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Title: Cost effectiveness analysis of subtraction scintigraphy in the acute LGH patient
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Abstract: 99mTc RBC scintigraphy offers a powerful detection and localisation tool that may be confounded by false positive and false negative findings. Subtraction scintigraphy has been utilised in the evaluation of acute LGIH to reduce the impact of interpretive confounders. The aim of this investigation was to evaluate the cost effectiveness of the addition of subtraction scintigraphy in the evaluation of the acute LGIH patient.Methods: The clinical phase of the research was a retrospective clinical study using a repeat-measures design of randomised control and experimental groups. A total of 49 patients studies were included in the sample. Studies were randomised and interpreted by four independent physicians. Decision tree analysis was utilised to model direct costs and the potential risks of procedures for two diagnostic strategies in the acute LGIH patient; conventional scintigraphy alone and conventional scintigraphy combined with subtraction scintigraphy. The transition probabilities for scintigraphy were then based on the clinical results of this investigation. All other transition probabilities were derived from previously cited data.Results: Combining subtraction methods with conventional scintigraphy reduced the overall costs of procedures in the acute LGIH patient by $74 per patient and reduced deaths by 17.6% and complications by 15.7%. For conventional scintigraphy alone, 8.8% of patients presenting with acute LGIH for scintigraphy will undergo unnecessary angiograms and 2.8% will have unnecessary surgery. These figures were reduced to just 5.4% and 1.8% respectively with the addition of subtraction scintigraphy.Conclusion: Utilising subtraction scintigraphy as an adjunct to conventional scintigraphy in the acute LGIH patient may extend both cost and outcome benefits.

Cost effectiveness analysis of subtraction scintigraphy in the acute LGH patient.

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Foot line: COST EFFECTIVENESS OF SUBTRACTION SCINTIGRAPHY

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ABSTRACT

^{99m}Tc RBC scintigraphy offers a powerful detection and localisation tool that may be confounded by false positive and false negative findings. Subtraction scintigraphy has been utilised in the evaluation of acute LGIH to reduce the impact of interpretive confounders. The aim of this investigation was to evaluate the cost effectiveness of the addition of subtraction scintigraphy in the evaluation of the acute LGIH patient.

Methods: The clinical phase of the research was a retrospective clinical study using a repeat-measures design of randomised control and experimental groups. A total of 49 patients studies were included in the sample. Studies were randomised and interpreted by four independent physicians. Decision tree analysis was utilised to model direct costs and the potential risks of procedures for two diagnostic strategies in the acute LGIH patient; conventional scintigraphy alone and conventional scintigraphy combined with subtraction scintigraphy. The transition probabilities for scintigraphy were then based on the clinical results of this investigation. All other transition probabilities were derived from previously cited data.

Results: Combining subtraction methods with conventional scintigraphy reduced the overall costs of procedures in the acute LGIH patient by $74 per patient and reduced deaths by 17.6% and complications by 15.7%. For conventional scintigraphy alone, 8.8% of patients presenting with acute LGIH for scintigraphy will undergo unnecessary angiograms and 2.8% will have unnecessary surgery. These figures were reduced to just 5.4% and 1.8% respectively with the addition of subtraction scintigraphy.

Conclusion: Utilising subtraction scintigraphy as an adjunct to conventional scintigraphy in the acute LGIH patient may extend both cost and outcome benefits.

Key words: bowel hemorrhage, GIT bleed, subtraction scintigraphy, LGIH

INTRODUCTION

Despite the difficulties confronting diagnostic evaluation of acute lower gastrointestinal hemorrhage (LGIH), accurate localisation of the site of bleeding is crucial in treatment and patient management (*1*,*2*). While diagnostic evaluation of acute LGIH has improved significantly over the last 25 years, there is currently no 'gold standard' due to the intermittent nature of the bleeding (*2*-*4*). ^{99m}Tc RBC scintigraphy offers a powerful detection and localisation tool that may be confounded by false positive and false negative findings.

Subtraction scintigraphy has been utilised in the evaluation of acute LGIH (*5*). Subtraction scintigraphy should allow elimination of background activity, providing high target-to-background images of the extravasated blood. In short, a dataset is produced that theoretically offers the advantages of both conventional ^{99m}Tc sulfur colloid and ^{99m}Tc RBC scintigraphy (*5*).

The aim of this investigation was to evaluate the cost effectiveness of interpretation utilising conventional scintigraphy compared to that of conventional scintigraphy combined with subtraction scintigraphy in the evaluation of the acute LGIH patient.

METHODOLOGY

The clinical phase of the research was a retrospective clinical study using a repeat-measures design of randomised control and experimental groups. A total of 49 patients studies were included in the sample. Acquisition parameters for all data sets included a 128x128 matrix and a 60 seconds per frame continuous dynamic acquisition. Studies were generally performed with an *in vitro* ^{99m}Tc RBC label using a commercially available kit preparation.

The 49 original raw patient data sets which were displayed conventionally without subtraction (CS), using reference subtraction scintigraphy (RSS) and using alternate sequential subtractions scintigraphy (ASSS). Studies were randomised and interpreted by four independent physicians as CS data only in the first instance. The CS, RSS and ASSS studies were subsequently combined and randomised for re-interpretation. While studies were randomised within each of the two pools of data, CS studies were reported prior to the combined CS and subtraction data to remove possible bias. The clinical phase of this research was approved by the CSU Ethics in Human Research Committee.

Reference Subtraction Scintigraphy (RSS)

In an acquisition with ‘n’ consecutive image frames with each individual image frame given by ‘F(f)’ where ‘f’ equals (1,2,3,………….,n), any subtracted image in the sequence is given by:

$$S(f) = F(f) – F(1)$$

For example,

$$S(10) = F(10) – F(1)$$

Alternate Sequential Subtraction Scintigraphy (ASSS)

In an acquisition with ‘n’ consecutive image frames with each individual image frame given by ‘F(f)’ where ‘f’ equals (1,2,3,………….,n), any subtracted image in the sequence is given by:

$$S(f) = F(f+1) – F(f-1)$$

For example,

$$S(9) = F(10) – F(8)$$

Decision tree analysis was utilised to model direct costs and the potential risks of procedures for two diagnostic strategies in the acute LGIH patient; conventional scintigraphy (CS) alone and CS combined with subtraction scintigraphy. All diagnostic strategies were based on the diagnostic algorithm depicted in figure 1.

The decision tree analysis was based on a hypothetical population of 3000 subject presenting for scintigraphic evaluation of acute LGIH. Each of three diagnostic strategies evaluated 1000 randomly allocated patients with homogenous distribution of variables. The transition probabilities (A% and B% in Figure 1) for scintigraphy were then based on the clinical results outlined below. All other transition probabilities were derived from previously cited data (Table 1). Complication rates and mortality rates were also derived from previously cited data (Table 1). Costs were estimated based on the Australian Commonwealth Medicare Benefits Schedule (*6*) and reported in Australian dollars. Tables 1 and 2 provide an overview of the key information utilised in this decision tree analysis and cost effectiveness analysis.

There were a number of assumptions made during this analysis. Firstly, apart from the 15% of positive scintigraphy studies that were directed to surgery without angiograms, the remaining positive scintigraphy studies were all directed to angiograms. In theory this is entirely plausible given the role of scintigraphy in directing patients to angiography although in practice as many as 45% of patients with a positive scintigraphy study are simply observed (*7*). Secondly, the analysis included a single iteration of patients recirculating in the diagnostic algorithm after an initial negative scintigraphy study. There seemed no tangible benefit for this analysis to continue the negative scintigraphy / re-bleed cycle to infinitum. Thirdly, the complication rates and mortality rates, where reported in the literature as a range with no obvious best or most recent practice, were approached conservatively using the lowest value.

RESULTS

The mean age of the study population was 68.9 years (95% CI 64.0 to 73.9 years) with a range of 18.8 to 92.8 years and median of 71.8 years. Females represented 61.2% (30/49) of the study population and males 38.8% (19/49) although no statistically significant variation to gender distributions was noted ($P = 0.11$). No statistically significant difference was noted for the mean age between genders ($P = 0.50$). Just seven (14.3%) studies were positive for GIT bleeding as determined by expert panel consensus. The remaining 42 patient studies were not actively bleeding at detectable bleeding rates during the data acquisition.

The decision tree analysis for the 1000 patients evaluated with CS alone (Figure 2) demonstrated a total of 34 deaths, 83 complications and a cost of $943128. Eighteen deaths and 49 complications are attributed to performing ‘blind’ surgery in true negative (TN) scintigraphy studies. A further complication is associated with performing ‘blind’ surgery in false negative (FN) scintigraphy studies. More importantly, 10 deaths and 25 complications were associated with unnecessary procedures performed on false positive (FP) studies. This was associated with an additional cost burden of $157256 which reflects the increase in per patient cost from $492 (true negative) to $2019 (false positive). The larger true positive (TP) cohort has six deaths and eight complications.

Decision tree analysis for CS, RSS and ASSS combined (Figure 3) demonstrated a total of 28 deaths, 70 complications and a cost of $869284. Nineteen deaths and 53 complications are attributed to performing ‘blind’ surgery in true negative scintigraphy studies. CS, RSS and ASSS combined reduced deaths in the false positive group from 10 for CS alone to four for CS, RSS and ASSS combined. Furthermore, a corresponding reduction was noted for complications in the false positive group; from 25 to just nine. While the cost per patient for the false positive group only marginally changed to reflect the effects of rounding to whole patient numbers, the total reduction in costs of false positive patients was $112428. The addition of subtraction techniques decreased the overall cost by $73844 ($74 per patient).

Decision tree analysis for CS and ASSS combined where a positive study was only identified when ASSS provided supporting evidence (Figure 4) provided 26 deaths, 64 complications and a cost of $787344. These changes reflect the elimination of false positive findings and provide a cost saving over CS alone of $155784 ($156 per patient).

Sensitivity Analysis

Sensitivity analysis is a technique used in economic analysis to assess the robustness of calculations. In the case of cost effectiveness analysis, sensitivity analysis repeats calculations based on a 'worst case' and 'best case' scenarios to determine whether the conclusions are valid within a broader clinical window. In this cost effectiveness analysis, sensitivity analysis was used to assess the impact of the variability of proportions reported in Figure 1. The conservative nature of the original analysis virtually provides a 'worst case' scenario, however, some minor adjustments to proportions in the diagnostic algorithm might negatively impact on the performance of scintigraphy (Figure 5). A 'best case' scenario can be accomplished by being less conservative with variables in Table 1. Table 3 provides a summary of the key variables for the sensitivity analysis.

Decision tree analysis for the 1000 patients evaluated with CS alone as a 'worst case' scenario demonstrated a total of 28 deaths, 70 complications and a cost of $757588. Six deaths and 16 complications were associated with unnecessary procedures performed on false positive studies. 'Worst case' scenario decision tree analysis for CS, RSS and ASSS combined demonstrated a total of 26 deaths, 67 complications and a cost of $725342. This corresponded to no change in deaths or complications in the false positive group compared to CS alone. The addition of subtraction techniques reduced the overall cost by $32246 ($32 per patient). Decision tree analysis for CS and ASSS combined as a 'worst case' scenario provided 25 deaths, 63 complications and a cost of $692480. These changes reflect the elimination of false positive findings and provide a cost saving over CS alone of $65108 ($65 per patient).

Decision tree analysis for the 1000 patients evaluated with CS alone as a 'best case' scenario demonstrated a total of 38 deaths, 103 complications and a cost of $943128. Sixteen deaths and 34 complications were associated with unnecessary procedures performed on false positive studies. ‘Best case’ scenario decision tree analysis for CS, RSS and ASSS combined demonstrated a total of 30 deaths, 83 complications and a cost of $869284. CS, RSS and ASSS combined reduced deaths in the false positive group from 16 for CS alone to seven for CS, RSS and ASSS combined. Furthermore, a corresponding reduction was noted for complications in the false positive group; from 34 to just 11. The addition of subtraction techniques reduced the overall cost by $73844 ($74 per patient). Decision tree analysis for CS and ASSS combined as a ‘best case’ scenario provided 24 deaths, 75 complications and a cost of $787344. These changes reflect the elimination of false positive findings and provide a cost saving over CS alone of $155784 ($156 per patient).

DISCUSSION

The decision trees were burdened by large mortality and complication rates associated with blind surgery in the true negative scintigraphy. This perhaps highlights the role subtraction scintigraphy might play in improving the negative predictive value of scintigraphy, reducing 'blind' surgery. None the less, the impact of subtraction scintigraphy in reducing the costs and consequences of patient management in false positives is highlighted by this analysis.

Combining subtraction methods with CS not only reduced the overall costs of procedures in the acute LGIH patient, but it also reduced mortality and morbidity. Combining CS, RSS and ASSS reduced deaths by six (0.6%) and complications by 13 (1.3%) while providing a net saving of $73844. Thus, subtraction scintigraphy in the acute LGIH patient extended a saving of $74 per patient, while saving six lives or, on average, 69.6 life years. This translates to a cost of -$12307 per life saved or -$1061 per life year saved.

Utilising CS and ASSS reduced deaths by eight (0.8% per 1000) and complications by 19 (1.9% per 1000) while providing a net saving of $155784 over CS alone. Thus, ASSS in the acute LGIH patient extended a saving of $156 per patient, while saving eight lives or, on average, 92.8 life years. That translates to a cost of -$19473 per life saved or -$1679 per life year saved.

These findings were shown to be robust under the scrutiny of sensitivity analysis with subtraction scintigraphy offering cost, complication and mortality reductions even in the 'worst case' scenario (Table 4). The sensitivity analysis indicated that, with respect to cost reductions at least, that the cost effectiveness of the CS, RSS and ASSS technique is performing close to 'best case' while the CS and ASSS technique is performing close to 'worst case'. Thus, the cost benefits of the former may not be fully realised in a clinical model while the latter may afford greater cost savings in the clinical model. It should be noted that 'best case' refers to the comparative performance of scintigraphy rather than patient outcome. Similarly, 'worst case' refers to scintigraphic performance rather than patient outcome.

In the cohort of patients modelled (clinical phase data), 8.8% of patients presenting with acute LGIH for scintigraphy will undergo unnecessary angiograms and 2.8% will have unnecessary surgery. The former is associated with significant cost and radiation burden while the latter is associated with significant mortality and morbidity. Combining CS with RSS and ASSS in the clinical phase of this research allowed unnecessary angiograms to be reduced to just 5.4% of the cohort and unnecessary surgery to just 1.8%. Exploiting the distinctive competencies of ASSS in collaboration with CS interpretation and eliminating the potential false positive findings associated with RSS eradicated unnecessary angiograms and surgery altogether. This strategy may introduce a small number of false negative studies although this was not revealed in this evaluation. One should note that unnecessary surgery and angiography was defined by those performed in false positive studies rather than simply those that returned a negative outcome.

CONCLUSION

The gastrointestinal hemorrhage study utilising ^{99m}Tc RBCs introduces a number of interpretive confounders that may manifest as either false positive or false negative studies. False positive findings may direct a patient unnecessarily to more expensive and higher risk procedures. Generally, cost effectiveness analysis is used to make decisions about implementation of strategies that add costs while justifying the additional costs against improved outcomes. In this case, subtraction scintigraphy not only improved outcomes but also reduced costs. Utilising subtraction scintigraphy as an adjunct to conventional scintigraphy in the acute LGIH patient may extend both cost and outcome benefits. Moreover, decision tree analysis demonstrated the superior cost effectiveness of combining CS and ASSS over CS alone and CS, RSS and ASSS combined. This reflects the high false positive rate associated with the RSS technique.

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TABLES

Table 1: Summary of data used in analysis.

Variable	Value
Mean life expectancy	80.5 years (*8*)
Mortality rate of acute LGIH*	4% (*3*,*9*)
Scintigraphy mortality	0% (*10*)
Scintigraphy complication rate	0% (*10*)
Scintigraphy cost	$492 (*6*)
Angiogram mortality	0% (3,*10*,*11*)
Angiogram complication rate*	2% (3,*10*,*11*)
Angiogram cost	$1376 (*6*)
Embolisation complication rate*	0% (*12*)
Embolisation cost	$144 (*6*)
Surgery mortality with localisation	13% (*13*,*14*)
Surgery mortality without localisation	30% (*13*,*14*)
Surgery complication rate with localisation	15% (*15*)
Surgery complication rate without localisation	83% (*15*)
Surgery cost	$1124 (*6*)
Surgery from positive scintigraphy	15% (*7*)
Angiogram from positive scintigraphy	85%
Positive angiograms with positive scintigraphy	39% (*7*)
Negative angiograms with positive scintigraphy	61% (*7*)
Positive angiograms only suggestive of a bleed	42% (*7*)
Re-bleed rate in acute LGIH	15% (*16*,*17*)
Positive angiograms to surgery	25% (*7*)
Positive angiograms to embolisation	50% (*7*)
Blind surgery	12% (*18*)

* Conservative estimates based on lower end of reported ranges.

Table 2: Summary of clinical results data used in analysis.

Variable	Value
Mean age of patient cohort	68.9 years
False positive rate for CS alone	10.3%
False negative rate for CS alone	1.1%
True positive rate for CS alone	14.8%
True negative rate for CS alone	73.8%
False positive rate for CS and subtraction	4.0%
False negative rate for CS and subtraction	1.7%
True positive rate for CS and subtraction	14.4%
True negative rate for CS and subtraction	79.9%
Negative scintigraphy re-scanned due to re-bleed*	8%

* Only a single iteration was used.

Table 3: Summary of data used in sensitivity analysis.

Variable	**Value**
Angiogram complication rate	11% (*19*)
Surgery mortality with localisation	10% (*20*)
Surgery mortality without localisation	57% (*20*)

Table 4: Results of the sensitivity analysis for the decision tree data with subtraction techniques compared directly to CS alone.

	Reduction In:	**Results**	**'Worst Case' Scenario**	**'Best Case' Scenario**
CS, RSS and ASSS	Cost per patient	$74	$32	$74
	Complications	13	3	20
	Deaths	6	2	8
CS and ASSS	Cost per patient	$65	$65	$156
	Complications	19	7	28
	Deaths	8	3	14

FIGURE LEGENDS

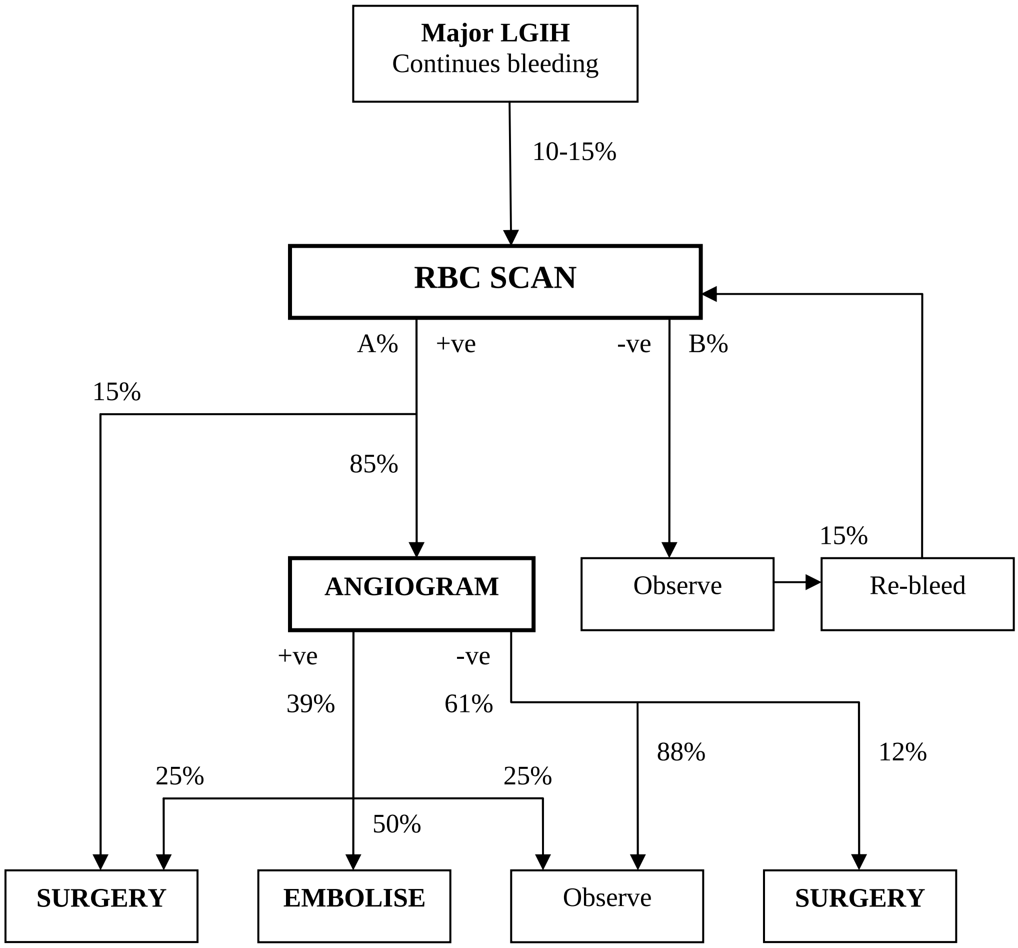
Figure 1: A composite diagnostic algorithm with LGIH patient flow where A% and B% are defined by the alternative diagnostic strategies.

Figure 2: Decision tree analysis for CS alone with a total of 34 deaths, 83 complications and costs of $943128.

Figure 3: Decision tree analysis for CS, RSS and ASSS combined with a total of 28 deaths, 70 complications and costs of $869284.

Figure 4: Decision tree analysis for CS and ASSS with a total of 26 deaths, 64 complications and costs of $787344.

Figure 5: A composite diagnostic algorithm with LGIH patient flow.



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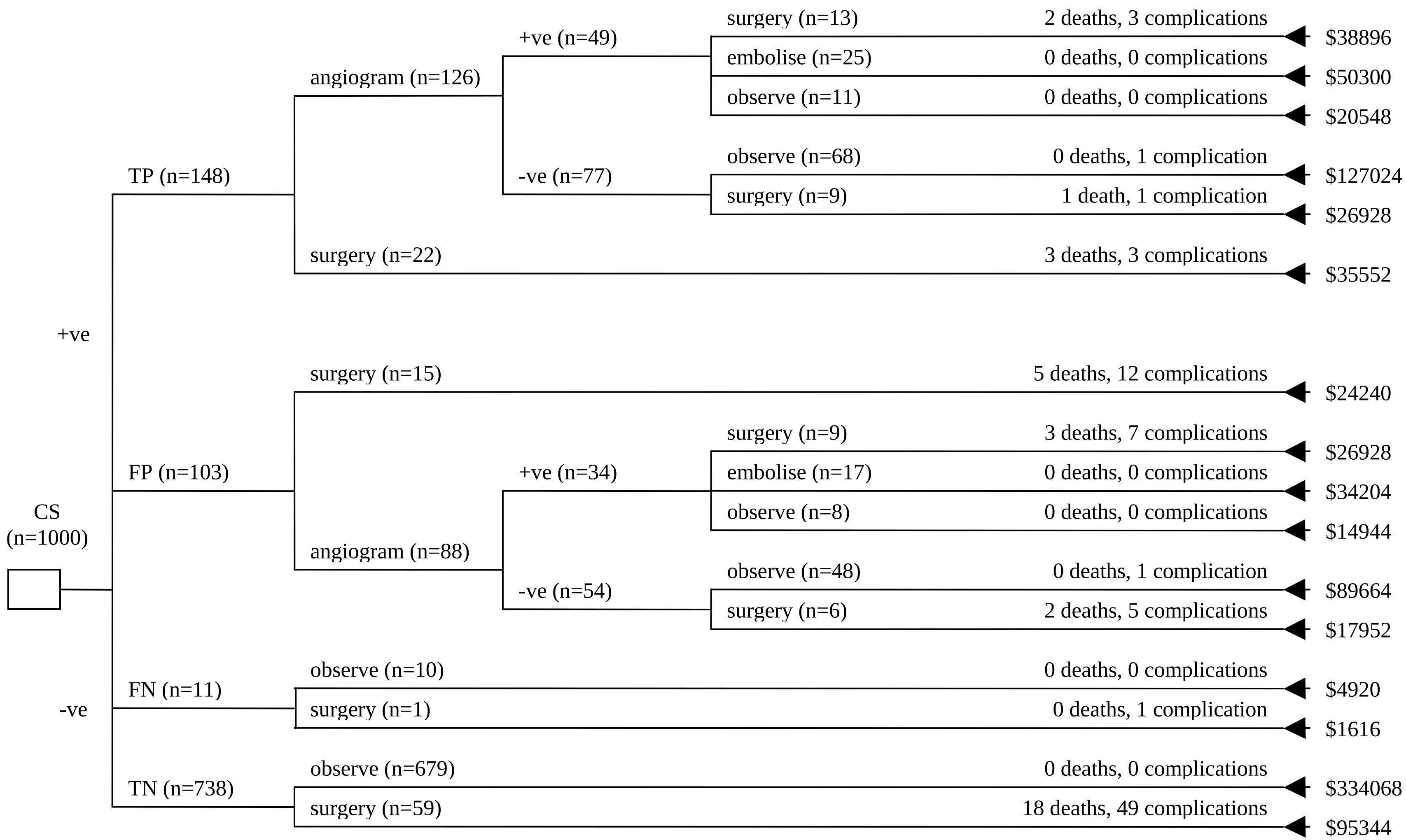

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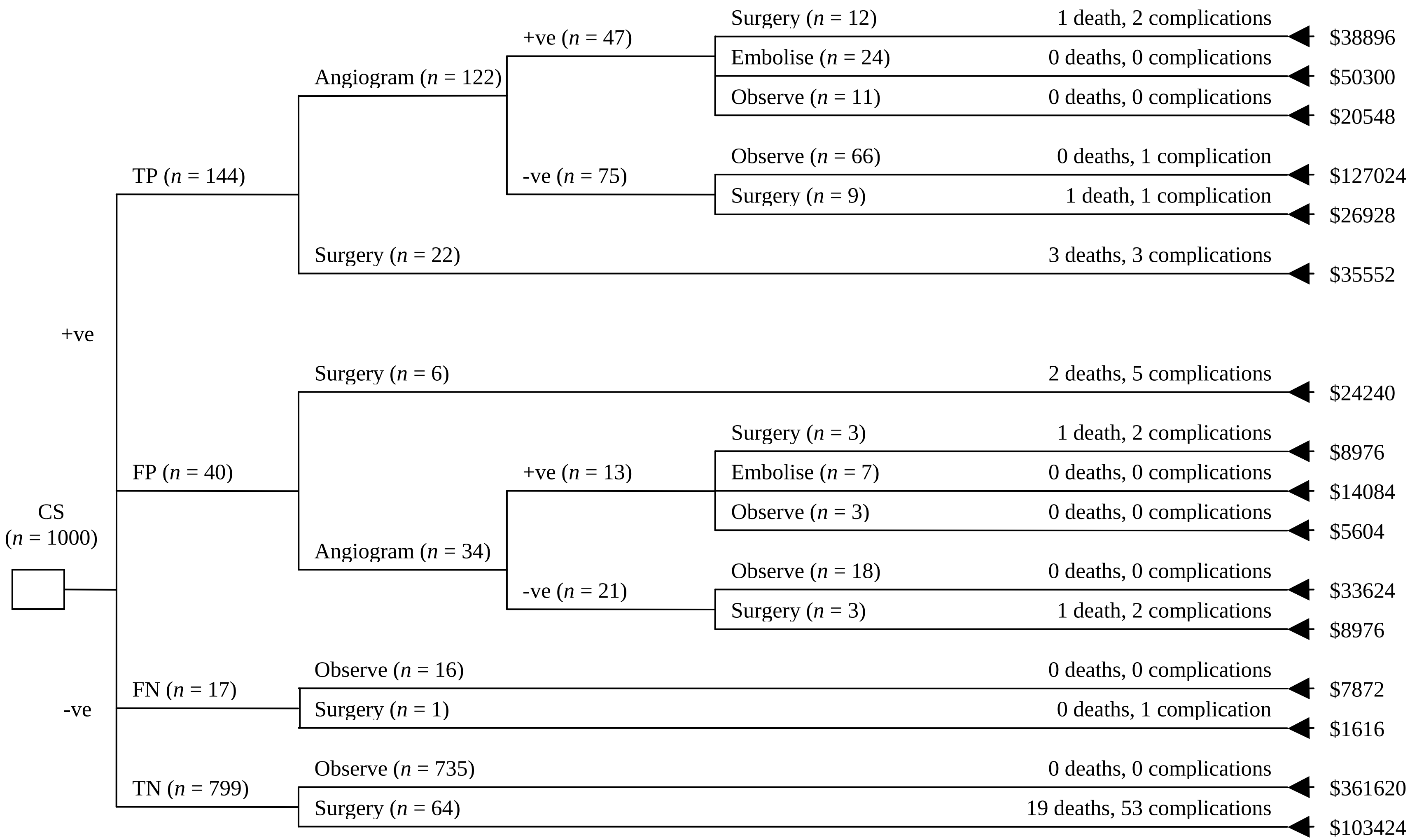

Figure 3: Decision tree analysis for CS, RSS and ASSS combined with a total of 28 deaths, 70 complications and costs of $869284.

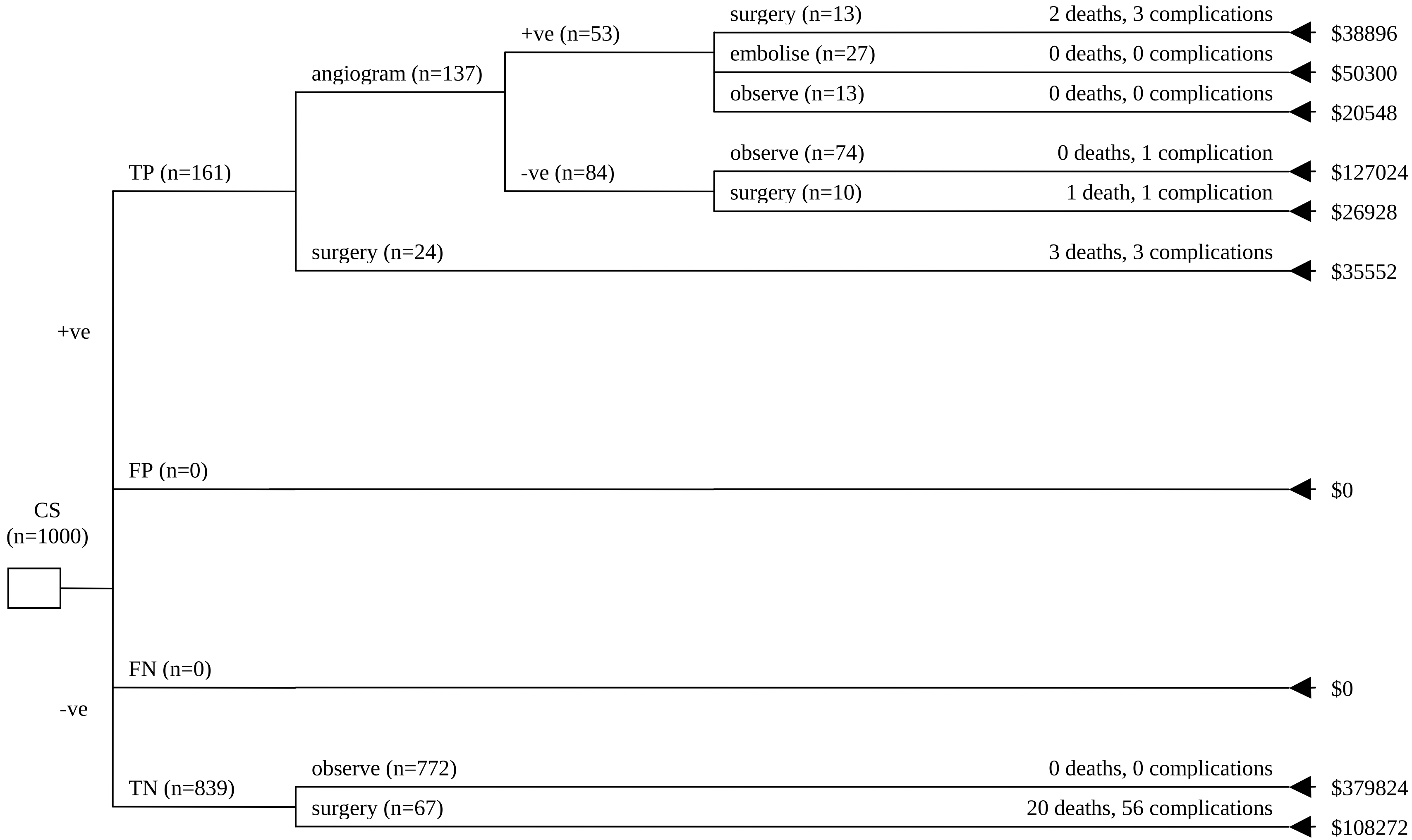

Figure 4: Decision tree analysis for CS and ASSS with a total of 26 deaths, 64 complications and costs of $787344.

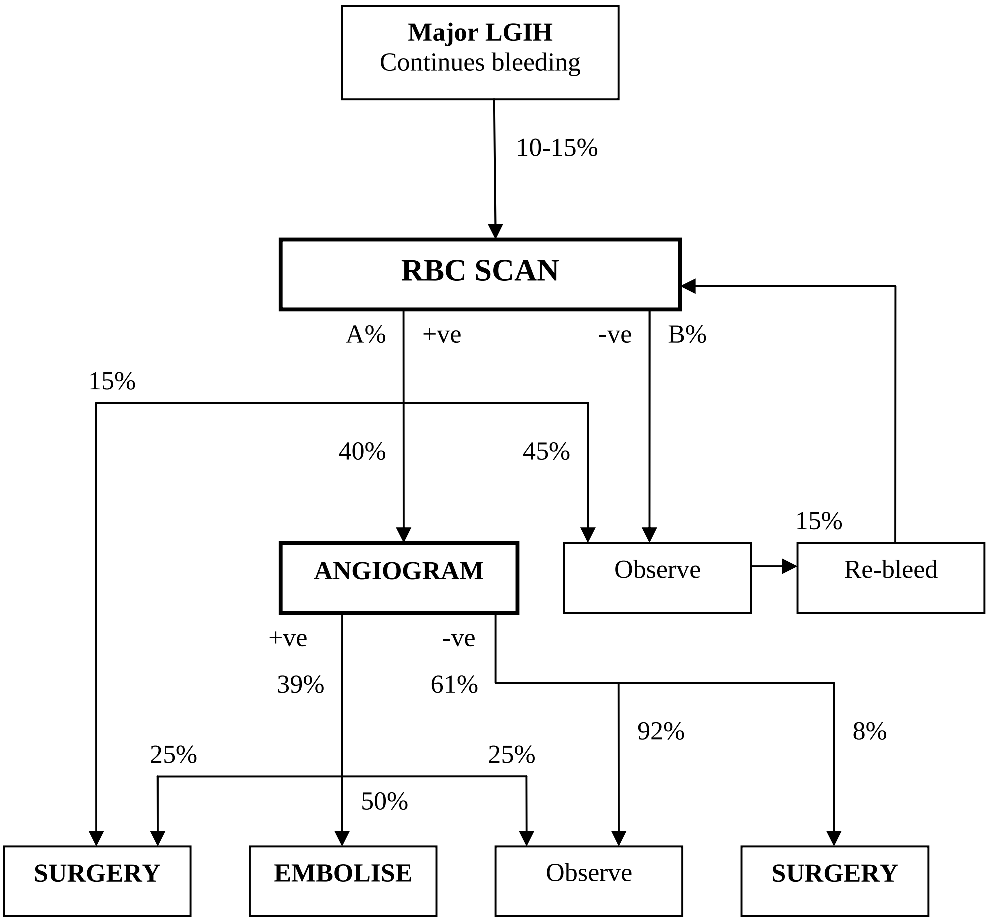

Figure 5: A composite diagnostic algorithm with LGIH patient flow.