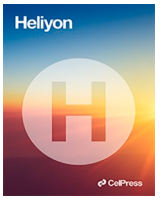
Heliyon 10 (2024) e39407

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Research article

Prevalence of perioperative pulmonary embolism in patients with renal cell carcinoma undergoing nephrectomy

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ARTICLE INFO

Keywords:
Pulmonary embolism
Renal cell carcinoma
Nephrectomy
Tumor thrombus
Perioperative

ABSTRACT

This study aims to determine the prevalence of perioperative PE and outcomes in patients with RCC scheduled for nephrectomy. A total of 418 patients were included in this single-center, observational study. Three hundred patients with RCC were retrospectively reviewed between 2016 and 2020, and the remaining patients were prospectively collected between 2020 and 2022 to minimize the effect of the long-time span. Patients with incomplete medical data and those who refused to participate were excluded. The primary outcome was the prevalence of perioperative PE. Secondary outcomes were associated factors, method of PE prophylaxis, rate of intraoperative transesophageal echocardiography (TEE) utilization, and 30-day mortality. The prevalence of perioperative PE was 1.9 % and most commonly occurred during the postoperative period (75 %). The prevalence rose to 7.5 % in patients with tumor thrombus. Significant factors related to PE included smoking (OR 6.78, 95 % CI 1.13–40.56) and change in tumor thrombus stage (OR 21.55, 95 % CI 3.69–125.71). There was no difference in the rate or method of PE prophylaxis between the two groups. Of the patients, 2.9 % underwent intraoperative TEE monitoring and 0.2 % received rescue TEE. Pneumonia and acute respiratory distress syndrome were significantly correlated with PE ($P < 0.001$ and $P = 0.03$, respectively). Finally, there was no significant difference in 30-day mortality ($P = 0.07$). The overall prevalence of PE in patients with RCC scheduled for nephrectomy was rare but more likely to occur in those with tumor thrombus.

1. Introduction

Pulmonary embolism (PE) is a significant cause of perioperative morbidity and mortality [1,2]. Previous studies have reported that the incidence of perioperative PE in patients undergoing urologic surgery ranges from 0.9 % to 1.1 %, and the mortality rate is <0.2 % [1,3–5]. A recent study found that patients with renal cell carcinoma (RCC) had a high prevalence (11 %) of perioperative PE from nephrectomy and a mortality rate of >33 % [6]. This finding might be because patients with RCC have many risk factors for PE development, including renal cell cancer [7,8], major abdominal surgery [1,9], massive bleeding, cardiac arrhythmia [3], deep vein thrombosis (DVT), and tumor thrombus in the inferior vena cava (IVC) [8,9], and PE occurs from both DVT and tumor thrombus.

The perioperative detection of PE is therefore crucial. Preoperative imaging such as computed tomography (CT) or magnetic

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https://doi.org/10.1016/j.heliyon.2024.e39407
Received 27 August 2024; Received in revised form 14 October 2024; Accepted 14 October 2024
Available online 18 October 2024

resonance imaging of the chest and whole abdomen are necessary to identify the stage of cancer, level of tumor thrombus, and presence of DVT or PE [1,6]. A longer duration between the date of imaging and date of surgery might be related to the changing stage of cancer and tumor thrombus. During surgery, transesophageal echocardiography (TEE) is useful for both surveillance and rescue of PE [10–12], along with information regarding the diagnosis of tumor thrombus level [11]. Increasing the use of TEE may enhance the intraoperative detection of PE via direct visualization of floating thrombus or indirect echocardiographic signs such as severe right ventricular dysfunction, tricuspid regurgitation, and McConnell sign [1,12]. Furthermore, TEE is also used to assess volume status and cardiac function in high-risk, non-cardiac surgical patients [12,13]. After surgery, PE can still occur and the patients require clinical monitoring. To diagnose PE, CT pulmonary angiography is commonly performed [1]. Treatment options of perioperative PE vary depending on the location of PE, the patient's hemodynamic stability, and the hospital's protocol. The occurrence of perioperative PE affects the patient's clinical outcome, increases complications, increases intensive care unit (ICU) admission, and prolongs the length of hospital stay [6].

Accordingly, the aim of this study was to determine the prevalence of perioperative PE in patients with RCC undergoing nephrectomy at a tertiary care university hospital. The secondary objectives included identifying the risk factors, rate and methods of DVT prophylaxis, methods of PE detection, use of intraoperative TEE, required treatment, postoperative outcomes, and 30-day survival.

2. Materials & methods

This was a single-center, descriptive, observational study. Adult (>18 years) patients scheduled for nephrectomy were eligible for study inclusion. To limit the time span of the data, we retrieved the patient information retrospectively from the electronic medical record between November 2016 and August 2020 and collected prospective data from October 2020 to November 2022. We excluded patients with incomplete medical records and those who refused to participate. The study protocol was approved by the Siriraj Institutional Review Board (Si758/2020). Approval was obtained before patient enrollment with the waiver of written of informed consent for the retrospective chart review data. For the prospectively collected data, all patients provided written informed consent. This study was registered at clinicaltrial.gov (NCT04402749).

2.1. Data collection

We collected the demographic information of the patients, including age, sex, body weight, height, comorbidities, DVT prophylaxis, and relevant preoperative laboratory values. Preoperative characteristics of the renal tumor were also recorded, including size, site, the presence of tumor thrombus and its level according to Mayo Clinic criteria [6], and the duration between the last imaging investigation and the operative date. We carefully collected information on intraoperative hemodynamic variables, the use of intraoperative TEE, other methods of PE detection, postoperative complications, and patient outcomes.

Mayo Clinic criteria define the level of tumor thrombus as level 0, I, II, III, and IV. Level 0 refers to a tumor thrombus limited to the renal vein or its tributaries. When the thrombus grows into the IVC with <2 cm above the renal vein, it is classified as level I. An IVC extension >2 cm above the renal vein orifice but below the hepatic veins or above the hepatic veins but below the diaphragm is defined as level II and III. Level IV thrombus is extended above the diaphragm.

Preoperative DVT screening and prophylaxis were considered based on the patients' tumor stage. All patients with tumor thrombus level I to IV underwent CT pulmonary angiogram to evaluate PE, and based on the CT findings, they underwent echocardiography by cardiologists. Given the low prevalence of DVT among the Thai population [14,15], DVT chemoprophylaxis was not prescribed to all patients concerning risk of bleeding. Only patients who demonstrated band thrombus on preoperative imaging were administered anticoagulants. Intraoperative pneumatic socking was used for all patients undergoing nephrectomy who did not have a known tumor thrombosis since 2018.

According to the study design, the investigators retrieved the data from a retrospective chart review of 300 patients and prospectively collected information from 118 patients after receiving written informed consent.

2.2. Outcome measurement

The primary outcome of the study was the prevalence of perioperative PE in patients with RCC undergoing nephrectomy. The perioperative period was defined as the intraoperative period until 7 days after the operation. Secondary outcomes were risk factors associated with PE, rate and method of DVT prophylaxis, rate and objectives of TEE use (e.g., monitoring or rescue), clinical outcomes, and mortality rate at 30 days.

2.3. Sample size calculation

Fukazawa et al. [6] reported that the prevalence of perioperative PE in patients with RCC was 11 %. Using a 95 % confidence interval and 3 % rate of accepted errors, a sample size of 418 was required for this study.

2.4. Statistical analysis

We conducted statistical analyses using PASW statistics (SPSS) version 18.0 (SPSS Inc., Chicago, IL, USA). Quantitative data were

expressed as mean ± standard deviation or median with range and analyzed by either a two-sample *t*-test or Mann–Whitney *U* test, whereas qualitative data were expressed as number and proportion in percentage and analyzed by either chi-square test or Fisher's exact test. To establish the risk factors associated with PE, we used univariate and multivariate analyses. *P* values < 0.05 denoted statistical significance.

3. Results

Based on the inclusion criteria, we accessed the charts of 765 patients for retrospective eligibility, and 300 patient files were enrolled. For prospective data, 122 patients were accessed, and the final enrollment was 118 patients; two patients declined participation, and the other two underwent a change in operation. The final number of patients enrolled was 418 (Fig. 1).

Perioperative PE was detected in eight patients (1.9 %), two during surgery and six in the early postoperative period. The prevalence rose to 7 % when we included only those patients with all-stage tumor thrombus invading the IVC.

Table 1 displays the preoperative patient characteristics. There was no statistically significant difference in age, sex, or body mass index between the two groups. Perioperative PE was significantly correlated with a history of smoking, history of lung cancer, changing stage of tumor thrombus, lower levels of hemoglobin and platelets, and prolonged international normalized ratio.

The rate of DVT prophylaxis for preventing adverse thromboembolic events with a pneumatic pumping machine was not different between the two groups, and pneumatic compression was the most commonly used method (43.3 %). However, the use of those preventive strategies for thromboembolic prophylaxis did not significantly lower the rate of perioperative PE.

Intraoperative data comparing perioperative PE with the control group showed significantly larger amounts of intraoperative crystalloid and red cell transfusion in the perioperative PE groups. The estimated intraoperative blood loss was also statistically

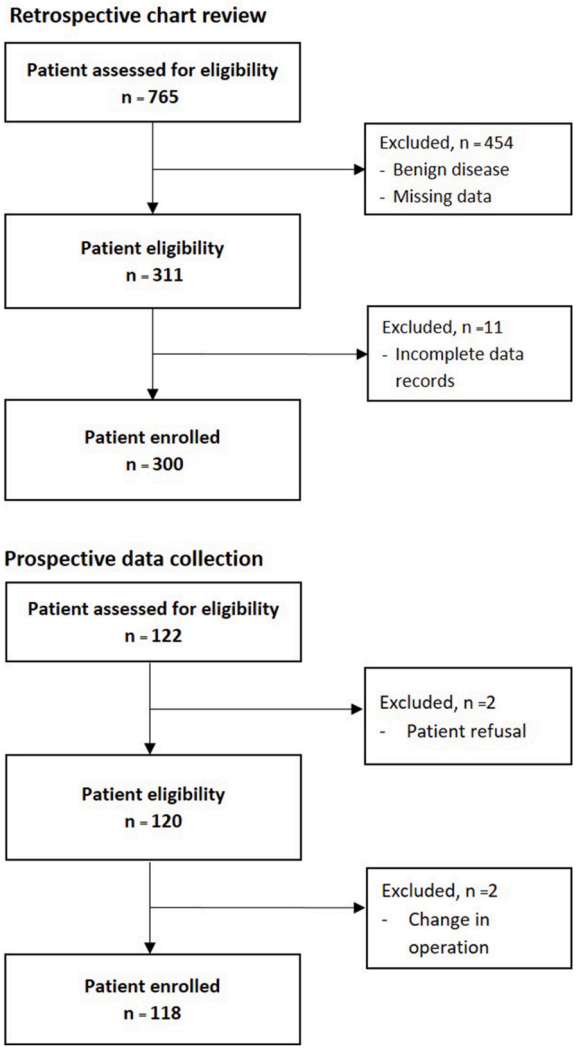

Fig. 1. Flow diagram for study patient enrollment.

Table 1
Demographic, preoperative and intraoperative data of the patients.

Characteristic	Perioperative PE n = 8 (1.9 %)	No Perioperative PE n = 410 (98.1 %)	*P* Value
Gender			
Male (n, %)	5 (62.5 %)	268 (65.4 %)	1.0
Age (years) (mean ± SD)	56.8 ± 16.8	58.9 ± 14.1	0.68
Body mass index (kg/m^2) (mean ± SD)	24 ± 7.5	24.8 ± 11.1	0.43
Comorbidities			
Diabetes mellitus (n, %)	2 (25 %)	97 (24 %)	1.00
Hypertension (n, %)	4 (50 %)	248 (61.4 %)	0.71
Dyslipidemia (n, %)	4 (50 %)	176 (43.6 %)	0.73
Smoking (n, %)	4 (50 %)	73 (18.1 %)	0.04*
CKD (n, %)	4 (50 %)	108 (26.7 %)	0.22
DVT/PE-related history			
History of DVT	0	2 (0.5 %)	1.0
History of cancer			
Lung	2 (25 %)	15 (3.7 %)	0.03*
Liver	0	10 (2.5 %)	1.0
Other	0	33 (8.2 %)	1.0
DVT prophylaxis			
Intraoperative pneumatic stocking	1 (12.5 %)	180 (44.6 %)	0.08
Medication	0	9 (2.2 %)	1.0
Preoperative laboratory data			
Hemoglobin (g/dL) (mean ± SD)	10.2 ± 1.7	12.5 ± 2.1	0.003*
Platelet (/uL) (mean ± SD)	351,625.0 ± 134,014.0	279,834.0 ± 102,518.0	0.05
BUN (mg/dL) (median, IQR)	14.3 (11.3–17.9)	13.9 (11.3–17.6)	0.91
Cr (mg/dL) (median, IQR)	1.1 (0.9–1.4)	1.0 (0.8–1.3)	0.32
INR (mean ± SD)	1.8 ± 0.2	1.0 ± 0.1	<0.001*
Renal tumor			
Right			
Size	5 (62.5 %)	198 (48.3 %)	0.49
Width (cm) (mean ± SD) (median, IQR)	8.2 ± 2.5	4.9 (2.9–8.2)	0.02*
Height (cm) (mean ± SD) (median, IQR)	8.3 ± 2.0	4.8 (2.7–8.0)	0.01*
Level of tumor thrombus	4 (50 %)	53 (12.9 %)	0.14
0	0	20 (37.7 %)	
I	3 (50 %)	9 (17 %)	
II	1 (12.5 %)	21 (39.6 %)	
III	0	2 (3.8 %)	
IV	0	1 (1.9 %)	
Preoperative CT (month) (median, IQR)	1.0 (1–2)	2.0 (1–2)	0.5
Intraoperative data			
Open surgery	8 (100 %)	229 (55.9 %)	0.01
Intraoperative ultrasound used	6 (75 %)	107 (26.1 %)	0.006
Change in stage of tumor thrombus	5 (62.5 %)	12 (2.9 %)	<0.001*
Operative time (hours) (mean ± SD)	7.0 ± 3.4	4.1 ± 1.6	0.05
Anesthesia monitoring			
Arterial line	5 (62.5 %)	141 (34.4 %)	0.13
Central venous line	2 (25 %)	39 (9.7 %)	0.18
TEE	2 (12.5 %)	11 (2.7 %)	0.23
Rescue TEE	1 (12.5 %)	0	0.01*
Fluid			
Acetar (mL) (median, IQR)	6500.0 (2530.5–9600.0)	1600.0 (1075.0–2475.0)	<0.001*
PRC (mL) (median, IQR)	2226.0 (677.0–2296.0)	500.0 (200.0–1250.5)	0.02*
Estimated blood loss (mL) (median ± IQR)	1950.0 (1075.0–6275.0)	300.0 (100.0–700.0)	0.01*

Note: CT, computed tomography; CKD, chronic kidney disease; DVT, deep vein thrombosis; BUN, blood urea nitrogen; Cr, creatinine; PCR, packed red cell.

Table 2
Factors associated with perioperative pulmonary embolism.

Factor	Univariate analysis		*P* Value	Multivariate Analysis		*P* Value
	Crude OR	95 % CI		Adjusted OR	95 % CI	
Smoking	4.61	1.11–18.88	0.04	6.78	1.13–40.56	0.03*
History of lung cancer	8.77	1.63–47.15	0.03	9.03	0.88–91.98	0.06
Tumor thrombus invading the IVC	6.73	1.63–27.74	0.14	2.22	0.39–12.40	0.36
Changing stage of tumor thrombus	55.2	11.8–258.4	<0.001	21.55	3.69–125.71	0.001*

significant in the perioperative PE group.

For intraoperative TEE monitoring, the results showed limited use of intraoperative TEE in 13 cases (3.11 %) and in only two cases (12.5 %) in the perioperative PE group. Unplanned TEE examination was performed as rescue TEE for one intraoperative PE case (Table 2).

We performed a multivariate analysis using interesting and previously reported associated factors with $P < 0.05$ to identify factors associated with perioperative PE. We found that smoking (adjusted odds ratio (OR) 6.78, 95 % confidence interval (CI) 1.13–40.56, $P = 0.03$) and change in tumor thrombus stage (adjusted OR 21.55, 95 % CI 3.69–125.71, $P = 0.001$) were significantly correlated with perioperative PE (Table 2).

As compared with patients without PE, those with perioperative PE were more likely to be admitted to the ICU postoperatively (75 % and 8.8 %, respectively; $P < 0.001$), be readmitted to the ICU (25 % and 0.5 %; $P = 0.002$), have a longer hospital stay (6 days vs. 14 days; $P = 0.001$), and have a longer ICU stay (2 days and 9.5 days; $P = 0.01$). In terms of postoperative sequelae, pulmonary complications such as pneumonia ($P = 0.002$) and acute respiratory distress syndrome (ARDS; $P = 0.03$) were significantly correlated with PE. On the other hand, acute kidney injury, renal replacement therapy, and 30-day survival rate were found to be nonsignificantly correlated with perioperative PE (Table 3).

Table 4 classifies the postoperative data in terms of the level of tumor thrombus of all patients. There was no statistically significant difference between the level of tumor thrombus and postoperative complications such as length of hospital or ICU stay, length of mechanical ventilatory support, organ sequelae, or 30-day survival rate.

Table (supplementary table 1) summarizes the details of patients' perioperative PE. Eight patients were diagnosed with perioperative PE, intraoperatively in two patients and in the early postoperative period in six patients. Unfortunately, one patient experienced intraoperative cardiac arrest and death and even underwent open thromboembolectomy; the other patient survived for 30 days.

4. Discussion

In the present study, the prevalence of perioperative PE in patients who underwent nephrectomy was 1.9 %, and prevalence of perioperative PE rose to 7.5 % in patients with tumor thrombus invading the IVC. In many previous reports [6,8,9], the prevalence of perioperative PE in this group of patients varies. Our rate was lower than that reported in the study by Fukazawa et al. [6], who reported 11 % prevalence of perioperative PE [6], mainly due to the difference in inclusion criteria. Interestingly, in this study, we found that perioperative PE was more likely to occur in the postoperative period, which differs from the findings of the previous study, in which the authors reported a likely intraoperative occurrence. This result emphasizes the importance of providing careful postoperative care for this groups of patients. Another study from Park et al. [8] reported a relatively low incidence of venous thromboembolism (VTE) in individuals undergoing surgery for RCC, and it is noteworthy that patients who presented with tumor thrombus demonstrated an augmented susceptibility to VTE. Consequently, diligent monitoring of such patients is advisable.

In this study, the rate of perioperative PE was significantly higher in patients who smoked. According to the findings of a systematic review and meta-analysis examining the relationship between smoking and VTE risk, smoking is indeed associated with an elevated risk of VTE. This association is attributed to several plausible mechanisms, including an increase in plasma fibrinogen levels, heightened factor VIII activity, impaired fibrinolysis that results in augmented blood viscosity, and induction of a hypercoagulable state [16]. Therefore, providers should conduct preoperative screening for smoking with perioperative care protocol vigilance for the risk of PE.

In this study, we did not find any statistically significant differences in perioperative PE rates in the comparison between the initial levels of tumor thrombus. In our study, only patients with tumor thrombus stage I and II demonstrated perioperative PE. This finding might reflect the surgical techniques used, given that patients who had a below suprahepatic IVC thrombus might experience silent thrown tumor emboli intraoperatively [17]. However, we did find an elevated incidence of perioperative PE in patients who exhibited alterations in the tumor stage from preoperative CT scans. However, unlike the study from Fukazawa et al. [6], we could not demonstrate the effect of the duration between the last CT investigation in the two groups, and this observation leads us to speculate that the tumor thrombus in patients with RCC requires careful observation to prevent perioperative PE.

Table 3
Postoperative data.

Characteristic	Perioperative PE n = 8 (1.9 %)	Control Group n = 410 (98.1 %)	*P* Value
Hospital discharge			
Alive	7 (87.5 %)	405 (98.8 %)	0.11
Length of hospital stay (days) (median, IQR)	14.0 (8.2–26.7)	6.0 (5.0–8.0)	<0.001*
Length of mechanical ventilatory support (days) (median ± IQR)	11.0 (3.5–20.5)	2.0 (1.0–2.5)	0.02*
Length of ICU stay (days) (median, IQR)	9.5 (4.0–20.7)	2.0 (1.0–3.0)	<0.001*
Organ complication			
AKI	5 (62.5 %)	194 (47.3 %)	0.48
RRT	0	12 (3 %)	1.0
Pneumonia	3 (37.5 %)	11 (2.7 %)	0.002*
ARDS	1 (12.5 %)	1 (0.2 %)	0.03*
30-day survival			
Alive	7 (87.5 %)	407 (99.3 %)	0.07

*$P < 0.05$ is considered statistically significant.

Table 4
Perioperative data and tumor level classification.

Variable	Level 0 (n = 20)	Level I (n = 12)	Level II (n = 22)	Level III (n = 2)	Level IV (n = 1)
DVT prophylaxis					
Intraoperative pneumatic stocking	12 (60 %)	1 (8.3 %)	4 (18.2 %)	0	0
Medication	0	1 (8.3 %)	6 (27.3 %)	0	0
Hospital discharge					
Alive	20 (100 %)	11 (91.7 %)	21 (95.5 %)	2 (100 %)	0
Length of hospital stay (days)					
(mean ± SD) (median, IQR)	7.3 ± 3.1	8.5 (7.2–16.2)	9 (7.0–17.2)	8.5 ± 2.1	10
Length of mechanical ventilatory support (days) (mean ± SD) (median, IQR)	1.5 ± 0.7	2.0 (1.2–2.7)	1.5 (1.0–2.75)	1.5 ± 0.7	1
Length of ICU stay (days)					
(median, IQR)	2.0 (1.0–2.0)	2.0 (2.0–6.0)	2.0 (1.0–3.5)	2.0 ± 0	1
Organ complication					
AKI	12 (60 %)	8 (66.7 %)	12 (54.5 %)	1 (50.0 %)	1 (100 %)
RRT	0	0	0	0	1 (100 %)
Pneumonia	0	2 (16.7 %)	3(13.6 %)	0	0
ARDS	0	1 (8.3 %)	1(4.5 %)	0	0
30-day survival					
Alive	20 (100 %)	11 (91.7 %)	22(100 %)	2(100 %)	0

In addition, in this study, we observed a higher frequency of perioperative PE among patients with a history of lung cancer. The data from previous studies lend support to the notion that patients with lung cancer, due to its inherent hypercoagulable characteristics, might be more predisposed to the development of PE as compared with patients with other types of malignant cancers [18]. Nevertheless, our study did not reveal statistically significant differences in the incidence of perioperative PE between patients with cancer and those without cancer.

In their 2008 guidelines for the prevention of VTE [19], the American College of Chest Physicians recommended that patients undergoing major general surgery should receive thromboprophylaxis in the form of enoxaparin or heparin. In addition, the American Society of Hematology 2021 guidelines advocate for the implementation of postoperative thromboprophylaxis and suggests continuing pharmacological thromboprophylaxis postdischarge [20].

A previous study found that intermittent pneumatic compression is less effective than pharmacologic prophylaxis but is still the method of choice in patients with a high bleeding risk [19]. These research data revealed that intraoperative pneumatic pumping was more commonly used for prophylaxis of thromboembolic events than anticoagulant medication. The presented data suggest the absence of preventive strategies associated with perioperative PE. However, to identify effective VTE prophylaxis strategies in this group of patients, a larger sample size is required.

Importantly, the intraoperative fluid data illustrate the results of the perioperative PE groups, showing that there were significantly larger amounts of intraoperative crystalloid, red blood cell transfusion, and higher estimated intraoperative blood loss. This association might reflect the intraoperative hemodynamic instability and resuscitation burden in patients with perioperative PE.

The postoperative sequelae for patients diagnosed with perioperative PE included significantly higher ICU admission, increased readmission, and longer ICU and hospital stays. In addition, we found that postoperative pulmonary complications including pneumonia and ARDS were significantly correlated with PE. However, there was no significant difference in the survival rate between the groups.

According to the guidelines and standards of the American Society of Echocardiography and American Society of Anesthesiologists (2013) and the Society of Cardiovascular Anesthesiologists (2010) [12], intraoperative TEE plays an important role in noncardiac surgery when major and adverse cardiovascular outcomes are predicted. A previous study [13] showed that rescue TEE can guide hemodynamic status and management, including the addition of fluids, inotropic drugs, and vasopressors. Intraoperative TEE also assists urologists in defining the progression of tumor thrombus intraoperatively and influences surgical decision making. The current analysis found limited use of intraoperative TEE, which may result in underdetection of intraoperative PE and nonsignificantly improve patient outcomes.

4.1. Limitations

This study has some limitations. First, PE is mostly diagnosed from clinical signs, followed by investigation; therefore, underdetection of subclinical PE might occur. Second, the retrospective and prospective observational design of this study along with the relatively small sample size might not allow for the detection of statistical significance among some variables, such as the rate of TEE use or association between the duration of CT and perioperative PE. Finally, missing data were unavoidable due to the nature of the retrospective study design.

5. Conclusions

Patients with RCC whose tumor has invaded the IVC are more prone to experience PE. Although perioperative PE was infrequent in

this study, with a 1.9 % overall prevalence, the consequences of this condition were serious. Thus, it is essential to meticulously consider early detection and appropriate management of this scenario. A preoperative protocol for smoking cessation and detection of the changing stage of tumor thrombus should be implemented.

Although intraoperative TEE application is not frequent at our institution, other studies have demonstrated that it has numerous benefits for hemodynamic management monitoring and guidance. Hence, additional TEE utilization should be considered.

CRediT authorship contribution statement

Chutima Leewatchararoongjaroen: Writing – review & editing, Writing – original draft, Formal analysis, Data curation. **Natjariya Mahavisessin:** Data curation, Writing – original draft, Formal analysis. **Kamheang Vacharaksa:** Investigation. **Siros Jitpraphai:** Investigation. **Chalairat Suk-ouichai:** Investigation, Writing – review & editing. **Araya Khamtha:** Data curation. **Aphichat Suphathamwit:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Formal analysis, Conceptualization.

Ethics approval statement

The study protocol was authorized by the Siriraj Institutional Review Board (approval number: Si 758/2020; approval date: September 15, 2020). All patients provided written informed consent. This study was registered at clinicaltrial.gov (NCT04402749).

Data availability statement

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

Funding statement

None.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The investigators acknowledge Ms. Chusana Rungjindamai, Research Technical Officer, Department of Anesthesiology, Faculty of Medicine Siriraj Hospital, Mahidol University. The authors also would like to thank Enago (www.enago.com) for the English language review.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.heliyon.2024.e39407.

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