SYSTEMATIC REVIEW

Identifying pulmonary embolism - high risk patients after total knee replacement: systematic review

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Abstract

Objective: To determine the incidence, onset, risk factors and mortality of pulmonary embolism in total knee replacement patients.

Method: The systematic review was conducted in September 2022, and comprised search on PubMed, ScienceDirect, Scopus and Crossref databases for studies published from 1977 till September 7, 2022, in the English language related to the incidence of pulmonary embolism after primary total knee replacement. Cochrane Handbook for Systematic Reviews of Interventions was used to assess risk of bias, and the Newcastle-Ottawa Scale was used to assess the quality of evidence.

Results: Of the 3,910 studies initially identified, 66(1.68%) were analysed in detail, which together had 13,258,455 total knee replacement patients. Pulmonary embolism was reported in 76,515(0.58%) cases. The onset of pulmonary embolism ranged 2-150 days post-surgery. Patients with older age, diabetes mellitus, higher body mass index, atrial fibrillation, previous venous thromboembolism, high Charlson Comorbidity Index score, hypertension, arrhythmia and chronic heart failure were at significantly higher risk ($p<0.05$). The overall mortality rate of pulmonary embolism in such cases ranged 10.53-100%.

Conclusion: Pulmonary embolism is a rare complication after orthopaedic surgery, but it has a very high mortality rate. By recognising the risk factors, attending physicians can optimise the use of chemoprophylaxis, thus preventing pulmonary embolism.

Key Words: Venous thromboembolism, Orthopaedic, Pulmonary, Arrhythmias, Cardiac, Bibliometrics, Comorbidity.

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Introduction

Total knee replacement (TKR) is one of the orthopaedic procedures that significantly and successfully improves medical condition, functional activity and productivity of the patient[1]. This procedure is one of the most common orthopaedic procedures, with an estimated 4 million adults or 4.2% people aged >50 years living with TKR in the United States[2]. The number of TKR procedures is significantly increased on an annual basis. However, TKR is not a complication-free procedure, and one of the most fatal complications is pulmonary embolism (PE). Venous stasis during surgery and immobilisation phase increases the risk of venous thromboembolism (VTE). In addition, dissected tissues and bone cause the release of pro-thrombotic molecules, like thromboplastins, that promote thrombus formation[1]. When the thrombus in any deep peripheral vein dislodges and/or is carried away to pulmonary circulation, PE occurs. Thrombus in peripheral veins could also obstruct extremity veins, termed deep venous thrombosis (DVT). Both PE and DVT are VTE cases.

PE is associated with right ventricular dysfunction, arrhythmia, haemodynamic instability and shock. The symptoms vary from asymptomatic, dyspnoea and sudden death[3]. If not diagnosed or treated immediately, PE can be fatal. Thromboprophylaxis is one of alternative ways to prevent VTE in TKR. However, the benefits of thromboprophylaxis are unclear[1]. Aggressive pharmacological prophylaxis potentially causes haemorrhagic side effects, such as cerebral or peritoneal bleeding. Pharmacological prophylaxis is also associated with prolonged recovery, wound failure, and periprosthetic infection[4]. The roles of pharmacological prophylaxis in preventing VTE, especially PE, remain controversial due to the paucity of research on its effectiveness in preventing PE compared to haemorrhagic side effects.

To the best of our knowledge, no systematic review is available in literature on the topic. The current systematic review was planned to fill the gap by analysing the prevalence, clinical characteristics and mortality of PE in TKR cases.

Materials and Methods

The systematic review was conducted in September 2022, and comprised search on PubMed, ScienceDirect, Scopus and Crossref databases for retrospective or prospective studies published from 1977 till September 7, 2022, in the English language related to PE incidence after primary TKR. The search was performed based on the recommendations of the Cochrane Handbook for **Systematic Reviews of Interventions.**[5] The review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) link: https://www.crd.york.ac.uk/prospero (CRD42022379643).

Plain text and medical subject heading (MeSH) terms were used in the search. These included "Total Knee Arthroplasty" OR "Total Knee Replacement" OR "Knee Arthroplasty" OR "Knee Replacement" AND "Pulmonary Embolism". Reference lists of the reviewed articles were also manually screened for potentially relevant articles that may have eluded the initial search. When there were multiple studies found that had been done at the same centre or used the same dataset, the study with the longer duration or larger population was included, while the rest were excluded.

Outcomes of interest included the incidence, onset, risk factors and mortality related to PE in TKR patients. All authors independently reviewed each study by title and abstract, and, if necessary, full text to determine its eligibility for inclusion in the quality evidence synthesis. The **Cochrane Handbook for Systematic Reviews of Interventions**[5] was used to assess the risk of bias, and the **Newcastle-Ottawa Scale (NOS)**[6] was used to assess the quality of the evidence.

Results

Of the 3,910 studies initially identified, 66 studies were analysed[7–72]; 56 studies (84.84%) were retrospective and 10 studies (15.15%) were prospective. The mean age of the population was 67.4 ±1.2 years. From the 55 studies that reported gender, there were 4,804,484 (65.62%) female patients and 2,517,699(34.38%) male patients. The reason for primary TKR was mostly osteoarthritis (94.4%) or rheumatoid arthritis (RA) (4.4%). Other primary TKR indications include psoriatic arthropathy, systemic lupus erythematosus, osteonecrosis, chondrocalcinosis, Paget's disease, avascular necrosis, and haemachromatosis.

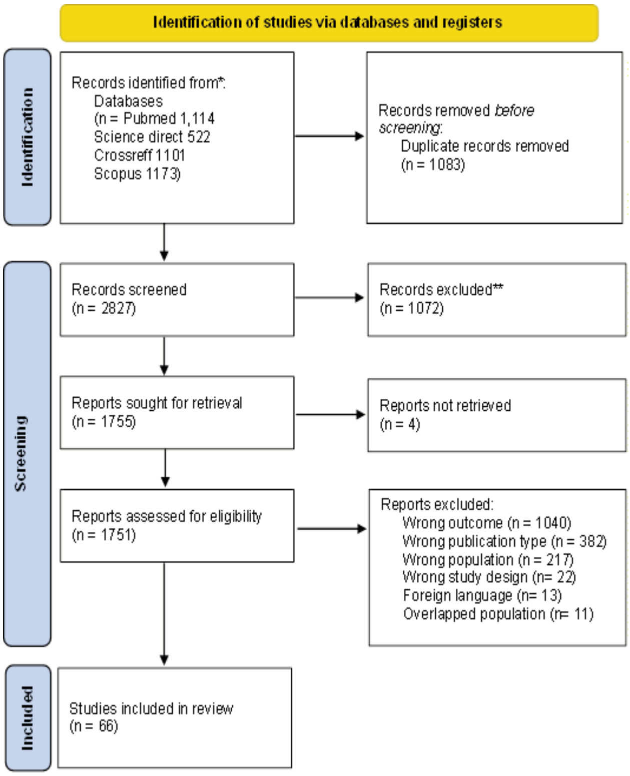

Figure: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

Overall, there were 13,258,455 TKR patients, and PE was reported in 76,515(0.58%) cases. The onset of PE ranged 2-150 days post-surgery. Patients with older age, diabetes mellitus (DM), higher body mass index (BMI), atrial fibrillation (AF), previous VTE, high Charlson Comorbidity Index (CCI) score, hypertension (HTN), arrhythmia and chronic heart failure (CHF) were at significantly higher risk ($p<0.05$). The overall mortality rate of PE in such cases ranged 10.53-100% (Tables 1-2).

Discussion

All of the studies reviewed currently discussed the incidence of PE, which was found to be 0.58% overall. Among such patients, 141 had symptomatic PE. Most frequently diagnostic modality used on asymptomatic PE were ventilation/perfusion (VQ) scanning and computed tomography pulmonary angiography (CTPA).

The diagnosis of PE can be difficult because patients may present with non-specific clinical manifestations and the typical signs and symptoms are often absent.[73] In recent decades, the diagnosis of PE with high-resolution CTPA has become the gold standard.[74] Imaging modalities, such as CTPA and VQ scan, are associated with negligible radiation doses and are also expensive. Given the low incidence of confirmed PE among the patients, systematic

Table- 1: Pulmonary embolism (PE) risk factors identified by the studies analysed.

Risk factor	Study
Diabetes mellitus	Pedersen, 2011[30] : (Adjusted RR = 1.07; 95 % CI, 0.661-1.73) Kang, 2015[40] : (p = 0.014) Raddaoui, 2019[56]: (p = 0.01 OR 5.5) Dai, 2020[58] : (OR 0.92 95% CI 0.87–0.96, p <0.0001) Hu, 2020[59] : (p <0.0001) Petersen, 2020[64] : (p = 0.001)*
BMI	Kang, 2015[40] : (p = 0.014) Fujita, 2015[42] : (p = 0.011 OR 1.089) Dai, 2020[58] : (OR 1.11, 95% CI, 1.06–1.16, P<0.0001)** Baghbani, 2022[71] Obese 1 : OR 2.73, 95% CI, 1.37–5.51 P < 0.001 Obese 2 : OR 2.77, 95% CI, 1.34–5.71 P < 0.001 Obese 3 : OR 3.62, 95% CI, 1.37–7.56 P < 0.001
Cardiovascular Disease	Pedersen, 2011[30] : (Adjusted RR = 1.33; 95% CI 1.01-1.71) Baghbani, 2022[71] : (OR 4.89, 95% CI, 2.47–9.70 P <0.001) Atrial fibrillation ● Zahir, 2013[35] : (OR = 2.60; 95% CI 2.36 - 2.87, p < 0.001) ● Lee, 2016[44,59] : (OR 4.7 95% CI 3.3-6.6, p<0.001) ● Hu, 2020[59] : (p=0.004) Arrhythmia ● Lee, 2016[44] : (OR 2.1, 95% CI 1.5-3.0, p<0.001) ● Dai, 2020[58] : (OR 2.44 95% CI, 2.34–2.55 P<0.0001) Heart Failure ● Lee, 2016[44] : (OR 2.8, 95% CI, 2.1-3.8, p<0.001) ● Dai, 2020[58] : (OR 1.67 95% CI 1.54–1.80 P<0.0001) Hypertension ● Dai, 2020[58] : Hypertension (OR 1.04 95% CI, 1.00–1.08 P < 0.0001) ● Hu, 2020[59] : Hypertension (P<0.001) Peripheral Vascular Disorder Dai, 2020[58] : (OR 1.41, 95% CI, 1.27–1.57, P<0.0001) Coronary heart disease ● Hu,2020[59] : (p< 0.0001) Valvular Disease ● Dai, 2020[58] :(OR 1.45, 95% CI, 1.34–1.57, p< 0.0001)
History of VTE	Warwick, 199[78] : (RR = 1.59, 95% CI, 1.07 - 2.35, p = 0.02) Pedersen, 2011[30] : (Adjusted RR = 5.30; 95% CI, 3.99-7.05) Lee, 2016[44] : (OR 9.7 95% CI 6.9-13.5 p<0.001)
Age	Fong SooHoo, 2006[16]: (p < 0.05) Fujita, 2015[42] : (p = 0.043 OR 1.036) Dai, 2020[58] : (OR 1.44, 95% CI, 1.31–1.59 p < 0.0001) Hu, 2020[59] : (p<0.0001) Brown, 2020[66] : (p= 0.0006)
High CCI	Fong SooHoo, 2006: (p < 0.05) Pedersen, 2011[30] : (Adjusted RR = 1.73; 95% CI, 1.24 to 2.41) Zahir, 2013[35] : (OR = 2.60; 95% CI , 1.04 - 1.19, p= 0.002) Hu, 2020[59] : (p< 0.0001)

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Pulmonary Disease	Dai, 2020[58] : (OR 1.19 95% CI,1.14–1.25, P<0.0001) Baghbani, 2022[71] : (OR 7.51, 95% CI, 2.46–2.29 <0.001) Pulmonary circulation disorders ● Dai, 2020[58] : (OR 91.21, 95% CI, 87.29–95.32, P<0.0001)
Type Of Surgery TKR	Fujita, 2021[42] : (p=0.027 OR 2.151 95% CI 1.091–4.240) Bilateral TKR Ko, 2021[67] : (HR 1.632; P<.0001) Alameri, 2020[61] : (p = 0.266) Yeager, 2014[38] : (P< 0.004) Shin, 2019[55] : (Adjusted OR: 0.43–0.74)

Table-2: Mortality rate of pulmonary embolism (PE) patients.

Author	Mortality	No. of PE Patients	%
Kaushal, 1976[7]	0	3	0.0
Warwick, 1997[8]	2	19	10.5
Mantilla, 2002[10]	10	30	33.3
Pookarnjanamorakot, 2004[12]	0	8	0.0
O'Reilly, 2005[13]	3	78	3.8
Mahomed, 2005[14]	0	1000	0.0
Sliva, 200515	0	1	0.0
Fong SooHoo, 2006[16]	0	913	0.0
Hutchinson, 2006[17]	0	30	0.0
Bjørnarå, 2006[18]	0	4	0.0
Chotanaphuti, 2007[19]	0	1	0.0
Seah, 2007[20]	1	3	33.3
Prejbeanu, 2007[21]	2	2	100.0
Samama, 2007[22]	2	2	100.0
Kim, 20072[3]	0	0	0.0
Xu, 2008[24]	0	233	0.0
Pulido, 2008[25]	0	94	0.0
Khatod, 2008[26]	0	73	0.0
Ryu, 2010[27]	0	12	0.0
Baser, 2010[28]	0	732	0.0
Dimitris, 2011[33]	0	5	0.0
Gandhi, 2012[34]	0	11	0.0
Zahir, 2013[35]	3296	13317	24.8
Kang, 2015[40]	0	7	0.0
Fujita, 2015[42]	0	19	0.0
Park, 2016[43]	0	16	0.0
Tay, 2016[46]	1	1	100.0
Senay, 2018[50]	0	3	0.0
Karayiannis, 2018[51]	0	66	0.0
Hu, 2020[59]	0	58	0.0
Alameri, 2020[61]	0	1	0.0
Johnson, 2020[62]	0	1273	0.0
Petersen, 2020[64]	0	5	0.0
Millar, 2020[65]	0	18	0.0
Brown, 2020[66]	0	5420	0.0
Total	3317	23458	14.1

imaging is not cost-effective and is possibly dangerous.[75]

Clinical assessment to determine patients with suspected PE could be done using the 8-item Pulmonary Embolism Rule-out Criteria (PERC): age <50 years, pulse <100bpm, arterial oxygen saturation (SaO2) >94%, no unilateral leg swelling, no haemoptysis, no recent trauma or surgery, no history of VTE or PE, and no exogenous estrogen use.[76] Kline et Al. explained that the prevalence of PE patients with negative PERC was only 1.4%. (5/362, 95% confidence interval [CI]: 0.4-3.2) which means that the patient does not need a confirmatory diagnosis.[77] The safety of PERC-based therapy is not yet clear, but cohort studies in Europe have reported that there was an increased incidence of thromboembolism in patients with a negative PERC in the first 3 months of follow-up.[78]

There are two scores for diagnosing PE; the Wells scoring method, and the Geneva scoring method. Both scores have proven their validity through meta-analysis research. However, these two scores should not be used in all patients with chest complaints, but only in patients with suspected PE who have had a clinical examination.[79]

In the current review, there were 12 articles that discussed the onset of PE. Park et al.[43] explained that symptomatic PE had the average onset 4±2.9 days (range: 1-10 days) after the surgery. Senay et al.[50] reported 3.1 days (range: 2-7 days), while Samama et al.[22] reported 2-3 days. Warwick et al. reported that symptomatic PE had median onset 6 days post-surgery.[8] On the other hand, asymptomatic PE overall had a more variable onset, ranging 2-150 days.

The risk of PE is high for at least 12 weeks post-surgery. However, the most significant increase in PE risk occurred in the first to the sixth postoperative week.[80] Another study reported that in patients with negative CTPA, 1.7% incidence of VTE was noted at 3-month follow-up.[81] Bjørnarå et al. reported that there was a rapid rise of PE incidence after surgery which stabilised in 1 month.[18] Another study showed that thromboembolism risk increased in the first 20 days before getting stabilised.[22]

The most commonly found risk factor for PE was DM (Table 1).[30,40,56,58,59,64] Petersen et al. reported VTE as being most frequently found in both insulin-dependent and non-insulin-dependent DM (p=0.001).[64] During physiological state, the process of coagulation and haemostasis are counterbalanced by fibrinolytic mechanisms which avoid the thrombus migration and vascular obstruction. However, this balance is disturbed in DM patients, leaning towards the pro-thrombotic state. The pro-thrombotic state in DM consists of platelet hypersensitivity, coagulation factor disorders and hypo-fibrinolysis.[82]

Platelet hypersensitivity in DM is described as the increase in both platelet number and enhanced aggregation capacity which contribute to the pro-thrombotic state. Patients with chronic hyperglycaemia (glycated haemoglobin [HbA1c] >8%) have higher platelet count compared to euglycaemia individuals[82]. Increased aggregation sensitivity of platelets is probably underlined by upregulated expression of pro-aggregatory factors, such a P-selectin, thromboxane A2, and von Willebrand factor (vWF) antigen.[83] Additionally, hyperglycaemia also impairs anti-aggregatory effects by interfering with signalling pathways of nitric oxide (NO), prostaglandin I2 (PGI2) and insulin. In patients with insulin resistance (IR) (type 2 diabetes mellitus [T2DM]), insulin fails to increase cyclic adenosine monophosphate (cAMP) levels within the platelets, thus impairing the anti-aggregation activity. The pathophysiology of type 1 diabetes mellitus (T1DM) involves insulin deficiency, not resistance. Thus, it may indicate that these impaired anti-aggregation effects are only found in T2DM, but not in T1DM patients.

DM patients have increased number and function of coagulation factors. Extrinsic coagulation factor (tissue factor [TF]) or factor VIIa transcription is enhanced in hyperglycaemia and hyperinsulinaemia.[84] Moreover, DM patients tend to be in a chronic inflammatory state, which further enhances TF expression in endothelial and vascular smooth muscle cells, and contributes to a pro-thrombotic state.[85] Intrinsic coagulation factors FXII, FXI, FIX also incur a dysfunction in hyperglycaemia and hyperinsulinaemia patients.[86,87] Overall, excessive thrombus formation could be prevented by the fibrinolysis mechanism, but DM patients are in a hypo-fibrinolysis state. Tissue plasminogen activator (tPA) is supposed to activate plasminogen to become plasmin, which then initiates fibrinolysis. The tPA is negatively correlated with HbA1c, which means patients with increased blood glucose level have reduced activated plasmin.[88] Additionally, plasminogen activator inhibitor-1 (PAI-1) and thrombin-activator fibrinolysis inhibitor (TAFI) as anti-fibrinolytic factors are elevated in DM patients.[89] Kang et al. explained that DM was significantly related to thrombus formation and prolonged ambulatory status in patients.[40] T1DM is identified as a strong risk factor for shock, stroke, right ventricular dysfunction, cardiopulmonary resuscitation, and in-hospital death, independently after adjusting for age, gender and comorbidities.[90,91] This suggests that overall, DM patients with PE carry a worse prognosis. Additionally, DM patients demonstrated earlier symptomatic PE onset compared to patients without DM.[59] Also, DM is known as a major risk factor for failure in orthopaedic surgery.[92]

Obesity and overweight BMI categories become the predisposing factor of PE (Table 1).[40,42,58,71] Baghbani et al. stated that patients with obesity classes I, II and III are significantly related with PE incidence.[71] There are various mechanisms that mediate the role of BMI as the risk factor of PE. Factor II (FII) G20210A is known to be the genetic factor associated with increased risk of VTE, including PE. A study found that the odds ratio (OR) for VTE patients with obesity and FII G20210A mutation was 12.03 compared to matched controls, while the OR for VTE patients with BMI <25kg/m2 and FII G20210A mutation was only 1.67 compared to the matched controls[93]. This suggests that FII G20210A mutation interacts with obesity in increasing the risk factor of VTE. On the other hand, excessive visceral adipose tissue in obese patients causes hypoxia and enhances the migration of inflammatory adipocytokines and free fatty acids (FFAs) to the liver.[94,95] FFAs could induce reactive oxygen species (ROS) production. FFA alone or with inflammatory adipocytokines has the ability to activate endothelial cells and trigger systemic inflammation which leads to pro-thrombotic state.[96,97] It is postulated that the increase of circulating FFAs and over-activation of the renin-angiotensin system in obesity that cause insulin resistance, lead to hypercoagulable state in the same mechanism as hyperglycaemia.[98] This will result in increased platelet activation, increased plasma level of fibrinogen, factors VII and VIII and vWF, and higher level of pro-coagulant microparticles[99]. Additionally, patients with obesity tend to have other comorbidities, such as DM and cardiovascular diseases, which further increases the PE risk in obese patients.

Heart diseases that are often related to PE incidence are arrhythmia, especially AF and CHF.[35,44,58,59,71] Dilatation and strain in the ventricular chamber contribute to thrombus formation.[100] AF can cause thrombus formation in the right atrial chamber, then migrate to the pulmonary vasculature, leading to PE. Interestingly, AF incidence is 40% higher in RA patients compared to the general population.[101] RA was the second most common indication for TKR in the current review. Moreover, the presence of AF in PE patients is related with prognosis, as the AF history or presentation at admission was associated with higher mortality risk.[102]

The incidence of PE is increased in heart failure (HF), attributed to haemostasis abnormality, platelet and endothelial dysfunction.[103] Endothelial dysfunction in HF consists of reduced bioavailable NO which impairs vasodilation, plaque rupture which exposes tissue factor and leads to thrombin generation, elevated levels of inflammatory cytokines tumour necrosis factor-alpha and interleukin-2, decreased antithrombotic factors NO and thrombomodulin, and increased vWF.[104] HF in low flow state also imposes higher risk to thrombus formation due to blood stasis. This is contributed by impaired contractility, dilated chambers and abnormalities in regional wall motion. Lastly, platelet hyper-activation supports the hyper-coagulable state in HF patients. On the other hand, PE also can induce HF through sudden increase pulmonary pressures that trigger right ventricular dysfunction (acute cor pulmonale). However, this phenomenon can only happen when more than half of the pulmonary vasculature is obstructed, thus the pressure is significant enough to cause strain and dysfunction in the right ventricle.[105] Other cardiovascular comorbidities showing significantly higher PE incidence included HTN,[58,59] peripheral vascular disorder[58], coronary heart disease[59] and valvular disease[58].

Surgical technique is found to be related to PE. Zahir et al. and Yeager et al. described that patient with bilateral TKR had a higher risk of PE compared to unilateral TKR.[35,38] Goel et al. stated that the risk of VTEI was doubled in bilateral compared to unilateral TKR.[106] It may be related to higher mean BMI in patients with bilateral TKR[61]. However, Yeager et al. categorised patients with several comorbidities, such as age >75 years and American Society of Anaesthesiologists (ASA) class III, ischaemic heart disease, poor ventricular function, oxygen-dependent pulmonary disease, insulin-dependent DM, renal insufficiency, steroid-dependent asthma, pulmonary HTN, morbid obesity (>250lb), chronic liver disease and cerebral vascular disease, as ineligible for bilateral TKR[38]. It implies that increased incidence of PE is not related with comorbidities in patients with bilateral TKR. Additionally, Fujita, et al. demonstrated that patients with TKR faced greater risk of PE compared to total hip replacement (THR) cases[42].

The CCI predicts 10-year mortality of a patient from a wide range of comorbidities. It is classified as low (score 0) for patients who previously do not have any recorded disease, medium (score 1-2), and high (score ≥3). It was found that PE incidence is significantly higher in patients with high CCI.[16,30,35,59] CCI score also showed significant association with rates of mortality and readmission due to infection.[16]

Patients with chronic pulmonary disease had increased risk of developing PE58,[71]. Diseases such as chronic obstructive pulmonary disease (COPD) and interstitial lung disease (ILD) increase the likelihood of PE probably due to these mechanisms. COPD and ILD patients possess thrombogenic ability within its pulmonary circulation, and changes in the vascular bed may impair resolution of PE.[43]

Dai et al. explained that other conditions could also increase PE incidence, such as deficiency anaemia, chronic blood loss anaemia, alcohol abuse, RA, coagulopathy, lymphoma, fluid and electrolyte disorder, neurological disorder, paralysis, peripheral vascular disorder, pulmonary circulation disorder, renal failure, solid tumour without metastasis, peptic ulcer, valvular disease and coronary heart disease[21]. A history of VTE also is one of the PE risk factors.[1,30,44]

In the current review, 36 studies stated PE mortality, and 8 among them reported deaths caused by PE (Table 2). Total mortality in PE patients was 3,317 (4.33%), with the mortality rate ranging from 10.53% to 100%. Trend in PE mortality rates seems to be increasing.[107] The underlying cause behind this remains unclear, but it is hypothesised that it is related to raised awareness and computed tomography (CT) scans.[108] The growing prevalence of obesity and cardiovascular diseases is also a cause in this regard.[109]

Conclusion

PE is a rare complication of major surgeries. However, the mortality rate in PE is considerably high. Several risk factors have been identified that may help surgeons determine patients' eligibility for receiving intensive prophylaxis preceding any major surgery or invasive intervention. Further studies are required to explore each risk factor and its direct relationship with PE incidence.

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