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Misdiagnosis of pulmonary embolism and missed pulmonary embolism: A systematic review of the literature

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Abstract

Pulmonary embolism (PE) is a common and life-threatening condition. Misdiagnosis of PE is not uncommon as symptoms can overlap with other diagnoses and could cause potential harm. We conducted a systematic review to estimate rates of misdiagnosis and factors may be associated with misdiagnosis of PE. We searched MEDLINE and EMBASE for studies that evaluated the misdiagnosis of PE. The rate of misdiagnosis was pooled and results were narratively synthesized. A total of 18 studies were included which included 2,053 patients with a diagnosis of PE. Two different definitions were used for misdiagnosis of PE. The first refers to an initial diagnosis that is not PE and the patient is found to have PE. The second definition refers to patients who do not have a diagnosis of PE while they were alive and PE was subsequently found on autopsy. The pooled results across the studies suggest that in ED settings 27.5% of patients with PE are misdiagnosed initially and half of all patients in inpatient settings are misdiagnosed (53.6%). Among patients that die in intensive care who undergo autopsy 37.9% were found to have PE that was missed. The commonly diagnosed conditions instead of PE were respiratory infection, heart failure and acute coronary syndrome (ACS). Misdiagnosis in patients with an eventual diagnosis of PE is common. Clinicians should consider PE as differential diagnosis in patients who are initially suspected to have chest infection, heart failure or ACS who have negative diagnostic tests or poor response to treatment.

Keywords: pulmonary embolism; diagnosis; misdiagnosis

Introduction

Misdiagnosis can occur in everyday clinical practice and when an incorrect diagnosis is made, patients may receive suboptimal care.[1] Misdiagnosis has been reported for conditions such as acute myocardial infarction,[1] heart failure[2] and aortic dissection.[3] In the context of PE, a systematic review of harmful diagnostic errors in hospitalized adults suggests that PE is the second most frequently delayed or missed diagnoses.[4] Several studies have been conducted that evaluate misdiagnosis of PE in the emergency department settings[5,6] and inpatient settings[7-9] but there is no consistent definition for misdiagnosis of PE. In addition, there are studies which consider missed diagnosis of PE that were found on autopsy among patients that die after admissions to intensive care units and reported rates vary between 15.6-84.9%.[10-12]

The only review on this topic took place more than 10 years ago and only included studies that took place in China and were published in Chinese-language journals.[13] In view of the importance of understanding misdiagnosis of PE and missed PE, we conducted a systematic review of the literature to understand how misdiagnosis is defined, how common it occurs, what factors are associated with misdiagnosis and what conditions are diagnosed when patients actually had PE.

Methods

This review was reported in accordance to the recommendations of the MOOSE checklist.[14]

Study inclusion criteria

We selected studies that evaluated the misdiagnosis of PE and missed diagnosis of PE. Those included had to report one or more of the following: i) the number of misdiagnoses of PE cases within a group of patients with a diagnosis of PE, ii) the number of missed PE diagnosis within a population, iii) factors that are associated with misdiagnosis of PE or iv)

the diagnoses of conditions that were incorrect when a patient had a diagnosis of PE. There was no restriction on the definition of misdiagnosis of PE, and in fact it was one of the aims to determine how it was defined in the literature. We aimed to look for studies where PE was subsequently picked up in patients who were initially admitted and treated for another conditions. Outcomes included the rates of misdiagnosis and factors associated with the misdiagnosis. There was no restriction based on study design, or language of the report but original data had to be presented and we excluded individual case reports.

Search strategy

We searched MEDLINE and EMBASE using OVID with no date or language restriction in 5 January 2022. The exact search terms were: (missed pulmonary embolism) OR (missed pulmonary embolus) OR (missed diagnos* adj3 pulmonary embolism) OR (missed diagnos* adj3 pulmonary embolus) OR (unrecogni* adj1 pulmonary embolism) OR (unrecogni* adj1 pulmonary embolus) OR (misdiagnosis and pulmonary embolism) OR (misdiagnosis and pulmonary embolus) OR (missed diagnosis and pulmonary embolism) OR (missed diagnosis and pulmonary embolus). The search terms used in the current study are based open the terms used for a previous systematic review on the topic of misdiagnosis of acute myocardial infarction.[1] We reviewed the bibliography of relevant studies and reviews for additional studies that met the inclusion criteria.

Study selection and data extraction

Two reviewers (CSK and SL) screened all titles and abstracts retrieved from the search for studies that met the inclusion criteria. The studies that potentially met the inclusion criteria were reviewed and the final decision to include or exclude studies was made by consensus. The data extraction was carried out by CWW and SL and independently checked by CSK. Data collected were study design, country of study origin, year, sample size, mean

age, % male, inclusion criteria, definition of missed PE, rate of missed PE, patient outcomes, initial diagnosis of misdiagnosis and factors associated with misdiagnosis.

Risk of bias assessment

Methodological quality assessment of the included studies was conducted with consideration of the following based on our pervious study: i) study design, ii) reliability of ascertainment of PE, iii) loss to follow up or missing data, iv) generalizability to a general PE cohort. For the definition of PE, studies were considered high quality if they evaluated the participants using imaging of the aorta to confirm the diagnosis of all patients. This was carried out by two reviewers (CWW and SL), and checked independently by another reviewer (CSK).

Data analysis

Data was extracted into pre-designed and piloted tables. Considerable heterogeneity in the study methodology meant that we could not perform meta-analysis and thus the study findings were narratively synthesized. In order to pool the rates across studies, the total number of patients with misdiagnoses of PE were added together across individual studies and this was divided by the total number of patients across the individual studies to determine a percent misdiagnosis across studies.

Description of included studies

A total of 18 studies were included.[5-12,15-24] The process of study selection is shown in Supplementary Figure 1. All studies were retrospective in design aside from a prospective study of patients who died in intensive care who underwent autopsy for cause of death.[18] These studies took place in Spain, Italy, Belgium, France, Turkey, China, Korea and the United States. There were a total of 1533 patients with a diagnosis of PE and the number of patients ranged from 13 to 375. Five studies did not report the mean age and proportion of

male patients among the patients who had PE. Three studies evaluated patients who died in intensive care for missed PE from autopsy evaluation.[10-12]

Quality assessment in included studies

Supplementary Table 1 shows the quality assessment of the included studies. The diagnosis of PE was classified as reliable in most studies aside from the study by Liang et al where clinical assessment was part of the basis for PE diagnosis[9] and the study by Patel et al which was publish in 1994 which used echocardiography to identify thromboemboli in the main pulmonary artery.[21] There was no consistent definition for misdiagnosis of PE and most of the studies did not report missing data. The study populations were generalizable to hospitalized adults in 10 studies and 3 studies took place in intensive care settings,[10-12] 4 studies took place more than 20 years ago[22-24] and one study only included submassive PE.[7]

Rate of misdiagnosis on missed pulmonary embolism

Table 2 shows the variable definitions of misdiagnosis of PE and missed PE together with the rate of misdiagnosis of PE in emergency department and inpatient settings and missed PE among patients that die in intensive care. Two different definitions were used for misdiagnosis of PE. The first refers to an initial diagnosis that is not PE and the patient is found to have PE. The second definition refers to patients who do not have a diagnosis of PE while they were alive and PE was subsequently found on autopsy. For patients, the study by Ray et al, suggests that a final diagnosis of PE was associated with an adjusted odds of 9.27 95%CI 4.72-18.22, $p<0.001$ for misdiagnosis.[6] In inpatient settings, missed PE on abdominal CT was observed in 81.8% of patients who later had PE on chest CT scan.[18] The pooled results across the studies suggest that in ED settings 27.5% of patients with PE are misdiagnosed initially and half of all patients in inpatient settings are misdiagnosed (53.6%)

(Figure 1). Among patients that die in intensive care who undergo autopsy 37.9% were found to have PE that was missed.

Misdiagnosed conditions instead of pulmonary embolism

Table 3 shows the conditions which were incorrectly diagnosed when the underlying problem was PE. The most common diagnoses were pneumonia, bronchitis, exacerbation of chronic obstructive pulmonary disease (COPD), heart failure and acute coronary syndrome. Out of all the misdiagnosed conditions the proportion with a wrong diagnosis of pneumonia, bronchitis or exacerbation of COPD represented 37.4% while those wrongly diagnosed with heart failure and coronary artery disease or acute coronary syndrome were 18.2% and 12.4%, respectively.

Other pertinent findings related to delay and misdiagnosis of pulmonary embolism

There was delay from symptom onset to diagnosis of 2.5 days for patients with correct initial diagnosis compared to 10 days for patients with incorrect initial diagnosis.[6] The delay can also be significant as 50% have delay longer than 6 days while 10% have delays more than 21 days. Initial wrong diagnosis was associated with higher age, more days of delay up to diagnosis of pulmonary embolism and lower Wells score.[6] Ilvan et al reported a difference time to diagnosis of 20 days compared to 8 days for patients with misdiagnosis and correct diagnosis, respectively.[5] In their cohort of 100 patients, 17 patients received thrombolysis and 4 were misdiagnosed with PE. Kayhan et al found that the mean time in patient delays occurred by late presentation of the patients which was 7 days while diagnostic delay caused by initial misdiagnosis of the health care provider was 0.5 days.[8] There was increased odds of delay for current smokers and reduced odds of delay if embolism was detected on CT pulmonary angiogram. Lim et al reported that the average delay to treatment

for patients with missed PE was 5 days.[18] Liu et al evaluated a group of patients initially suspected to have acute coronary syndrome which was later found to be PE and found that one patient out of 22 died from respiratory failure.[20] Ray et al found that the diagnostic accuracy for emergency physicians for PE was 78% and over one in five patients (22.2%) had inappropriate initial treatment.[6]

Discussion

This review has several key findings. First, misdiagnosis of PE is frequent and dependent on the setting where the evaluation take place affecting over one in four patients with PE in emergency departments and half of all patients in inpatient settings. Among patients that die in intensive care who undergo autopsy more than a third have PE that was missed. Second, the major conditions which were incorrectly diagnosed in patients with PE were chest infection (pneumonia, bronchitis, exacerbation of COPD), heart failure and acute coronary syndrome and these accounted for 37.4%, 18.2% and 12.4%, respectively. Third, the delay to diagnosis varied from 5 to 14 days for patients with correct compared to incorrect initial diagnosis and another study suggests that 10% of patients have more than 21 days delay to diagnosis. Fourth, one study suggests that smokers are at three-fold increase in odds of misdiagnosis of PE compared to patients who are non-smokers. Finally, the implications of misdiagnosis can be significant as one study suggests that over one in five patients had inappropriate initial treatment.

Our results suggest that the misdiagnosis of PE is common but how it impacts patient care requires more studies. The heterogeneous presentation and prognosis of patients with PE presents a problem in terms of urgency of treatment as patients may be relatively well with few symptoms while other patients may be hemodynamically unstable requiring emergency life-saving therapy. It is possible that those who are clinically stable and are misdiagnosed

initially, may deteriorate to the extent that reassessment will lead to an eventual diagnosis of PE. The case may be different for patients who are unstable such as those in cardiorespiratory failure or cardiogenic shock where identification of PE and emergency treatment may advert cardiac arrest or multiorgan failure. Therefore, it may be worth considering whether the misdiagnosis of PE resulted in any adverse outcome to patients because if there was no difference in outcome it may be less important. This raises the issues of missed opportunities which refer to incidents where different actions by those involved could result in more desirable outcomes.[25] If earlier identification of PE and treatment could have improved patient outcomes then this would have been a missed opportunity otherwise the misdiagnosis less clinically significant. It is evident that the clinical implications can be significant as the studies of patients that die in intensive care demonstrate that failure identify the major cause of death occurs. Real-world practices are complex as patients may be triaged to care in settings with different levels of monitoring. Even if PE was not diagnosed but patient was deemed to be low-risk they could be transferred to a setting which has less frequent monitoring and clinical deterioration due to PE may occur without prompt identification.

Another important consideration is what can be done to reduce misdiagnosis of PE. The use of D-dimer is not sufficient specific so it does not prove to be a very helpful test because a raised D-dimer can be due to many conditions. Also, it can take some time for clinicians to arrange a CT pulmonary angiogram or ventilation perfusion scans. The role of echocardiography may be useful in identifying patients who may have underlying pulmonary embolism and this investigation has been shown to impact mortality.[26] In addition to considering possible testing, the concept of misdiagnosis calls upon review of clinical practices. Often the demands on the health service is such that they lack the resources to regularly review the care they deliver. Furthermore, there may be no interest by healthcare professionals and services to identify misdiagnosis as it only potentially raises problems

related to care. It is underreported in the literature because it raises concerns about the competency of clinicians and this can affect the trust between doctors and patients. In cases where patients come to harm because of misdiagnosis there can even be medicolegal action or even formal investigations. Ideally, there should be mechanisms and efforts to consider misdiagnosis in clinical practice which can take place in the form of health service evaluations (e.g. significant event review, morbidity and mortality meetings) and clinical audits. Identification of the problem is key as once it is identified then the rationale for clinical decision making can be reviewed and it can be determined if any intervention is needed such as education of clinicians, pathway development or knowledge exchange could improve outcomes for future patients.

An important consideration regarding misdiagnosis of PE is that there is actually no agreed definition. As identified in the current review, the rate of misdiagnosis depends on the setting where it takes place which could be in the emergency department or inpatients care but also in primary or community care which is not reported in the literature. There may be different levels of expectations for diagnostic accuracy depending on the setting as there is variation in experience of managing PE and availability of testing. PE is not an uncommon diagnosis in patients in the emergency department and hospital settings so it should be expected that most patients with symptoms that could fit with the diagnosis should have testing with D-dimer with or without CT pulmonary angiography. The suspicion of PE based on clinical assessment among primary care clinicians may be different from those who see patients who review patients in hospital. As highlighted in the current study, there can be some overlap of clinical features of PE with other conditions such as chest infection, acute coronary syndrome and heart failure which can results in delays to diagnosis and initial misdiagnosis. There may also be some patients that present atypically or with those with more than one diagnosis. Nevertheless, because PE is treatable and potentially life

threatening it is important that clinicians that assess patients early in their care journey consider this diagnosis.

From a healthcare service perspective, misdiagnosis is undesirable as it wastes resources including tests, treatments and prolonged hospital stay which are unnecessary and patients may come to harm from deterioration from incorrect treatment or side effects from therapies that are not needed. Furthermore, from a patient perspective it is a marker of poor quality care. Misdiagnosis is a potential real-world element in the sequence of events in a patient pathway that is unwanted.[27] However, there is an implied expectation that clinicians make the correct diagnosis and sometimes the reality is that patient present atypically so that clinicians do not get the diagnosis correct at first evaluation. This raises the issue of whether there is a problem with patient care when misdiagnosis occurs and what is reasonable delay to diagnosis. In some ways, it depends on the skill of the physicians together with the hospital setting and available resources including protocols to manage patients with certain symptoms such as chest pain. Should clinicians who first review patients make a diagnosis which could potential be wrong or suggest a few potential diagnoses and conditions to exclude? There are advantages in making a firm suspected diagnosis as it may make the referral processes much easier for specialty clinicians to review and potentially take over the care of the patient. However, the disadvantage is that if the clinicians gets the diagnosis wrong then there may be delay and a missed opportunity for earlier diagnosis and treatment.

Future work needs to be conducted to better define and understand misdiagnosis of PE. In the current review, we identified two different broad definitions that were commonly used for misdiagnosis of PE. The first definition refers to an initial diagnosis that is not PE and the patient is found to have PE. The second definition refers to patients who do not have a diagnosis of PE while they were alive and PE was subsequently found on autopsy after the patient was deceased. The challenge related to an initial diagnosis that may be subsequently

revised is the fact that the patient may be reviewed by different professionals who have different experience and access to investigations. For example, a family doctor or general practitioner will have less experience of evaluating patients with PE compared to an emergency department doctor. Therefore, it is important in the definition for future studies to define where the study took place where it was in the context of a patient in the community or in hospital.

This review has some limitations. First, few studies evaluate outcomes for patients that are misdiagnosed compared to those that are correctly diagnosed. Second, the studies are observational, small in sample size (up to 425 patients) and retrospective in design which makes them potentially prone to confounding and biases (particularly selection biases in retrospective studies). Third, there are limited studies from primary care settings and several studies are out-of-date with contemporary practice. Fourth, there are limited studies which evaluate patient factors which may be associated with PE and studies which attempt to explain why the misdiagnosis occurred.

In conclusion, misdiagnosis of PE is common affecting between one in two to five patients depending on the setting. In particular, patients who are diagnosed with pneumonia, bronchitis, exacerbation of COPD, heart failure or acute coronary syndrome who have negative diagnostic tests or do not respond to treatments should be evaluated for the alternative diagnosis of PE. Misdiagnosis of PE has significant impact as it can prolong hospital stay and subject patients to unnecessary treatments and deterioration due to delay to appropriate treatment.

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List of Tales and Figures

Declaration of interests

☒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.

Table 1: Study design and patient characteristics

Study ID	Study design; Country; Year	No. of patients with PE	Mean age	% male	Patient inclusion criteria
Alonso-Martinez 2010	Retrospective cohort study; Spain; 1998 to 2009.	375	Median 75	50.4	Participants were admitted due to acute PE.
Bedell 1986	Retrospective cohort study; United States; 1981 to 1983.	18	-	-	Participants had a diagnosis of PE on autopsy.
Berlot 2011	Retrospective cohort study; Italy; 1996 to 2007.	86	70.4	60.8	Autopsies were performed for patients who died in the intensive care unit.
Cai 2009	Retrospective cohort study; China; 1999 to 2008.	8	-	-	Participants had died at hospitals in China.
Gurzu 2014	Retrospective cohort study; Romania; 2004 to 2013.	46	-	-	Autopsies were performed for patients who died as a result of cardiovascular diseases at the University of Medicine and Pharmacy of Tirgu-Mures.
Ilvan 2015	Retrospective cohort study; Turkey; 2007 to 2012.	100	58.3	54.0	Participants were admitted with a diagnosis of PE.
Kayhan 2012	Retrospective cohort study; Turkey; 2009 to 2010.	189	58.0	44.7	Participants were admitted with PE at the department of chest disease of Ondokuz Mayis University Hospital.
Liang 2001	Retrospective cohort study; China; 1985 to 1999.	149	49	66.4	Participants had a diagnosis of PE at Beijing Anzhen hospital.
Liang 2009	Retrospective cohort study; China; 2001 to 2008.	63	51.3	58.7	Participants had a diagnosis of PE at Beijing Anzhen hospital.
Lim 2014	Retrospective cohort study; Korea; 2011 to 2012.	329	-	-	Participants had a diagnosis of PE.
Liu 2004	Retrospective cohort study; China; 2000 to 2003.	76	-	-	Participants had a misdiagnosis of PE at the Emergency Department of Anshen Hospital.

Liu 2012	Retrospective cohort study; China; 2001 to 2010.	22	Median 51	59.1	Participants were patients who were initially suspected of having acute coronary syndrome and finally confirmed of having PE.
Patel 1994	Retrospective case series; United States; Published in 1994.	14	61	42.9	Participants had PE not clinically suspected at the time of admission and was diagnosed later by transthoracic echocardiography.
Ray 2006	Prospective cohort study; France; 2001 to 2002.	93	-	-	Participants were aged 65 and above with acute dyspnea admitted to the emergency department of Centre Hospitalo-Universitaira Pitie-Salpetriere.
Rusu 2020	Retrospective cohort study; Belgium; 2016 to 2018.	13	-	-	Participants had died in the intensive care unit of Erasme University Hospital.
Tejerina 2011	Prospective cohort study; Spain; 1982 to 2008.	24	-	-	Participants had died in the intensive care unit of the Hospital Universitario de Getafe.
Sun 1996	Retrospective cohort study; China; 1951 to 1994.	23	-	78.3	Participants had PE identified during autopsy at the Beijing Hospital.
Walden 1985	Retrospective cohort study; Israel; Published in 1985.	425	-	-	Participants had a post mortem examination and pulmonary emboli were found.

PE=pulmonary embolism

Table 2: Definition of misdiagnosis and rate in different settings

Study ID	Definition of misdiagnosis	Setting	Misdiagnosis rate
Emergency care settings			
Ilvan 2015	Misdiagnosed group were had diagnosis other than pulmonary thromboembolism at outpatient center or in hospital.	ED	26/100 (26.0%)
Liu 2004	Incorrect initial diagnosis.	ED	15/76 (19.7%)
Ray 2006	Inaccurate emergency physician diagnosis was recorded if any diagnosis of PE was missed. The ED diagnosis was recorded before investigations.	ED	33/93 (35.4%) Adjusted odds of misdiagnosis: final diagnosis of PE: OR 9.27 95%CI 4.72-18.22, p<0.001
Inpatient settings			
Alonso-Martinez 2010	Wrong initial diagnosis.	Inpatient	187/375 (50.0%)
Cai 2009	PE identified at the autopsy but not diagnosed clinically.	Inpatient	8/8 (100%)
Bedell 1986	PE discovered at the autopsy but the diagnosis was missed.	Inpatient cardiac arrest	8/16 (50.0%)
Gurzu 2014	PE misdiagnosis defined by discordance between clinical diagnosis and autopsy findings.	Likely inpatient.	30/46 (65.2%)
Kayhan 2012	Misdiagnosis defined by delay in diagnosis by more than 7 days after symptom onset.	Inpatient	76/189 (40.2%)
Liang 2001	Incorrect initial diagnosis.	Inpatient	86/149 (57.7%)
Liang 2009	Misdiagnosis defined as the lack of consideration for PE as a potential initial diagnosis.	Inpatient	40/63 (63.5%)
Lim 2014	Missed PE on abdominal CT scan done within 3 months (before or after) of the PE-positive chest CT scan.	Likely inpatient	18/22 (81.8%)
Liu 2012	Wrong initial diagnosis.	Inpatient	22/22 (100%)
Patel 1994	Incidental finding of PE on echocardiography.	Inpatient	Incidental PE 14/14 (100%)
Sun 1996	PE identified at the autopsy but not diagnosed clinically.	Likely inpatient	20/23 (87.0%)
Walden 1985	PE identified in post-mortem but diagnosis of PE was not made or suspected while patient was alive.	Inpatient	236/425 (55.5%)
Intensive care settings			
Berlot 2011	PE identified at the autopsy but not diagnosed clinically.	ICU	Missed diagnosis of PE: 73/86 (84.9%)

Rusu 2021	Discrepancy between antemortem clinical diagnoses and postmortem histological findings.	ICU	Missed diagnosis of PE: 13/47 (27.7%)
Tejerina 2011	Discrepancy between clinical diagnoses and autopsy findings.	ICU	Missed diagnosis of PE: 24/157 (15.6%)

ED=emergency department, ICU=intensive care settings, PE=pulmonary embolism

Table 3: Misdiagnosed conditions that were actually pulmonary embolism

Study ID	Misdiagnosed conditions
Alonso-Martinez 2010	Pneumonia 25/187, bronchitis 65/187, exacerbation of COPD 15/187, HF 58/187, cardiorespiratory failure 5/187, others 18/187.
Gurzu 2014	Acute myocardial infarction, postoperative shock, septic shock, cirrhosis and liver failure, decompensated heart failure, bronchopneumonia, lung tumor, lung tuberculosis, intestinal infarction, psychiatric disorders delirium tremens, malignant tumor of brain, cervix, sudden death unknown cause.
Ilvan 2015	Pneumonia 5/100, DVT only 4/100, ACS 3/100, nonspecific chest pain 3/100, nonspecific dyspnea 2/100, pulmonary hypertension 2/100, tuberculosis 1/100, asthma 1/100, HF 1/100, COPD 1/100, urinary tract infection 1/100, epilepsy 1/100, lung mass 1/100.
Liang 2001	Coronary artery disease or ACS 12/86, pneumonia 6/86, bronchitis 5/86, pulmonary hypertension 4/86, congenital heart disease 3/86, cardiomyopathy 3/86, cor pulmonale 3/86, cerebrovascular disease 3/86, asthma 2/86, others 7/86, unclear diagnosis 38/86.
Liang 2009	Pneumonia 15/40, coronary heart disease 5/40, exacerbation of COPD 3/40, bronchitis 2/40, heart failure 2/40, pericarditis 1/40, others 8/40, missed diagnosis 4/40.
Liu 2004	Pneumonia 5/22, heart diseases 7/22, cerebrovascular disease 3/22.
Liu 2012	ACS 22/22.
Patel 1994	HF 8/14, cardiogenic shock 2/14, atrial septal defect 2/14, aortic dissection 1/14, pneumonia 1/14.

COPD=chronic obstructive pulmonary disease, HF=heart failure, DVT=deep vein thrombosis, ACS=acute coronary syndrome

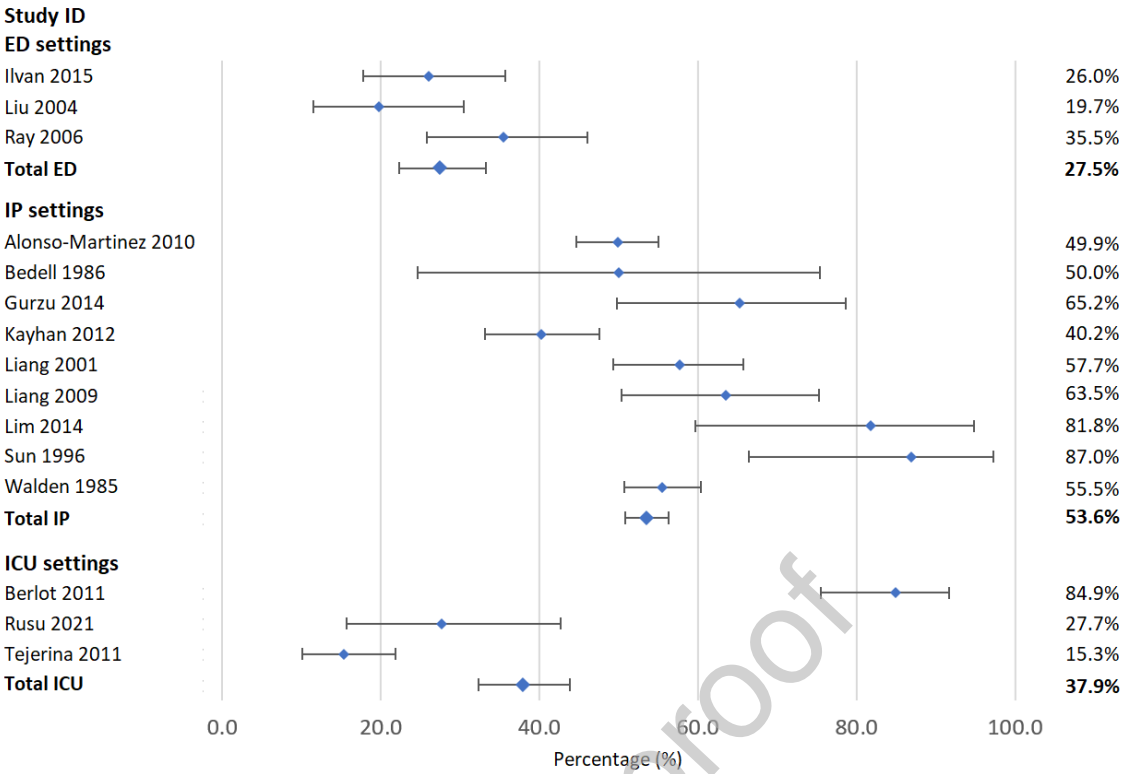

Fig. 1