

ORIGINAL ARTICLE

Comparison of In-Hospital Costs in End-Stage Renal Disease Patients Who Received Comprehensive Conservative Management with Advanced Care Planning

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ABSTRACT

Background: End-stage renal disease (ESRD) is a major public health concern in Thailand, contributing to high healthcare costs, especially among patients receiving Renal Replacement Therapy (RRT). Advanced care planning (ACP) can reduce unnecessary interventions and align care with patient preferences, yet uptake among Thai ESRD patients remains low. This study aims to assess whether early ACP, initiated when Karnofsky Performance Status (KPS) >70 , is associated with reduced in-hospital costs and first Emergency Department (ED) visits in ESRD patients receiving comprehensive conservative management (CCM) with ACP.

Methods: A retrospective cohort study was conducted at Pathum Thani Hospital, including 102 ESRD patients who met SPICT criteria and were managed with CCM. Patients were classified into early ACP (KPS >70) and late ACP (KPS ≤ 70) groups. Outcomes included six-month total in-hospital costs (primary) and first ED visits (secondary). Statistical analyses included the Mann-Whitney U test, generalized linear modeling (GLM), and Cox proportional hazards models.

Results: Among 102 patients who received CCM with ACP, 55 received early ACP. Median in-hospital costs were lower in the early ACP group (8,020 THB vs. 9,300 THB), though not statistically significant ($p = 0.113$). However, the adjusted analysis showed a 27% cost reduction with early ACP (95%CI: 1%–46%, $p = 0.043$). The incidence of the first Emergency Department visit after ACP, between the two groups (4.49 visits per 100 person-months in the early ACP group versus 3.38 visits per 100 person-months in the late ACP group), showed no statistically significant difference (IRR 1.33, 95%CI: 0.57–3.06, $p = 0.508$). After adjusted analysis using the Cox proportional hazards model, no statistically significant difference was found either (HR 0.91, 95%CI: 0.36–2.30, $p = 0.840$).

Conclusion: Early ACP was associated with significantly lower treatment costs without increasing the number of first ED visits, suggesting it may be a cost-effective and safe strategy for conservatively managed ESRD patients. Larger studies and the incorporation of home-based palliative care are recommended.

Keywords: Supportive and Palliative Care Indicator Tool (SPICT), Karnofsky Performance Scale (KPS), comprehensive conservative management (CCM)

นิพนธ์ต้นฉบับ

ศึกษาเปรียบเทียบค่าใช้จ่ายในโรงพยาบาลในผู้ป่วยไตวายเรื้อรังระยะท้ายที่ได้รับการดูแลแบบประคับประคองร่วมกับวางแผนการดูแลล่วงหน้า

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บทคัดย่อ

ที่มา: โรคไตวายระยะสุดท้าย เป็นปัญหาสาธารณสุขสำคัญในประเทศไทย ก่อให้เกิดค่าใช้จ่ายด้านสุขภาพสูง โดยเฉพาะผู้ป่วยที่ได้รับการรักษาทดแทนไต การวางแผนการดูแลล่วงหน้าสามารถลดการรักษาที่ไม่จำเป็นและทำให้การดูแลสอดคล้องกับความต้องการของผู้ป่วย แต่ถึงอย่างไรก็ตาม อัตราการได้รับการวางแผนดูแลล่วงหน้าในผู้ป่วยประชากรไทย ที่เป็นโรคไตเรื้อรังระยะท้ายยังคงน้อย การศึกษานี้มีวัตถุประสงค์เพื่อประเมินว่าการวางแผนการดูแลล่วงหน้า ตั้งแต่ช่วงแรก ที่เริ่มเมื่อ Karnofsky Performance Status (KPS) มากกว่า 70 มีความเกี่ยวข้องกับการลดค่าใช้จ่ายในโรงพยาบาลและการมาแผนฉุกเฉินครั้งแรก หลังวางแผนการดูแลล่วงหน้า ในผู้ป่วยโรคไตเรื้อรังระยะท้าย ที่ได้รับการจัดการแบบประคับประคองหรือไม่

วัสดุและวิธีการ: การศึกษาเชิงสังเกตแบบย้อนหลัง (retrospective cohort) ณ โรงพยาบาลปทุมธานี กับผู้ป่วยโรคไตเรื้อรังระยะท้าย จำนวน 102 คน ที่เข้าเกณฑ์ SPICT และได้รับการจัดการโดยไม่ใช้การบำบัดทดแทนไต ผู้ป่วยถูกแบ่งเป็นกลุ่มที่ได้รับการวางแผนดูแลล่วงหน้าเร็ว (KPS มากกว่า 70) และ ได้รับการวางแผนดูแลล่วงหน้าช้า (KPS น้อยกว่าหรือเท่ากับ 70) ผลลัพธ์ที่วัดรวมถึงค่าใช้จ่ายรวมในโรงพยาบาล 6 เดือน และการมาใช้บริการห้องฉุกเฉินครั้งแรกหลังวางแผนการดูแลล่วงหน้า การวิเคราะห์ทางสถิติ ประกอบไปด้วย Mann-Whitney U test, generalized linear modeling (GLM) และ Cox proportional hazards models

ผลการศึกษา: จากผู้ป่วย 102 คน มี 55 คนได้รับการวางแผนดูแลล่วงหน้าเร็ว มีค่าใช้จ่ายในโรงพยาบาลคิดเป็นค่ามัธยฐานต่ำกว่า กลุ่มที่ได้รับการวางแผนดูแลล่วงหน้าช้า (8,020 บาท เทียบกับ 9,300 บาท) แต่ไม่มีนัยสำคัญทางสถิติ ($p = 0.113$) อย่างไรก็ตาม การวิเคราะห์ถดถอยแบบปรับตัวแปรร่วม โดย GLM แสดงให้เห็นว่า การวางแผนดูแลล่วงหน้าเร็วลดค่าใช้จ่าย 27% (95%CI: 1%-46%, $p = 0.043$) ส่วนอุบัติการณ์การมาใช้บริการห้องฉุกเฉินครั้งแรกหลังการวางแผนการดูแลล่วงหน้า ระหว่างสองกลุ่ม (4.49 ครั้ง ต่อ หนึ่งร้อยคน-เดือน ในกลุ่มที่ได้รับวางแผนล่วงหน้าเร็ว เทียบกับ 3.38 ครั้ง ต่อ หนึ่งร้อยคน-เดือน ในกลุ่มที่ได้รับวางแผนล่วงหน้าช้า) ไม่มีความแตกต่างที่มีนัยสำคัญทางสถิติ (IRR 1.33, 95%CI: 0.57-3.06, $p = 0.508$) โดยหลังจากได้รับการ adjusted analysis โดย Cox proportional hazards model ยังไม่พบความแตกต่างอย่างมีนัยสำคัญทางสถิติ (HR 0.91, 95%CI: 0.36-2.30, $p = 0.840$)

สรุป : การวางแผนการดูแลล่วงหน้าเร็วมีความเกี่ยวข้องกับการลดค่าใช้จ่ายการรักษาที่ต่ำกว่าอย่างมีนัยสำคัญโดยไม่เพิ่มการมาใช้บริการห้องฉุกเฉินหลังได้รับการวางแผนการดูแลล่วงหน้า ซึ่งชี้ให้เห็นว่าอาจเป็นกลยุทธ์ที่คุ้มค่าและปลอดภัยในผู้ป่วยโรคไตเรื้อรังระยะท้าย ที่ได้รับการดูแลแบบประคับประคอง แต่อย่างไรก็ตามแนะนำให้มีการศึกษาที่มีจำนวนกลุ่มตัวอย่างขนาดใหญ่กว่าและรวมถึงการดูแลแบบประคับประคองที่บ้าน

คำสำคัญ: Supportive and Palliative care Indicator Tool (SPICT), Karnofsky Performance Scale (KPS), การดูแลรักษาแบบประคับประคองในผู้ป่วยไตเรื้อรังระยะท้าย

Introduction

End-stage renal disease (ESRD), though affecting a small fraction of the global population, exerts a disproportionate burden on healthcare systems worldwide, accounting for 2-4% of national healthcare budgets in some countries due to the high costs of treatments like dialysis and transplantation.¹

According to epidemiological data in Thailand, approximately one million people have chronic kidney disease (CKD), with 10% having stage IV CKD and 5% having stage V CKD. Moreover, approximately 10,000 deaths occur annually due to CKD.²

Worldwide data, including that from Thailand, show that as CKD progresses, healthcare costs increase. In particular, the cost of care for ESRD is approximately four times higher than for Stage III CKD, and costs are even higher for ESRD patients who receive RRT.³

Thailand's Universal Health Coverage data from the 2018 to 2022 fiscal years showed a continuous increase in the number of patients receiving RRT, from 57,682 to 82,463. The average cost per patient was 200,000 THB.⁴

Thailand's Universal Health Coverage data also show that terminally ill patients who received in-hospital care during the last month of life had in-hospital costs approximately twice as high as those who died at home, with most of the costs attributed to procedures and medications.⁵

ESRD is defined as an abnormality in kidney structure or function lasting for more than three months, with a GFR of less than 15 mL/min/1.73m².⁶

Only 60% of ESRD patients who visited the EDs of tertiary hospitals in Thailand had prior advanced care planning (ACP) discussions, and only 5% had a documented living will. Additionally, in-hospital deaths among ESRD patients were usually associated with a newly initiated palliative care consultation.⁷⁻¹⁰

Palliative care is defined as quality-of-life care for patients with severe, non-curable illnesses, with ACP being an essential component of this process.¹¹⁻¹³

Comprehensive conservative management (CCM) for ESRD is a specialized form of palliative care that adopts a holistic approach, incorporating rigorous symptom management, shared decision-making, proactive ACP, comprehensive

psychosocial support, and spiritual care.¹⁴

ACP is the process of establishing health-care decisions before a patient progresses to a condition of lacking decision-making capacity or reaching the terminal stage of life. Essential components include communication, identifying a surrogate decision-maker, and documenting an Advanced Directive or Living Will.

Advantages in the context of Public Health include reduced hospitalizations, avoidance of unnecessary life-sustaining treatments, and lower healthcare costs.^{15,16} At present, there remains a notable lack of studies comparing the impact of early versus non-early ACP on in-hospital costs and healthcare utilization among ESRD patients receiving CCM in tertiary care.

This study aims to compare in-hospital costs and the incidence of first Emergency Department (ED) visits within six months among ESRD patients who received CCM with ACP. This study also provides evidence on the effectiveness of ACP initiated at the early stages of ESRD in reducing in-hospital costs and Emergency Department visits, supporting the development of administrative strategies for terminal illness care.

Methods

This study utilized data from the Hemodialysis Center and the Outpatient Palliative Care Department of Pathum Thani Hospital, using retrospective six-month data from patients who registered at the ACP Clinic between January 1, 2024, and December 31, 2024. The starting point was the first assessment of Karnofsky Performance Status (KPS) by a palliative care nurse. KPS was assessed at the patient's initial visit to the ACP Clinic at the Hemodialysis Center. Cost data and Emergency Department utilization were obtained from the summary of expenses in the electronic medical records.

The ACP was conducted by a palliative care nurse, with documentation recorded in the medical records. A copy of the documentation, in the form of a living will be derived from the ACP discussion, was also kept by the patient.

This study population consisted of ESRD patients who had not received renal replacement therapy (RRT) or who had indications for CCM.

*Inclusion criteria*¹⁷

1. Patients who have been referred for consultation with a nephrologist

2. Patients with indications for palliative care for CKD according to the SPICT criteria. (The SPICT tool flags ESRD patients for palliative care when they have advanced kidney failure (eGFR < 30 mL/min), alongside multiple life-limiting conditions, or when dialysis is withheld or stopped.)¹⁸

3. Age 18 years or older

4. Patients must still possess decision-making capacity

5. Availability of baseline data and follow-up records in the medical chart, including documentation of the KPS on the date of the first ACP session

Exclusion criteria

1. Patients who have received a kidney transplant

2. Patients who switched from CCM to RRT.

3. Patients who died within the study period

The independent variable was the timing of ACP, categorized into two groups based on functional status: early-ACP (KPS > 70) versus non-early ACP (KPS ≤ 70). This categorization is based on evidence that ESRD patients with a KPS score ≤ 70 experience higher mortality rates and greater physical decline during the last year of life.^{19,20}

Outcome variables

1. Total hospital costs over six months

2. First Emergency Department visit

Control variables are age, sex, healthcare coverage type, cardiovascular disease, and polypharmacy, as these factors have been independently associated with healthcare costs.²¹⁻²⁵

The appropriate sample size was calculated to detect a difference in mean hospital care costs between groups. The calculation was based on a significance level (α) of 5% and a power of 80%, with an expected mean difference of 1,000 units and a standard deviation of 1,200 units for the outcome variable. The required sample size was determined to be 23 participants per group.²⁶

The baseline clinical characteristics between the two study groups were compared. For categorical variables, the Chi-square test or Fisher's exact test (when expected cell counts were small) was used. For continuous variables, either the independent samples t-test or the Mann-Whitney U test was applied, depending on the distribution of the data.

For missing data, we imputed using the mode for categorical data and the mean or median for continuous data, depending on whether the data were normally or non-normally distributed, respectively.

The primary outcome, which is the difference in hospital care costs between the two groups over six months, was analyzed using the independent samples t-test or the Mann-Whitney U test, depending on the data distribution.

Linear regression was used to adjust for covariates when the dependent variable (i.e., cost) was normally distributed. If the distribution of the dependent variable was not normal, a generalized linear model (GLM), specifying a Gamma family and a log link function, was applied for covariate adjustment.

The secondary outcome was the hazard ratio for emergency department visits within six months. The hazard ratio was calculated using the Cox proportional hazards model, and the Nelson-Aalen estimator was used for visualization of the cumulative hazard.

Subgroup analysis for the primary outcome was conducted based on baseline characteristics that showed statistically significant differences between groups, or in specific subgroups such as healthcare coverage type.

In the Cox proportional hazards model, other covariates that showed statistically significant differences between the two groups were controlled for.

Data cleaning and analysis were performed using Python 3.10 and statistical packages including scipy, pingouin, and statsmodels.

Compose the research process and results according to the STROBE Reporting Guideline for Cohort Studies.²⁷

Results

The sample size was 102, with 55 in the early ACP group and 47 in the non-early ACP group (Figure 1). No ESRD patients withdrew from RRT in this study period. Baseline characteristics between the early ACP (KPS > 70) and non-early ACP (KPS ≤ 70) groups were generally comparable. The median age was lower in the early ACP group (72 years [IQR 64-79]) compared to the not-early ACP group (80 years [IQR 71-82.5]). Median KPS scores were higher in the early ACP group (90 [IQR 90-100]) versus the not-early ACP

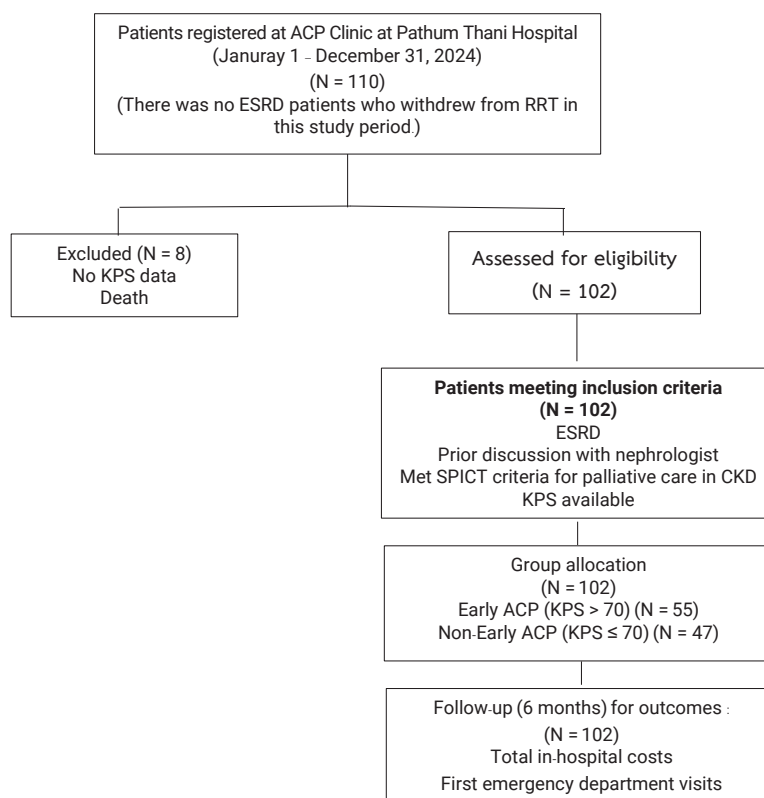


Figure 1. Flow diagram

group (60 [IQR 50-70]), reflecting the grouping criteria. Gender distribution was similar, although a slightly higher proportion of females were in the not-early ACP group (70.2% vs. 54.5%). There is no statistically significant difference in types of healthcare coverage between the early ACP and non-early ACP groups ($p = 0.269$). The majority of patients in both groups are covered under the Universal Coverage Scheme (UCS).

There were no statistically significant differences between the groups in terms of key clinical characteristics (Table 1), including glomerular filtration rate (GFR), polypharmacy, or the prevalence of comorbidities such as cardiovascular disease, diabetes mellitus, hypertension, dyslipidemia, ischemic heart disease, stroke, and gout. Similarly, the proportion of patients under the UCS was comparable between the groups.

Median in-hospital costs were lower in the early ACP group (8,020 THB [IQR: 3,704-14,560]) compared to the not-early ACP group (9,300 THB [IQR: 5,428-18,726.5]) based on the Mann-Whitney U test; however, this difference was not statistically significant (Mann-Whitney U = 1111.5, $p = 0.1128$). The subgroup analysis of patients under universal coverage (UC) showed a similar trend.

Adjusted analysis using a GLM (controlling for age, GFR, UC, polypharmacy, and cardiovascular disease) indicated that early ACP was associated with a 27% reduction in treatment cost, with a 95% CI ranging from 46% reduction to 1% reduction (percent reduction = $(1 - e^{\text{coef}}) \times 100$) (p -value 0.043). (Table 2)

The incidence of the first ED visit after ACP, between the two groups (4.49 visits per 100 person-months in the early ACP group versus 3.38 visits per 100 person-months in the late ACP group), showed no statistically significant difference (IRR 1.33, 95%CI: 0.57-3.06, $p = 0.508$). After adjusted analysis using the Cox proportional hazards model (controlling for age, GFR, UC, polypharmacy, and cardiovascular disease), no statistically significant difference was found either (HR 0.91, 95%CI: 0.36-2.30, $p = 0.840$). (Figure 2). Uncontrolled dyspnea was the cause of 100% of the first emergency department visits after ACP in both groups.

These findings support the integration of early ACP into routine care for ESRD patients eligible for conservative management, highlighting its potential to reduce healthcare costs without increasing acute care utilization. Early ACP may thus represent a valuable strategy for aligning

Table 1. Baseline characteristics comparison between the early and non-early ACP groups

Baseline characteristics	early ACP group	Not-early ACP group	p-value
Number of participants	55	47	-
Median age (Q1, Q3) (years)	72 (64, 79)	80 (71, 82.5)	0.004
Median KPS (Q1, Q3)	90 (90, 100)	60 (50, 70)	< 0.001
Gender, n (%)	Male 45 (45.4) Female 30 (54.5)	Male 14 (29.7) Female (70.2)	0.156
Healthcare coverage types	UCS 50 (90.9) SSS 3 (5.4) CSMBS 1 (1.8) Cash 1 (1.8)	UCS 43 (91.4) CSMBS 3 (6.3) Cash 1 (2.1)	0.269
Median GFR (Q1, Q3)	10 (6.54, 13.88)	12.8 (8.65, 18.05)	0.088
Place of death in a living will, n (%)	Home 30 (57.6) Hospital 7 (13.4) Not select 15 (28.9)	Home 19 (48.7) Hospital 4 (10.2) Not select 46 (41.0)	0.473
Polypharmacy, n (%)	36 (65.4)	19 (34.5)	0.684
Comorbidities, n (%)			
Cardiovascular diseases	12 (21.8)	17 (36.1)	0.167
Diabetes mellitus	28 (50.9)	26 (55.3)	0.805
Hypertension	49 (89.1)	43 (91.4)	0.942
Dyslipidemia	32 (58.1)	25 (53.1)	0.759
Gout	9 (16.3)	7 (14.8)	0.944

ACP, advanced care planning; KPS, Karnofsky Performance Status; GFR, glomerular filtration rate; UCS, Universal Coverage Scheme; SSS, Social Security Scheme; CSMBS, Civil Servant Medical Benefit Scheme

Table 2. Primary outcomes

Outcome	Early ACP group	Not-early ACP group	Statistical test	p-value
Median In-hospital costs (THB)	8,020 (IQR: 3,704–14,560)	9,300 (IQR: 5,428–18,726.5)	Mann–Whitney U = 1111.5	0.113
Subgroup (UCS patients) (THB)	7885.5 (IQR: 3,565.75–13,745)	9300 (IQR: 5,149–17822)	Mann–Whitney U = 927.5	0.129
Adjusted analysis (Generalized Linear Model) (Control : age, GFR, UC, polypharmacy, cardiovascular diseases)	Early ACP associated with 27% reduction in costs	Reference	95%CI: 46% to 1% reduction in costs	0.043

Median in-hospital costs were lower in the early ACP group (8,020 THB [IQR: 3,704–14,560]) compared to the not-early ACP group (9,300 THB [IQR: 5,428–18,726.5]); however, this difference was not statistically significant (Mann–Whitney U = 1111.5, p = 0.1128). The subgroup analysis of patients under universal coverage (UC) showed a similar trend.

Adjusted analysis using a Generalized linear model (controlling for age, GFR, UC, polypharmacy, and cardiovascular disease) indicated that early ACP was associated with a reduction in treatment cost, with a 95%CI ranging from 46% reduction to 1% reduction (p-value 0.043)

treatment with patient values while enhancing overall healthcare system efficiency.

Discussion

According to the recent Thailand Development Research Institute (TDRI) report (2568 BE), the average cost per ESRD patient who received RRT, excluding kidney transplantation, was approximately 200,000 THB in the last year of life.

For patients who chose not to receive RRT, the average cost was approximately 30,000 THB in the last year of life. In this study conducted at a secondary care hospital, the average cost per patient who received CCM for ESRD was less than 10,000 THB over six months. In addition, early advance care planning was associated with a reduction in in-hospital costs of approximately 10% and 27% after adjusting for age, GFR, polyphar-

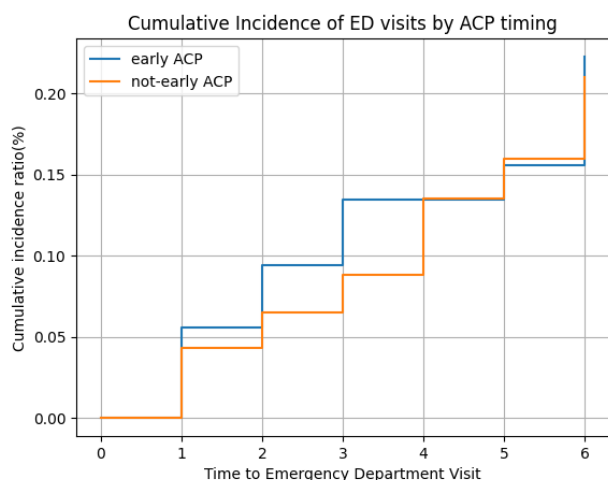


Figure 2. The Nelson-Aalen Estimator shows the cumulative hazard rate of First Emergency Department Visits, comparing the groups: First ED visit rates were similar between early ACP (20.0%) and not-early ACP (19.1%), with both groups showing a similarly increasing cumulative incidence over time

macy, cardiovascular disease, and UCS eligibility.

The main reasons expected for these results are that patients with advanced chronic disease who received early ACP had fewer invasive procedures, reduced hospital stays, and decreased anxiety, which might otherwise lead to unnecessary and unbeneficial medication.^{28,29}

This study explored the potential impact of early ACP initiation on healthcare utilization and cost outcomes in ESRD patients receiving conservative care.³⁰ Although early ACP was associated with a trend toward lower in-hospital costs in adjusted analyses, the difference did not reach statistical significance in unadjusted analyses. Similarly, no significant reduction in first ED visit rates was observed among patients who received early ACP. This suggests that although early ACP may reduce invasive procedures, hospital stays, and unbeneficial treatments, it does not lead to under-treatment or missed opportunities for necessary urgent care.

Several factors could explain these findings. First, the limited sample size and variability in patient trajectories might have underpowered the study to detect statistically significant differences. Second, while early ACP may help align care with patient preferences³¹, its impact on acute care utilization, particularly in a context where dyspnea remained the primary reason for first ED visits, may be limited without broader system-level interventions (such as home-based

palliative care or 24/7 symptom management support).³²⁻³⁵

This study has several limitations that should be acknowledged. Notably, the early ACP group had better functional status (KPS > 70) at baseline, which may be associated with longer life expectancy and better overall health, potentially confounding the observed association between early ACP and reduced hospital costs. Additionally, the retrospective design limits causal inference, and the relatively small sample size from a single hospital restricts generalizability. Due to limitations in data linkage, first ED visits at other hospitals were not captured, potentially underreporting the total number of events.

For effective implementation, care coordination between palliative care specialists, nephrologists, and other relevant specialties should be supported by guidelines recommending the referral of ESRD patients, especially those with good functional status or early diagnosis, for early goals-of-care discussions.

Based on these findings, we suggest integrating early ACP discussions into structured care models, including community-based palliative services, and exploring additional outcomes such as patient-reported quality of life, caregiver burden, and adherence to end-of-life care preferences. Future research should explore barriers to ACP uptake and key factors influencing its effectiveness, such as strong opioid use and palliative care specialist involvement, to guide more effective implementation.

Conclusions

For the implementation of early ACP in hospitals, guidelines should be established recommending that CKD patients diagnosed with stage V, after discussing RRT options with a nephrologist, be referred for co-management with palliative care. This would support ACP discussions and symptom management, aiming to reduce unnecessary treatments that may not benefit quality of life in the future and to ensure care aligns with the patient's end-of-life preferences.

As uncontrolled dyspnea was the cause of 100% of the first Emergency Department visits after ACP in both groups, the prescription of symptom-controlling medication, such as strong opioids or anxiolytics, may be necessary for ESRD patients receiving conservative care man-

agement (CCM) to prevent further unnecessary healthcare utilization or invasive procedures.

Highlight

1. Advance care planning (ACP) for patients with end-stage chronic kidney disease (CKD) during the stage where their Karnofsky Performance Status (KPS) is greater than 70—or while they are still capable of self-care—can help reduce hospital healthcare expenditures.

2. In addition to reducing hospital healthcare costs, implementing Advance Care Planning at this stage does not increase emergency department (ED) visits compared to patients who undergo ACP only after they have begun to lose their ability to perform self-care.

3. The primary symptom that drives end-stage chronic kidney disease patients to the emergency department is dyspnea (shortness of breath). Nevertheless, reducing treatment costs does not result in an increase in emergency department visits, as it specifically eliminates interventions that do not contribute to the patient's quality of life.

Author contributions

Chawanwat Jindamporn was responsible for literature review, methodology design, data collection, data analysis and interpretation, and manuscript writing. Pichet Noihoon contributed to drafting the introduction and provided methodological consultation. Somsin Buatong assisted with data acquisition. All authors critically reviewed and revised the manuscript for intellectual content and approved the final version for submission.

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Ethics approval and consent to participate

This study was approved by the Ethics Committee of Pathum Thani Hospital (Ethics Committee Approval Code: EC-PTH A089-68, Approval Date: February 24, 2025). Informed consent was waived due to the retrospective nature of the study, and all patient data were anonymized before analysis.

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Availability of Data and Materials

The datasets analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Competing Interests

The authors declare that they have no competing interests.

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