplantation, a total of 750,000 THB is paid for all recipients before and for up to 1 year after transplantation. The benefit coverage is similar to kidney transplantation. The direct medical costs of post-transplant care are covered by the three schemes, but depend on the criteria, terms and conditions, and the guidelines.[5]

Direct non-medical and indirect costs are out-of-pocket expenses incurred by patients. Direct non-medical costs are defined as expenditure arising as the result of an illness but not from the direct purchase of medical services. These may include costs such as travel, lodging, and home services. Indirect costs are losses in earnings and productivity for the patient or caregiver related to morbidity and mortality arising from the illness.[6] Transplantation is a resource-intensive therapy.[7] Many current drugs and novel technologies used after transplantation are not included in the protocol and economic evaluation evidence is needed to support reimbursement decisions.[8–14]

Oral valganciclovir, a high-cost anti-cytomegalovirus drug, has been proposed for inclusion in the NLEMs, because it is more convenient for recipients than intravenous ganciclovir. The strategies of pre-emptive or prophylactic treatment, or wait-and-treat, can also affect both clinical outcomes and frequency of hospital visits.[15–17] Drug and treatment strategies that do not require frequent hospital visits are both more convenient for patients, and have lower direct non-medical and indirect costs for them. This affects the decision about the balance between minimizing the direct non-medical and indirect costs, and the higher purchasing costs of valganciclovir in considering the cost-effectiveness for societal purposes.

This study was part of the economic evaluation and budget impact analysis of the use of valganciclovir in solid organ and bone marrow post-transplantation care, with three indications proposed by the Infectious Drug and Vaccine Selection Expert Committee under the NLEMs Development Subcommittee 2016-2018. Researchers from Her Royal Highness (HRH) Princess Chulabhorn College of Medical Science were asked by the Health Economics Working Committee under the NLEMs Development Subcommittee 2016-2018 to carry out an economic evaluation and budget impact analysis for valganciclovir use, compared with intravenous ganciclovir (the current drug included in the NLEMs). Oral use of valganciclovir has a similar efficacy at an equivalent dosage, and was proposed as an alternative therapy option.[18,19] The criteria for inclusion of valganciclovir in the special access medicines category of the NLEMs were that valganciclovir offers lower direct non-medical and indirect costs for patients, although the drug costs are higher. It is therefore essential to include the direct non-medical and indirect costs in the economic evaluation of the drug. This study aimed to explore the direct non-medical and indirect costs occurring after

transplantation in a real-life Thai context, to provide a model input for the valganciclovir evaluation study.

Method

Three of the five kidney transplant centers with the highest number of transplants were selected as representative kidney transplant centers from statistics included in the annual report of the Thai Transplantation Society.[4] One was selected as a provincial site. These were Ramathibodi Hospital, King Chulalongkorn Memorial Hospital, and Srinagarind Hospital. The two bone marrow transplant centers selected, Ramathibodi Hospital and King Chulalongkorn Memorial Hospital, were chosen because they were the two main bone marrow transplant centers in Thailand.[20]

We estimated the sample size for each site as a proportion of the number of cases of kidney transplantation in each center in 2016. There were 50 cases in Ramathibodi Hospital, 13 in King Chulalongkorn Memorial Hospital and 25 in Srinagarind Hospital. The ethical committee of Srinagarind Hospital required a postal survey rather than face-to-face or phone interviews, and one questionnaire sent by mail was not returned. There were 36 bone marrow transplant cases at each of Ramathibodi Hospital and King Chulalongkorn Memorial Hospital. The limited data collection time and lack of appointments during that time meant that only 31 of the 36 cases were surveyed at King Chulalongkorn Memorial Hospital.

Recipients within 1 year of their transplant were recruited. A total of 87 kidney and 67 bone marrow transplant recipients or their caregivers were asked to recall their daily expenses associated with the transplant. If this was impossible, they were asked to estimate an average over a longer period of time, for example a year. The data record form (Figure 1) included sex, age, rights or benefit coverage, employment status, and income. It also asked about the number of caregivers, and the number of half or whole days lost from work by both recipients and caregivers for both outpatient and inpatient visits.

Direct non-medical costs on traveling to and from the hospital were considered to be the patients' expenses for the trip. They included expenses for Meals-on-Wheels or the additional costs of food because of travelling. The cost of accommodation was the expense of any hotel stays required for patients or caregivers during out-of-town treatment. The indirect costs were the loss of productivity for patients and caregivers. Caregivers were anyone accompanying the patient, including relatives, neighbors, or friends. Absence from work for recipients or caregivers caused by hospital stays or outpatient visits was analyzed using the human capital approach.

Actual salary and employment status from self-report or the data record form are shown as characteristics of the survey population, but not used in the analysis. The human capital approach was used to estimate wage or productivity losses by assuming that economic productivity was the Thai Gross National Income (GNI) per capita per day. The consumer price index was used to adjust GNI base years from 2015 to 2018. To calculate the indirect costs, the daily mean costs from the human capital approach were multiplied by the mean missed time in a day obtained from the survey. Both outpatient visits and time in hospital were analyzed. The caregivers' figures were also multiplied by the average number of caregivers per patient.

Statistical analysis

Sample size was determined from the annual transplantation statistics. The number of transplantations was considered as a finite population (636 and 200 for kidney and bone marrow transplant cases) using Yamane's formula (1973) with the margin of error set at 10%.[21] The results of this study will be used further as a parameter in the valganciclovir health economics

decision model, so the mean was calculated to identify the average daily costs of each unit cost component. It could also be estimated as the population mean unit costs. Standard error (SE) was calculated to manage and specify the uncertainty of the model input. The statistical testing compared each sociodemographic factor to find associations between kidney and bone marrow transplant recipients. Frequencies of categorical variables and means were calculated. The chi-squared test was used to test the categorical variables, and the Mann–Whitney U test for the differences in means for non-normally distributed variables. Fisher's exact test was used instead of the chi-squared test for categorical variables where the sample was small and the observed count less than five.

Data record form

Direct non-medical and indirect costs occurred in 1 year after transplantation

☐ **Kidney transplantation** ☐ **Bone marrow transplantation**

Gender male / female Age ..... years Date of transplantation ☐☐/☐☐/☐☐

Please give an estimation of the average value in each topic

Informant: ☐ Recipient ☐ Caregiver(s)

Rights:

☐ Universal coverage ☐ Social security benefit scheme
☐ Civil servant medical benefit scheme ☐ Out-of-pocket expenses

Patient income:

Salary per month ..... baht (THB) (from both main and part time jobs)

Direct non-medical costs:

1. Transportation expenses per round trip of recipient and caregiver(s), or transportation expenses per round trip of caregiver(s) in case of patient admitted ..... baht (THB)

2. The incidental food expenses from normal life per day of both recipient and caregiver(s) during hospital visit ..... baht (THB)

3. Overnight accommodation expenses during hospital visit
☐ No overnight stay, or no need to pay for any accommodation
☐ Have overnight stay, averaged in a year after transplantation ..... bath (THB)

Indirect costs:

1. Did the recipient have caregiver(s) taken to the hospital? How many?
☐ None
☐ Yes, ... person(s) come together
☐ Yes, ... person(s) alternately come

2. How many times did the recipient spend to travel and stay at the hospital during each outpatient visit?
☐ Half day, or less than half day
☐ Full day, or more than half day

3. How frequency did the caregiver(s) stay at the hospital to take care the patient during admission (inpatient service)?
☐ Everyday
☐ Every other day
☐ Every week
☐ Every ..... days

4. How many times did the caregiver(s) spend during each patient admission?
☐ Half day, or less than half day
☐ Full day, or more than half day

5. Does the first-person caregiver have a career? What are his/her average income?
☐ No
☐ Yes, ... baht (THB)

6. Does the second-person caregiver have a career? What are his/her average income?
☐ No
☐ Yes, ... baht (THB)

7. Does the third-person caregiver have a career? What are his/her average income?
☐ No
☐ Yes, ... baht (THB)

Medical services provided outside hospital

☐ No ☐ Other hospital..... ☐ Home service .....

Figure 1: Data record form

Results

The characteristics of the recipients are shown in Table 1.

The average number of caregivers per day of outpatient and inpatient visits was 0.6461 and 1.0260. The work time loss for caregivers was 0.3831 days for each visit to a hospitalized recipient. These numbers were used to create a "discounting factor" for productivity loss estimation.

Table 1: Characteristics of the study population

Characteristics	Kidney (n=87)	Bone marrow (n=67)	*p*-value
The annual number of transplantation of Thailand (Statistics)[1]	636	200	-
Informant, recipient n (%)	85 (97.70)	63 (94.03)	-
Sex, male n (%)	47 (54.02)	35 (52.24)	0.826[2]
Age			
18-30 years, n (%)	11 (12.64)	11 (16.42)	0.835[2]
31-40 years, n (%)	15 (17.24)	15 (22.39)	
41-50 years, n (%)	27 (31.03)	18 (26.87)	
51-60 years, n (%)	25 (28.74)	16 (23.88)	
> 60 years, n (%)	9 (10.34)	7 (10.45)	
Rights			
Universal coverage (UC), n (%)	27 (31.03)	25 (37.31)	0.637[4]
Social security benefit scheme (SSS), n (%)	25 (28.74)	21 (31.34)	
Civil servant medical benefit scheme (CSMBS), n (%)	33 (37.93)	19 (28.36)	
None, n (%)	2 (2.30)	2 (2.99)	
Employed, n (%)	57 (65.52)	35 (52.24)	0.096[2]
Average income per month (THB), mean			
Recipient	15,251.80	20,182.59	0.176[3]
Caregiver	11,510.77	13,519.35	
Average numbers of caregivers for each outpatient visit	0.5690	0.7463	0.623[3]
Average numbers of caregivers taking care for each admission	1.0460	1.0000	0.055[3]
Average time loss of recipient and accompanying caregivers for outpatient visit per day, day	0.9655	0.7910	0.076[3]
Average time loss of recipient for hospitalization per day, day	1.0000	1.0000	<0.001[3]
Average time loss of caregivers for hospitalization per day, day	0.4310	0.3209	0.068[3]

[1]Annual report of Thai Transplantation Society 2016 for kidney and expert estimation for bone marrow

[2]Chi-square test

[3]Mann–Whitney U test

[4]Fisher's exact test

Table 2: The average direct non-medical and indirect costs for the study population

Type of costs	per unit	Value (THB) mean (SE)
Direct non-medical costs		
• Travel costs	day	400.4286 (28.1833)
• Incidental food costs	day	162.7792 (13.6701)
• Accommodation costs	year	402.2727 (200.2631)
Thai Gross National Income (GNI) per capita[1]	day	390.7139
Indirect costs		
• Productivity/wage loss, a recipient from GNI[2]	day	347.5831
• Productivity/wage loss, a caregiver from GNI[3]	day	189.0142

[1]adjusted by consumer price index (CPI)

[2]adjusted by the work time loss per outpatient visit

[3]adjusted by the work time loss and the number of caregivers

The participants were asked to estimate their out-of-pocket expenses per day for the previous year. If they had mostly stayed with relatives, they were asked to estimate the cost of accommodation for one year. The mean and standard error for the kidney and bone marrow transplant groups were calculated and are shown in Table 2. The mean daily traveling cost was 400.4286 THB (SE = 28.1833). The daily incidental costs for food were 162.7792 THB (SE = 13.6701) and the annual accommodation costs were 402.2727 THB (SE = 200.2631).

Thai Gross National Income (GNI) per capita in the base year (2015) was collected from National income of Thailand 2015. Chain volume was measured as 137,899 THB per year or approximately 383.0528 THB per day and was adjusted by consumer price index (CPI) inflation rates for the year 2018. For all commodities, the latest index in July 2018 equaled 102% of 2015, and this figure was used to adjust by comparing to 100% in the base year 2015. Thai Gross National Income (GNI) per capita per day was therefore approximately 390.7139 THB.

The productivity loss per day was calculated as:

(1) For recipients, for both outpatient visits and hospital admissions:

*productivity loss = 390.7139 * time loss*

- The productivity loss was estimated in baht per day
- Time loss was estimated as the average proportion of a day lost

(2) For caregivers, for both outpatient visits and hospital admissions for the recipient:

*productivity loss = 390.7139 * time loss * number of caregivers*

- The productivity loss was estimated in baht per day
- Time loss was estimated as the average proportion of a day lost
- Number of caregivers was the number of caregivers who accompanied the recipients on that outpatient visit or admission.

The average monetary value of productivity loss is shown in Table 2. It was estimated to be 347.5831 THB for a recipient and 189.0142 THB for a caregiver. The time loss and the number of caregivers were used as the discounting factors as shown in Table 3.

Table 3: The discounting factor for post-transplant productivity loss costs

Variant	Discounting value
The mean daily work time loss of a recipient for outpatient visit, kidney	0.9655
The mean daily work time loss of a recipient for outpatient visit, bone marrow	0.7910
The mean daily work time loss of a recipient for hospital admission	1.0000
The mean daily work time loss of a caregiver for outpatient visit, kidney	0.9655
The mean daily work time loss of a caregiver for outpatient visit, bone marrow	0.7910
The mean daily work time loss of a caregiver for hospital admission	0.3831
Number of caregivers for outpatient visit	0.6461
Number of caregivers for hospital admission	1.0260

Discussion

Post-transplant care is associated with intensive resource use and a significant economic burden. In Thailand, transplant centers are in medical universities in each region. The national policy on the inclusion of the high cost anti-cytomegalovirus drug, valganciclovir, into the NLEMs needed evidence for consideration. This study therefore aimed to find the real direct non-medical and indirect unit costs for care after both kidney and bone marrow transplants. A systematic review on evaluation of ganciclovir and valganciclovir for prevention and treatment strategies[15] showed one study out of seven covered the costs of the use of healthcare facilities, home administration, home nursing, travel time, length of visit, and salary of nurses for the Spanish National Health System.[22] However, no study has explored travel, meal, and accommodation costs. Two of the seven studies explored the opportunity costs in term of wage loss. Both studies were by Luen et al and provided figures for the monetary value of the wages lost from inpatient care for CMV disease.[16,17] In Mexico, kidney transplant patients experienced extreme economic hardship because of the high cost of immunosuppressant medicines, attending medical appointments and loss of earnings.[23] Direct medical costs and travel costs were obtained from healthcare data from reimbursement and official records.[24,25] The use of new drugs, including anti-cytomegalovirus drugs, aimed to reduce graft rejection and prolong graft survival but had high costs.

Evidence of cost-effectiveness is needed for decisions on national reimbursement requirements. An economic evaluation of immunosuppressive agents in the UK included the NHS costs, but not societal costs or estimates of loss of productivity, because the study relied on the NICE technology appraisal[26] methodology. The evaluation of rabbit anti-thymocyte globulin versus basiliximab in Germany focused only on the treatment costs.[27]

This study aimed to establish the real-world costs for the Thai population to support the economic evaluation of valganciclovir and ganciclovir. It therefore followed seven previous studies,[15] but used a societal perspective. Recipients and caregivers incur direct non-medical and indirect costs from follow-up for laboratory monitoring under a pre-emptive or treatment strategy. The anti-cytomegalovirus drug chosen therefore explains why there are relevant differences. The frequency of patient visits to the transplant center depends on the strategies and the laboratory testing schedule. These treatment plans were started after transplantation, but estimated to start differences after hospital discharge, following a hospital stay of 14 days for kidney transplantation and 21 days for bone marrow transplantation. For example, pre-emptive valganciclovir is given orally as two 450mg tablets (900mg), twice daily until the viral load test was negative. The prescription needed to be refilled every 2 weeks, and patients are tested every week for 3 months. Pre-emptive ganciclovir requires a daily intravenous dose of 5 mg/kg ganciclovir twice a day for

the same period of time, with a similar testing schedule to pre-emptive valganciclovir. Moreover, treatment valganciclovir (no prevention strategy) is given orally the same dosage, but shorter period of time comparing to pre-emptive therapy (prevention strategy).

This study had some limitations. The human capital approach may be biased against unemployed individuals, but this group is approximately 50% of the survey population. However, Thai health technology assessment guidelines recommend the use of GNI to mitigate any uncertainty in economic status of the selected population, and avoid inequity, especially if the assessment is to be used to support national policy decisions. This minimizes the selection bias, and does not emphasize the wealth of participants.

The study did not consider the cost of illnesses occurring after transplantation, only the daily costs for food, accommodation, productivity loss, and annual costs of travel. However, these could be multiplied by the frequency of hospital admission or outpatient visit, as required. We used these unit cost parameters to consider the pre-emptive use of anti-cytomegalovirus drugs, valganciclovir and ganciclovir, with treatment patterns giving different frequencies of hospital visit and treatment duration, as well as cytomegalovirus infection in the first year after transplantation. The informal care costs, such as the opportunity costs or time loss for personal care and household tasks were not considered in the indirect costs analysis. However, the purpose of this study was to compare the differences in time or productivity loss between two alternatives, less frequent hospital visits for oral valganciclovir versus daily hospital visits for intravenous ganciclovir. The measurement of the informal care costs may therefore not be relevant.

No valid conclusions could be drawn about the frequency of hospital visits and admissions. The length of hospital stay and admission rate were not investigated. The population in this study had heterogeneous clinical status. The duration of outpatient visits varied significantly between the kidney and bone marrow group, suggesting that there may be differences in medical services provided that were related to clinical status. We also did not collect clinical characteristic and other treatments which might act as confounders. We recommend that future studies collect more information about resource utilization and clinical variables to provide a better estimate of the cost of illness.

A figure of 18 outpatient visits per year was acquired from an empirical review of medical records, and the length of hospital stay following transplant was based on expert opinion. Trying to use 18 days of outpatient visit and 14 days of hospital stay for the first year after kidney transplant, we obtained estimates of the direct non-medical and indirect costs of recipients and caregivers of 41,596.9223 THB or 29.57% of the 2018 GNI per capita per year (140,657 THB). Using 18 days of outpatient visits and 21 days in hospital for the first year after bone marrow transplant gave direct non-medical and indirect costs of recipients and caregivers of 50,608.2519 THB or 35.98% of the 2018 GNI per capita per year. The simple survey data suggested that the mean and SE of daily productivity loss for a recipient and a caregiver were more than the figures obtained from the human capital approach estimation, 485.6645 (68.8287) and 238.4605 (28.8121) THB. This information implies that there is a significant social and economic burden.

The direct non-medical costs obtained in this study were from primary data collection. There are no social cost studies related to post-transplant care in Thailand. We performed a direct survey with respondents, so our data can be considered reliable for further economic evaluation in Thailand. We also showed the discounting factor value separately for outpatient and inpatient care, and for recipients and caregivers. Other studies can use these values adjusted by CPI for further analysis. These

discounting factors provide a suitable Thai context for the number of caregivers accompanying patients and the time lost from work.

Conclusion

This study reflects real-life evidence of societal constraints in Thailand. The direct non-medical and indirect costs may be used as unit cost model parameters for valganciclovir cost-utility analysis. The results may also be useful for evaluating the cost-effectiveness of other post-transplant care in Thailand, provided information is available about frequency of use and hospital stays.

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Declarations

- **Ethics approval and consent to participate**

Ethics approval was obtained from the Human Research Ethics Committee of Chulabhorn Research Institute (003/2561), Institutional Review Board (IRB), Faculty of Medicine, Chulalongkorn University (COA NO.360/2018), Ethical Clearance Committee on Human Rights Related to Research Involving Human Subjects, Faculty of Medicine Ramathibodi Hospital, Mahidol University (MURA2018/153), and Ethics Committee in Human Research, Khon Kaen University (HE611136).

We proposed to use telephone interviews in this study. The ethics committee of Chulabhorn and Ramathibodi approved this proposal, but Khon Kaen ethics committee recommended a change to postal interviews for hospital service reasons. The patients from the Khon Kaen site already receive many phone calls from the hospital and it was thought that another call would disturb them. Informed consent was obtained verbally before participation. Patients could refuse to answer if they felt uncomfortable both by phone and mail, so approval was given for verbal consent from Human Research Ethics Committee Chulabhorn Research Institute, Ethical Clearance Committee on Human Rights Related to Research Involving Human Subjects, Faculty of Medicine Ramathibodi Hospital, Mahidol University, and Ethics Committee in Human Research, Khon Kaen University.

The Institutional Review Board (IRB), Faculty of Medicine, Chulalongkorn University refused permission to contact patients by mail before receiving a consent form from them at follow-up. Written consent forms were therefore obtained from the patients at Chulalongkorn before face-to-face interviews were held.

- **Consent for publication**

The data were reported in general, not individually. The information sheet and informed consent form for participants were reviewed by the IRB of Chulalongkorn. Verbal consent or consent by action were approved by the other committees.

- **Availability of data and material**

The datasets used and/or analyzed during this study are available from the corresponding author on reasonable request.

- **Competing interests**

  The authors declared that they have no competing interests.

- **Funding**

This study was conducted as a part of the economic evaluation and budget impact analysis of valganciclovir used in solid organ and bone marrow post-transplantation, funded by the Health Systems Research Institute (HSRI), Thailand. HSRI had no role in the design of the study, collection, analysis, and interpretation of the data, or writing the manuscript.

- **Authors' contributions**

PS organized the project and made substantial contributions including conceptualization, design, analysis, interpretation of the data, drafting, and revising the manuscript. CK, PN, UB, CP, and NT are all specialists in kidney and bone marrow transplantation. They provided useful suggestions and clinical data about their patients. They also proposed and provided ideas to support the conceptualization and design of the work. SJ performed the data collection. All authors read and approved the final manuscript.

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