A Decision Analysis Approach to the Treatment of Patients with Suspected Pulmonary Emboli and an Intermediate Probability Lung Scan

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There remains no clear consensus as to the appropriate further investigation and management of the patient suspected of pulmonary embolism (PE) who has an intermediate lung scan. Clinical assessment is documented as unreliable, yet many of these patients are unlikely to be treated or to have further tests despite a 36% chance of having PE. Using Medical Decision Analysis, four management strategies for such patients have been examined in terms of mortality and morbidity up to 6 mo post-presentation. The strategies were: (1) treat all patients; (2) treat no patients; (3) perform pulmonary angiography; and (4) perform contrast venography. In the last two strategies, the patients with positive examinations are treated; those with negative examinations are not treated. An extensive literature review was performed to provide probability estimates of chance events and outcomes. If all patients are treated, there is 96.8% chance of survival, with an 85.8% chance of survival with no major complications. If no patients are treated, survival is 89.3% and complication-free survival is 89.3%. Angiography and venography results were 96.7%, 93.1% and 94.6% and 89.6%, respectively. We conclude that in patients suspected of PE who have intermediate lung scan results, the optimal strategy is pulmonary angiography since this results in the highest survival with the lowest complications.

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Pulmonary embolism (PE) continues to be a major contributing factor to in-hospital mortality in both medical and surgical patients and is responsible for approximately 10% of deaths (*1*). Clinical diagnosis of pulmonary embolism is notoriously unreliable (*2–7*), and there has been little improvement in such clinical diagnoses over the past four decades (*8*). It is generally accepted that pulmonary angiography is the definitive examination for excluding or confirming the presence of pulmonary emboli and, as such, is the "gold standard" to which other diagnostic modalities are compared (*9–11*). The role of ventilation-perfusion (V/Q) lung scanning in the diagnosis of PE is still debated (*12–15*).

The intermediate probability lung scan remains a major problem for most physicians because there is no clear consensus as to the appropriate further investigation and management for PE patients (*16–18*). Using widely accepted criteria (*9*), an intermediate V/Q scan is used when there is either: a perfusion defect corresponding to radiologic opacity, a single V/Q mismatch widespread ventilation abnormalities, or widespread airways disease is present. It has been demonstrated that patients with an intermediate probability lung scan are unlikely to have had either a pulmonary angiogram or anticoagulation therapy (*19–21*).

There are essentially four options for a clinician when faced with a patient suspected of having PE who has an intermediate probability lung scan:

1. Treat with anticoagulation.
2. Do not treat with anticoagulation.
3. Perform a pulmonary angiogram and treat all the positive cases with anticoagulation and do not treat the negative cases.
4. Assess the legs for peripheral venous thrombosis and treat the positive cases with anticoagulation and do not treat the negative cases.

We investigated these four strategies using a decision analysis approach. By assigning probabilistic estimates to the diagnostic and therapeutic decisions of this complex clinical problem, an optimal management strategy in terms of survival and morbidity can be deduced (*22–30*).

MATERIALS AND METHODS

Assignment of Numerical Values for Probabilities

First, a decision tree detailing the courses of action, chance events and patient outcomes was created (Fig. 1). The four courses of action are:

1. Treat all patients.
2. Treat no patients.
3. Perform pulmonary angiography on all patients.
4. Perform bilateral contrast venography on all patients.

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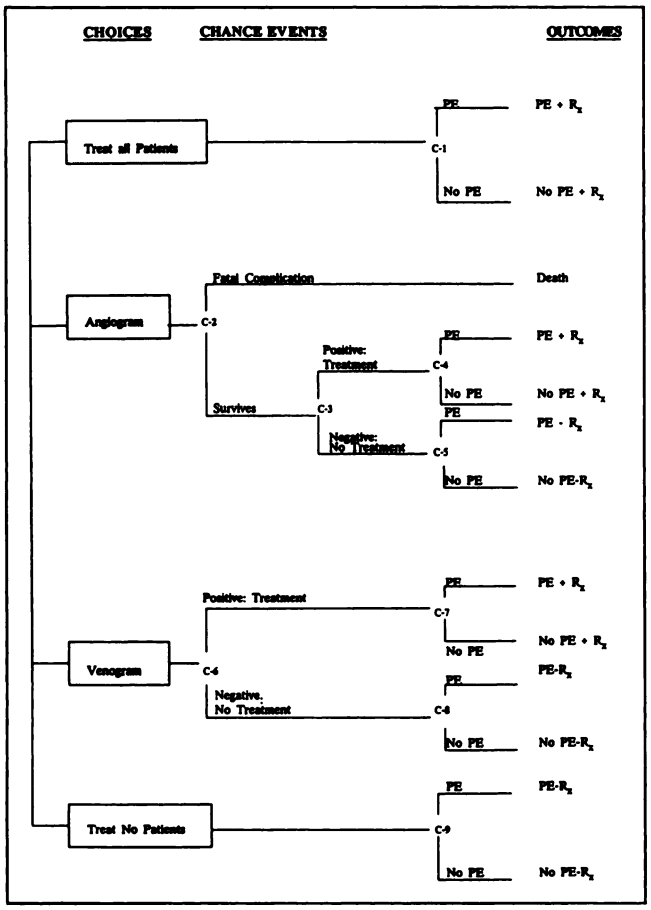

FIGURE 1. Decision tree detailing the choices available (treat all patients; perform angiography; perform venography; treat no patients), the chance events associated with each management choice, and the possible outcomes (PE treated, PE untreated, no PE treated, no PE treatment not treated and death).

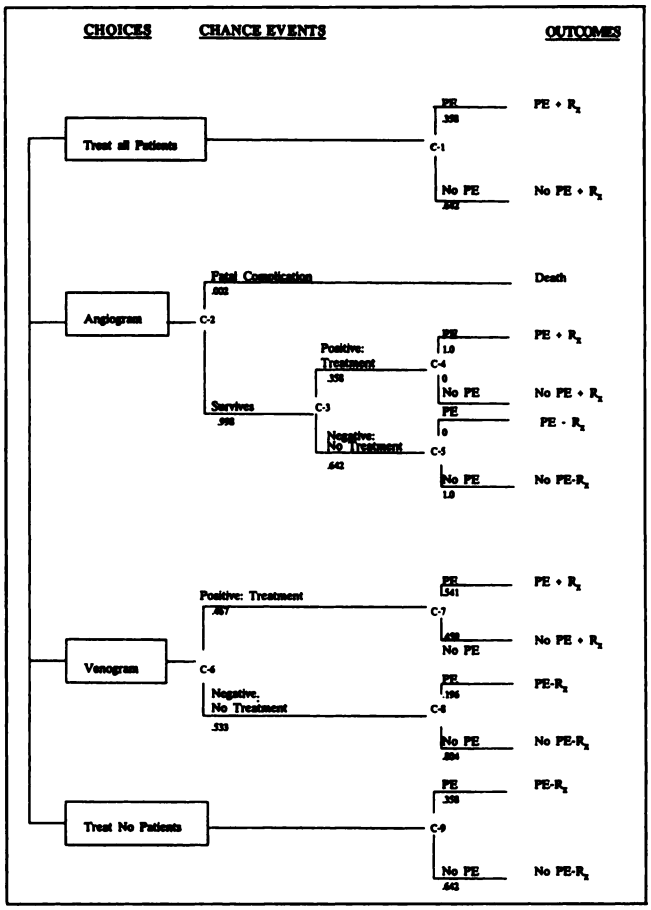

FIGURE 2. Decision tree following the addition of probabilities of each event. The numbers on each branch represent the probability that each event will occur.

The probability that each chance event will occur was calculated using probability estimates obtained from the literature. Mortality and morbidity rates for each outcome then were combined with the probability of reaching that outcome. The strategy that provides the lowest mortality and morbidity rates and, hence, the preferred option thus was deduced.

Probability estimates for each chance event have been inserted into Figure 1 and are detailed in Figure 2. The basis for such estimates are summarized in Table 1 along with the appropriate references. Using the standard Biello criteria (*31*), there are three situations in which a lung scan is of intermediate probability. First, the perfusion defect is the same size as the radiologic opacity; second, there is a single ventilation perfusion mismatch; and third, widespread airways disease.

Using pulmonary angiography as the gold standard, Alderson et al. (*9*) demonstrated PE in 64 of 186 patients who had intermediate probability scans. Spies et al. (*32*) demonstrated PE in 36/73 patients with intermediate probability scans. Catamia et al. (*33*) reported similar results in 36/86 patients and Hull et al. (*34*) used pulmonary angiography to detect PE in 2/16 patients. In the recent PIOPED study (*35*), 105/322 patients demonstrated PE with intermediate probability scans. Overall, there were 243 patients with angiographically demonstrable PE in 678 patients with an intermediate probability lung scan. That is, there was a 243/678 (0.358) chance of PE if a patient had an intermediate probability scan.

Pulmonary angiography is widely accepted as the gold standard (*9–11*) and, as such, it has been assigned a sensitivity and specificity of 1.000. In spite of such widespread acceptance, false-negative angiograms have been reported on several occasions (*36–38*). These observations need to be contrasted with the excellent prognosis of patients with normal pulmonary angiograms (*39*). False-positive angiograms in detecting PE have been rarely reported (*40*).

The probability of surviving pulmonary angiography is considered to be 99.8%. Goodman (*41*) reviewed the mortality of pulmonary angiography in 15 separate series, in which 4,209 patients underwent pulmonary angiograms resulting in 10 deaths. Perlmutt et al. (*42*) reported 2 deaths in 1,434 patients. Thus, experiences with nearly 6,000 patients indicate that pulmonary angiography carries a mortality of 0.21%. Ninety-two percent (11/12) of these reported deaths occurred in patients with pulmonary hypertension and/or elevated right ventricular and diastolic pressures. Perlmutt et al. suggested that there was a threshold for mortality if right ventricular end-diastolic pressure was greater than 20 mmHg and pulmonary artery pressure was greater than 70 mmHg. Even above this threshold, there was only a 2%–3% risk of mortality.

Contrast venography is the gold standard for the diagnosis of

TABLE 1
Basis for Probability Estimates for Chance Events

Event		References
Probability of PE in a patient with indeterminate lung scan	0.358	9, 32–35
Sensitivity of pulmonary angiogram in detecting PE	1.000	9–11, 36–40
Specificity of pulmonary angiogram in detecting PE	1.000	9–11, 36–40
Probability of surviving a pulmonary angiogram	0.998	41–42
Sensitivity of venogram in detecting PE	0.707	34, 43–49
Specificity of venogram in detecting PE	0.667	34, 43–49
Probability of surviving venography	1.000	50–52

venous thrombosis in the extremities (*43–45*). While contrast venography is the standard method for detecting peripheral thrombosis, its accuracy in predicting the presence of associated PE is significantly lower. Hull et al. (*34*) performed bilateral contrast venography and pulmonary angiography in 74 patients suspected of PE. Of the 41 patients with PE, 29 had positive venograms; of the 33 patients without PE, 22 had positive venograms. Thus, bilateral contrast venography had a sensitivity of 70.7% (29/41) and a specificity of 67% (22/33) in detecting PE. Schiff et al. (*46*) performed noninvasive venous examinations (plethysmography and Doppler venous flow measurements) and pulmonary angiograms on 50 patients suspected of having PE. Of the 26 patients with PE, 10 had positive noninvasive venous studies; of the 24 patients without PE, 18 had negative noninvasive venous studies. Thus, these noninvasive techniques had a sensitivity of 38% (10/26) and a specificity of 75% (18/24). Cheely et al. (*47*) performed Doppler examinations in 79 patients with angiographically demonstrated PE. In that series, 28 studies were positive, resulting in sensitivity of 23%. Patients without PE did not undergo Doppler studies and so a specificity cannot be calculated. Hull et al. performed pulmonary angiography and impedance plethysmography on 85 patients in one series (*34*) and on 175 patients in a second series (*48*). Of the 37 patients with PE in the first series, 21 had positive impedance plethysmography, giving a sensitivity of 57% (21/37). Of the 48 patients without PE, 37 had negative impedance plethysmography, giving a specificity of 77% (37/48). In the second series, 36/83 patients with PE had positive impedance plethysmography (sensitivity of 43%) and 75/92 patients without PE had negative impedance plethysmography (specificity of 82%). These results are at variance with those of Sasahara et al. (*49*) who reported a sensitivity and specificity of 90%, respectively. For the purpose of the current analysis, the sensitivities and specificities for bilateral contrast venography were used other than that of Sasahara, since this method had the highest sensitivity and specificity in detecting PE.

The probability of surviving a contrast venogram is taken to be 1.000. Death due to anaphylaxis induced by the contrast material is approximately 1 in 40,000 and was too small to be included in these calculations (*50*). Similarly, the risk of dying secondary to contrast-induced renal failure was too low for inclusion into this calculation (*51,52*).

Assignment of Outcome Probabilities

The probabilities for each outcome are given for each branch in Figure 2 and were calculated as follows using the data in Table 1.

Node C-1. The probabilities used in this node were based upon the incidence of PE in patients with an intermediate probability lung scan, i.e. 0.358.

Node C-2. The probability of death due to a pulmonary angiogram was 0.002 and hence the probability of survival was 0.998.

Node C-3. Of the 35.8% of patients who have PE, all will have positive angiograms and of the 64.2% who do not have PE the angiograms will be negative.

Node C-4. The assignment of probabilities for Nodes C-4, C-5, C-6, C-7 and C-8 was calculated using Bayes' theorem. The probability that patients with a positive test do in fact have the disease is given by:

post-test probability =

$$\frac{\text{pretest probability} \times \text{sensitivity}}{\begin{array}{l}(\text{pretest probability} \times \text{sensitivity}) \\ + (\text{prior probability of not having} \\ \qquad \text{disease} \times [\text{1-specificity}])\end{array}}.$$

Thus, in the case of the upper branch for C-4, the probability is 1.00 and the lower branch is 0.

Node C-5. The same probability assignment as for Node C-4 was given.

Node C-6. Of the 35.8% of patients with PE, 70.7% will have a positive venogram and of the 64.5% who do not have PE 33.3% will have a positive venogram. Thus, the probability of a positive venogram is 0.467 (0.358 × 0.707) + (0.642 × 0.333).

Node C-7. The probability that a patient with a positive venogram has PE was 0.541. The probability of a patient without PE having a positive venogram was 0.459.

Node C-8. The probability that a patient with a negative venogram having PE was 0.196. The probability that a patient without PE having a negative venogram was 0.804.

Node C-9. The assignment of probabilities for this node was the same as for C-1.

Assessment of Utilities

Utilities were calculated for two endpoints: (1) survival at 6 mo after hospital discharge and (2) survival at 6 mo after hospital discharge without any major bleeding. There were four possible outcomes:

1. Patients with PE who are treated.
2. Patients with PE who are not treated.
3. Patients without PE who are treated.
4. Patients without PE who are not treated.

Patients with PE Who Are Treated. To calculate the expected survival for this group, three factors must be calculated: the inpatient mortality; the risk of death from recurrent PE or its sequelae up until 6 mo; and the mortality caused by the treatment. The hospital mortality for patients treated for PE is 8% (*53*). Death due to recurrent PE or chronic pulmonary hypertension in treated patients was not seen in 72 patients followed from 1 to 9 yr (*54*) since the long-term prognosis of treated PE patients was determined by the presence or absence of prior cardiac disease (*55–56*). Estimates of mortality caused by anticoagulation varied

considerably (*57–59*) due to many factors, including the patient population studied, the type of anticoagulation used and the length of anticoagulation. There are little data concerning anticoagulation-induced mortality in patients treated for PE. Landefeld et al. (*58*) reported the mortality risk of warfarin therapy in 565 patients on long-term anticoagulation and related it to the length of anticoagulation treatment. The risk of fatal bleeding in the first month is 0.4% and 0.08% for each month up to 12 mo. Thus, if we assume that patients considered to have PE are treated for 6 mo, then the probability of survival of patients with PE who are treated is 0.913 (0.920 × 0.996 × 0.996).

Patients with PE Who Are Not Treated. The mortality of untreated PE was 30% (*60*). Furthermore, there was an increased chance of fatal recurrence in untreated PE with a death rate of 18%, as reported in one series (*61*). A conservative estimate would consider only in-patient mortality and this figure was used for calculations. Thus, the probability of 6 mo survival in patients with PE who are not treated was 0.700.

Patients Without PE Who Are Treated. The probability of survival in patients without PE who are treated was the mortality due to heparin therapy plus 6 mo of out-patient anticoagulation. There was no large scale trial addressing anticoagulation-related deaths in patients treated for PE. In the Urokinase Pulmonary Embolism Trial (*36*), 78 patients were given heparin intravenously with 27% of the patients experiencing moderate or severe bleeding within the first two weeks. No deaths were directly attributable to anticoagulation therapy. Hull et al. (*62*) reported an in-patient mortality of 0.5% in 199 patients treated for proximal vein thrombosis, while Landefeld et al. (*59*) calculated the in-patient mortality rate due to anticoagulation therapy to be 0.16% in 617 patients commencing long-term anticoagulation treatment. The more conservative figure of 0.16% was used in this study. The risk of out-patient death due to anticoagulation is 0.8%. Thus, the probability of survival for patients without PE who are treated is 0.990 (1.00 × 0.998 × 0.992).

Patients Without PE Who Are Not Treated. The probability of survival in patients who do not have PE and who are not treated was 1.00.

Morbidity Outcomes. In calculating morbidity outcomes, only incidences of major bleeding events were considered. These were defined as either: (1) life-threatening bleeding (resulting in cardiopulmonary arrest, surgical or angiographic intervention to stop blood loss, or irreversible damage such as myocardial infarction, stroke, blindness or fibrothorax); (2) potentially life-threatening (bleeding leading to two of three consequences: loss of three or more units of blood, systolic blood pressure less than 90 mmHg, and clinical anemia with hematocrit of 0.20 or less). The probability of not having a major bleeding event during hospitalization was 0.955 (*59*) and 0.930 during 6 mo of out-patient anticoagulation therapy (*58*). Thus, the probability of survival at 6 mo after hospital discharge without a major bleeding event was 0.808 (0.913 × 0.955 × 0.930) in patients with PE who are treated. For patients without PE who are treated, the probability was 0.886 (0.998 × 0.955 × 0.930). The probability assignments of outcomes are detailed in Table 2.

TABLE 2
Probability Assignment of Outcomes

		References
Probability of 6-mo survival of patients with PE after proper treatment	0.913	53–59
Probability of 6-mo survival in patients with PE not treated	0.700	60–61
Probability of 6-mo survival in patients without PE who are treated	0.990	36, 59, 62
Probability of 6-mo survival in patients without PE who are not treated	1.000	
Probability of survival with no major bleeding in patients with PE who are treated	0.808	58–59
Probability of survival with no bleeding in patients without PE who are treated	0.886	58–59

RESULTS

Calculation of the expected mortality in each node of the decision tree is made by adding the product of the probability and the mortality and morbidity of each of the branches from that node.

Node C-1

The expected survival is (0.358 × 91.3) + (0.642 × 99.8) or 96.76%.

Node C-2

The expected survival for this node is calculated by summing the survival outcomes from C-3, C-4, and C-5. The survival outcome of C-4 is (1.00 × 91.3) + (0 × 100), or 91.30%. C-5 is (0 × 70.00) + (1.000 × 100), or 100%. C-3 is (0.358 × 91.30) + (0.642 × 100), or 96.89%. C-2 is (0.998 × 96.89), or 96.70%.

Node C-6

Calculations are the same for C-2. The survival outcome for C-7 is (0.541 × 91.3) + (0.459 × 99.8), or 95.20%. C-8 is (0.196 × 70.0) + (0.804 × 100.0), or 94.12%. C-6 is (0.467 × 95.20) + (0.533 × 94.12), or 94.66%.

Node C-9

The expected survival is (0.358 × 70.0) + (0.642 × 100), or 89.29%.

Morbidity Outcomes

The results for survival with no major bleeding are calculated in the same fashion and results for the four different strategies are shown in Table 3.

DISCUSSION

In the diagnosis of PE, the intermediate probability lung scan result presents a difficult clinical problem. We have used clinical decision analysis in an attempt to objectify some of the management strategies as they apply to a group of patients in terms of survival and major bleeding up to 6 mo. This method, although artificial, is useful in generating a diagnostic algorithm and avoids the "last worse case" response to diagnosis.

The intermediate probability scan by its very nature means that there is a probability of PE between 10% and 90%. The recent PIOPED study demonstrated that this

TABLE 3
Results for Four Different Patient Management Strategies

Strategy	%Survival at 6 mo	%Survival at 6 mo with no major bleeding
Treat all patients	96.76	85.81
Angiography	96.70	93.13
Venography	94.66	89.60
Treat none	89.29	89.29

TABLE 5
Strategy Outcomes with 66% Incidence of PE

Strategy	%Survival at 6 mo	%Survival at 6 mo with no major bleeding
Treat all patients	94.1	83.5
Angiography	94.1	87.16
Venography	89.8	83.94
Treat none	80.2	80.2

intermediate probability equated to a 33% chance of PE. In the same study, there was an overall prevalence of PE of 33% (251/755) in the patient population who had pulmonary angiograms.

In the individual patient, it has been argued that the lung scan must be interpreted in view of the pre-test probability. Polak and McNeil (*63*) and more recently the PIOPED study have demonstrated that this approach is limited and is only useful in a small number of patients (i.e., those with a high pre-test probability and a high probability lung scan and those with a low pre-test probability and low probability lung scan). As demonstrated by Polak and McNeil, in any group of patients, there will be a large proportion who will have an intermediate pre-test probability and who will then have an intermediate lung scan. Furthermore, the PIOPED study showed that 64% of these patients have an intermediate probability of PE on clinical grounds.

In the PIOPED study, of the patients with a low pre-test probability clinically and an intermediate lung scan, 16% were demonstrated as having PE. Those patients with a high clinical pre-test probability and an intermediate lung scan had a 66% incidence of PE.

These data were used in our decision analysis and the results for mortality and morbidity from PE with a 16% and 66% post-lung scan probability are shown in Tables 4 and 5.

From the results presented here, it is clear that the worst survival is achieved if no patients with an intermediate lung scans receive anticoagulation treatment. This is due to the high mortality of untreated PE. Thirty-six percent of the patients in this group will have untreated PE with a mortality of 30%.

The highest 6-mo survival rate is achieved when all patients with an intermediate probability scan undergo anticoagulation therapy. The problem with this mode of management is that 64% of the patients will be incorrectly diagnosed and treated, and there will be an increased morbidity associated with anticoagulation.

TABLE 4
Strategy Outcomes with 16% Incidence of PE

Strategy	%Survival at 6 mo	%Survival at 6 mo with no major bleeding
Treat all patients	98.4	87.4
Angiography	98.4	96.7
Venography	97.6	93.2
Treat none	95.2	92.5

It is clear then that in the majority of patients an intermediate lung scan should result in further investigations if one is to accurately diagnose PE. There has been considerable discussion as to which is the best examination to perform after an intermediate lung scan. For example, it has been suggested that investigation of the lower limbs is a reasonable next step (*17*). However, even with bilateral contrast venography, the results in terms of survival at 6 mo and major bleeding are inferior to pulmonary angiography as the next investigation. The proponents of peripheral limb assessment argue that demonstration of peripheral thrombosis negates the need to search for PE, since the treatment for PE and deep venous thrombosis (DVT) is essentially the same. As discussed above, peripheral thrombosis is a poor predictor of PE and this approach would lead to missed diagnoses for the symptoms and signs that originally made the clinician suspect PE.

Conditions such as left ventricular failure and pneumonia would be missed in a patient who has an additional DVT, and mortality and morbidity due to these untreated conditions could be expected to increase. Furthermore, if the venogram is negative, then angiography is still needed, since 30% of the patients with PE have negative bilateral venograms (*34*). Hull et al. (*17*) have suggested that patients with PE who do not have demonstrable proximal vein thrombosis have a good prognosis without anticoagulation. This suggestion is based on a study of highly selected patients with a low prevalence of PE. However, further work is needed to confirm this prior to its widespread clinical implementation.

In our opinion, except where absolutely contraindicated, the optimal method for further investigating patients with intermediate probability lung scans is still pulmonary angiography. Pulmonary angiograms, however, are performed less and less frequently in the diagnosis of PE due to the statistically unsustainable fear of mortality associated with the procedure. Pulmonary angiograms are no more life-threatening than 6 mo of anticoagulants (Table 1), yet many physicians currently avoid angiography and opt for anticoagulation or worse, no treatment at all.

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