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BMJ Open

Exploring the cost-effectiveness of blood biomarker tests to select patients with head injury and possible traumatic brain injury for CT brain scans in the UK setting

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ABSTRACT

Background Mild traumatic brain injury (mTBI) carries a risk of intracranial haemorrhage which may require observation, be prognostically significant, and in a small proportion of patients be life-threatening requiring urgent neurosurgical intervention. In the emergency department, a key component of the initial assessment is determining the need for a CT brain scan. An approach of providing CT scans to all patients is inefficient as more than 90% of CT scans performed for mTBI show no intracranial injury, and only 1%–2% result in neurosurgical intervention. However, delayed neurosurgery can result in avoidable deaths. Blood-based biomarker tests offer a potential solution by enabling improved risk stratification for CT imaging; however, their cost-effectiveness remains uncertain.

Objective To evaluate the potential cost-effectiveness of blood biomarker tests for triaging patients with mTBI for further neuroimaging.

Design Decision-analytic health economic modelling using parameter inputs based on data from a Collaborative European Neurotrauma Effectiveness Research mTBI (CENTER-TBI) cohort, published literature and clinical input. The model is composed of a 6-month decision tree followed by a lifetime state-transition model estimating health outcomes and costs based on whether treatment was prompt or delayed due to the diagnostic accuracy of the testing strategy. In the base case, all biomarker tests were assumed to have ≥95% sensitivity with specificity ranging from 8% to 42%; these data are derived from data from CENTER-TBI.

Setting UK National Health Service.

Participants Patients with mTBI who have been identified as needing a CT brain scan using UK National Institute for Health and Care Excellence Guidelines.

Interventions 'CT all' versus provision of CT only when blood biomarker result is positive.

Primary and secondary outcomes Incremental cost-effectiveness ratio, quality-adjusted life-years (QALYs) gained and costs valued at 2023/2024 prices.

Results The base case model suggests that current biomarker tests generate less QALYs gained and incur higher costs compared with 'CT all' strategy. This is driven by the lower sensitivity of biomarkers, leading to more false negative cases, delayed treatment and QALY losses. This is coupled with the higher costs of treating false negative patients and in some patients incurring both the costs of biomarkers and CT scans. This finding is consistent across all scenarios.

Conclusions Current biomarker tests are not estimated to be cost-effective in this setting compared with a 'CT all' strategy. However, should future biomarker tests achieve both a very high sensitivity and high specificity they could become a cost-effective alternative to CT scans for all.

Trial Registration number NCT02210221.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Robust diagnostic accuracy estimates of current biomarker tests used in the model are derived from a large prospective multinational cohort (Collaborative European Neurotrauma Effectiveness Research Mild Traumatic Brain Injury).
⇒ The economic model draws on clinical expertise to ensure that the model accurately captures the complexities of the clinical problem while maintaining transparency.
⇒ Due to the absence of data, sensitivity and specificity estimates of diagnostic strategies were assumed to be identical for detecting neurosurgical and non-neurosurgical lesions.
⇒ Long-term mortality risk was assumed to be the same for patients with and without intracranial lesions and independent of whether treatment was prompt or delayed.
⇒ The model did not consider that patients with negative CT or biomarker results could require hospital admission due to other injuries or illnesses.

INTRODUCTION

Mild traumatic brain injury (mTBI) patients, defined as those presenting with Glasgow Coma Scale (GCS) scores of 13–15 after head injury and clinical or radiological evidence

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of TBI, cost the UK approximately £15 billion annually.[1] Worldwide, over 60 million people are estimated to sustain a TBI each year of which >85% are classified as mild,[2] with a cost to the global economy exceeding US$400 billion.[3] A clinically important proportion of patients with mTBI sustain intracranial haemorrhage, which may require hospital observation and/or further follow-up and, in a small subset of cases, may be life-threatening and require neurosurgical and/or neurocritical care intervention. Current practice is to perform a CT to detect such injuries, which comes with a cost and radiation burden as well as increasing the time spent in the emergency department (ED) by the patients. For head injury patients with a GCS 13–15, the CT scan will reveal intracranial injury in 2%–8% of patients depending on the imaging clinical decision rule used.[4] Most patients with an intracranial injury identified on CT scan are admitted to hospital; however, only a quarter require active treatment, consequently resulting in a low therapeutic yield from imaging this population, apart from the value of observation and potentially in some settings a higher priority for follow-up.[5]

The potential development of blood biomarker tests with high sensitivity has raised the possibility that referrals for CT scans in mTBI patients who are at lower risk of subsequent deterioration could be reduced without endangering many patients, thereby lessening the workload of the ED caused by a long waitlist of CT scans.[6 7] There are a number of candidate biomarkers which are elevated after TBI and show promise in acting as a screening tool to change the pretest probability of an intracranial injury, potentially facilitating a reduction in radiation exposure while avoiding missing clinically important lesions. The most commonly studied blood biomarkers are proteomic and include those released from the astroglial cells (S100 calcium binding protein B (S100B) and glial fibrillar acidic protein (GFAP)); neurons (neuron-specific enolase (NSE), ubiquitin C-terminal hydrolase L1 (UCH-L1)); axons (neurofilament light (NFL), neurofilament heavy) and dendrites (Tau).[8] In particular S100B, and the combination of GFAP and UCH-L1, have gained regulatory approval in specific jurisdictions for this purpose and are integrated into some clinical guidelines.[9–11] However, even a high sensitivity biomarker could miss clinically important intracranial lesions in mTBI that would be detected by CT testing. Uptake into clinical practice has been slow indicating a need for more evidence of safe and cost effective implementation as identified in the recent National Institute for Health and Care Excellence (NICE) head injury guideline evidence review.[12] In the UK, the clinical and health economic benefits of using biomarkers for selecting patients for CT have not been validated; in particular in conjunction with NICE guidelines which have a higher specificity when compared with other TBI CT Clinical Decision Support Tools.[4]

Current NICE guidelines[12] recommend CT testing for all patients with suspected clinically significant intracranial injuries according to the clinical decision rule; a 'CT all' strategy, based on cost-effectiveness evidence indicating that benefits of detecting additional cases of intracranial injury outweigh the additional costs and potential radiation harms incurred by CT scans. We therefore aimed to evaluate the potential cost-effectiveness of highly sensitive blood biomarker tests for triaging patients with mTBI for neuroimaging.

METHODS

We developed a de novo economic model using Microsoft Excel to explore the cost-effectiveness of diagnostic strategies in patients with mTBI who have been identified as needing a CT brain scan using UK NICE Guidelines. The interventions considered were 'CT all' (standard practice) and blood biomarkers that would be used initially with only patients with a positive biomarker receiving a CT scan. Cost-effectiveness was measured as the incremental cost per quality-adjusted life-year (QALY) gained by each strategy compared with the next most effective alternative on the efficiency frontier (ie, non-dominated or non-extendedly dominated alternative). The economic analysis was conducted from the perspective of National Health Service (NHS) and Personal Social Services over a 44-year (lifetime) horizon. Unit costs were valued at a 2023/2024 price year, including uplifting of older cost estimates using inflation indices,[13] where necessary. All health outcomes and costs were discounted at a rate of 3.5% per annum as recommended by NICE.[14]

Model structure and assumptions

The diagnostic pathways in the model were informed by current clinical practice as per the NICE guideline and evidence review as to how blood biomarkers could inform the decision to carry out a CT brain scan.[10] The structure of the model is shown in figure 1. The model comprises a decision tree which models the first 6-month period using the estimated sensitivity and specificity for each test, followed by a long-term model estimating expected lifetime health outcomes and costs based on a patient's underlying health condition which is dependent on whether treatment was prompt or delayed as a result of diagnostic accuracy of the testing strategy. Three underlying health conditions are considered for the patient with mTBI: intracranial lesions which require neurosurgery, intracranial lesions which do not require neurosurgery and no intracranial lesions.

The decision tree estimates test results based on the diagnostic accuracy of each testing strategy. Patients with positive test results (true (TPs) or false positives (FPs)) are referred for a CT brain scan to confirm the diagnosis, followed by appropriate prompt treatment for specific intracranial lesions or discharge if no intracranial lesions are found. Patients with negative test results (true negatives (TNs) or false negatives (FNs)) are not referred for any test and discharged immediately. Patients with FN results are assumed to return to the ED with late symptoms (eg, deterioration), eventually leading to correct

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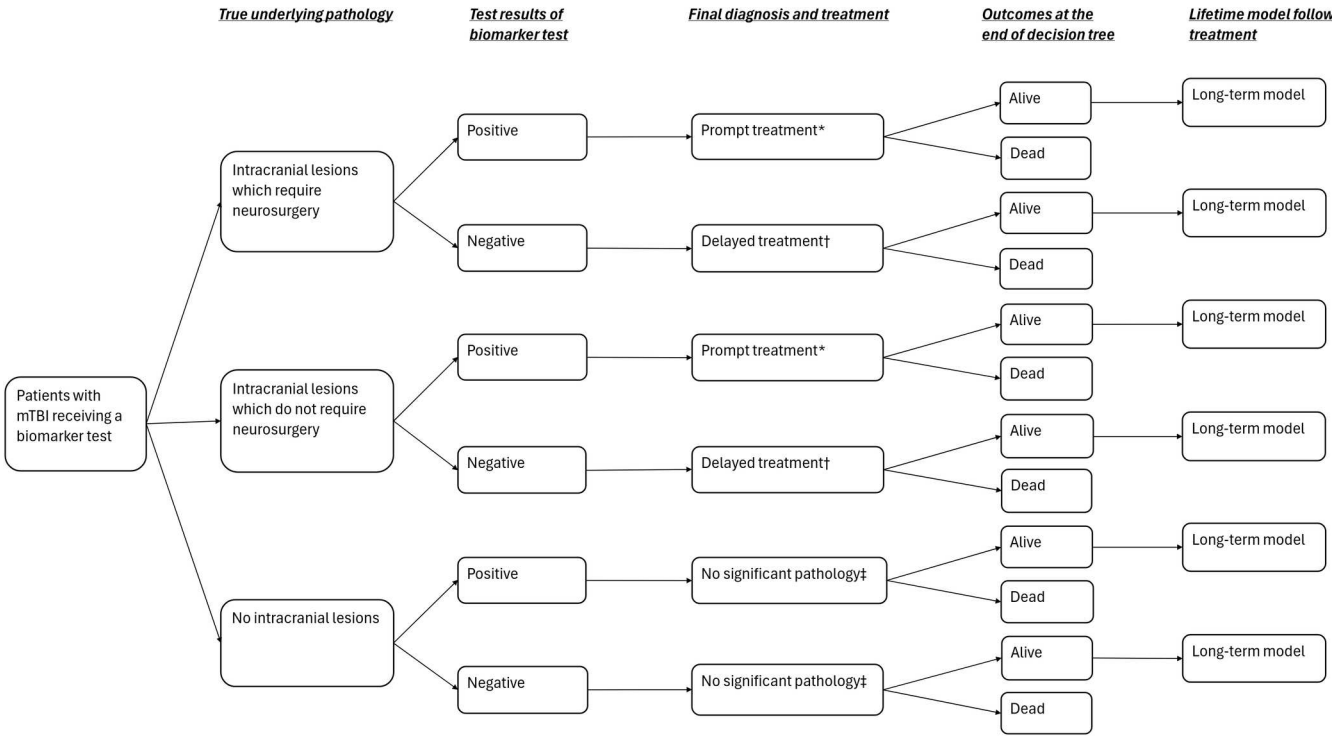


Figure 1 General model structure. *Patients with positive results are assumed to receive a CT scan to confirm the diagnosis at the same visit. †Patients with delayed treatment are assumed to receive the correct diagnosis via CT scan at a later visit. ‡Assumed immediate discharge with no further follow-up. mTBI, mild TBI; TBI, traumatic brain injury.

diagnosis via CT scans and delayed treatment. Death within 6 months depends on (1) the underlying health condition, (2) whether prompt or delayed treatment was provided and (3) age-matched and sex-matched general population mortality in England. Patients alive at the end of first 6 months enter the long-term model which is composed of two mutually exclusive and exhaustive health states: alive and dead. The expected long-term survival of each patient group was modelled by applying a constant relative risk to the estimated age-matched and sex-matched general population mortality risk in England. The utility of patients was based on Glasgow Outcomes Score (GOS) (declining as a patient ages in accordance with Hernández Alava *et al*[15]). Life expectancy and utility were combined to allow an estimate of the QALYs conditional on prompt or delayed treatment and on neurosurgical or non-neurosurgical lesion. The cycle length of the long-term model is 12 months, and half-cycle correction was employed in both short- and long-term models.

Evidence used to inform the model parameters

In the base case model, six groups of parameters are included: patient characteristics, disease prevalence, diagnostic accuracy, mortality risks (short-term and long-term), health-related quality of life and resource use and costs.

Patient characteristics

On model entry, patients are assumed to have a mean age of 52 years and with 34% being female, as reported by Whitehouse *et al*.[16] This represents a subset of patients (n=1589) from the Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI, https://www.center-TBI.eu) core dataset (n=4509) selected for having sustained a mTBI and had blood biomarkers measured within 24 hours of injury. CENTER-TBI is a prospective observational longitudinal cohort study on patients of all severities of TBI, presenting between 19 December 2014 and 17 December 2017, conducted at 65 sites centres across 18 countries in Europe and Israel (RRID/SCR_017004, Core Data V.3.0, EC Grant 602150, https://clinicaltrials.gov/ct2/show/NCT02210221).[17 18] Institutional affiliations of CENTER-TBI collaborators are provided in the online supplemental file 1 titled 'Collaborators' Institutional List'.

Prevalence

The prevalence of lesions in the mTBI patients in the model was estimated from a prospective, multicentre cohort study of 4557 patients in the Netherlands by Foks *et al*.[4] In the study, 3742 patients underwent CT scans, of whom 10.26% had an intracranial traumatic finding on CT and 1.97% had a potential neurosurgical lesion where neurosurgery and/or life-threatening deterioration could occur. In the model, 1.97% of patients are assumed to have lesions requiring neurosurgical treatment and 8.29% to have non-neurosurgical lesions (ie, 10.26%–1.97%).

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Diagnostic accuracy

Sensitivity and specificity were estimated from an analysis of the biomarker data from the CENTER-TBI core dataset.[17] For this analysis, patients aged >16 years with GCS 13–15 who had up to 6 blood-based biomarkers measured within 24 hours of injury were selected (N=1889). These biomarkers are S100B, NSE, GFAP, TAU, UCH-L1 and NFL. S100B and NSE were measured with a clinical-use automated system, using an electrochemiluminescence 149 immunoassay kit (ECLIA) (Elecsys S100B and Elecsys NSE assays) run on the e602 module of Cobas 8000 modular 150 analyser (Roche Diagnostics, Mannheim, Germany) at the University of Pecs (Pecs, Hungary).[19] GFAP, UCH-L1, NFL and t-tau were analysed with an ultrasensitive immunoassay using digital array technology (Single Molecule Arrays, SiMoA)-based Human Neurology 4-Plex B assay (N4PB) run on the SR-X benchtop assay platform (Quanterix, Lexington, Massachusetts, USA) at the University of Florida (Gainesville, Florida).[19]

To explore the effect of variation in threshold on decision-making, we tested the blood biomarkers at different diagnostic thresholds. More specifically, we calculated specificity (with 95% CIs) at biomarker threshold that resulted in varying sensitivity for detecting any intracranial lesion or depressed skull fracture (≥90%, ≥95%, ≥99%; online supplemental tables S1–S3). Where the exact sensitivity values could not be obtained the first available sensitivity value greater than the chosen value was used. The analyses were performed in R V.3.5.3. In the base case, all biomarker tests were assumed to have a sensitivity of ≥95% (with varying specificity ranging from 8% to 42%, as described in online supplemental table S2), while the CT scan was assumed to have perfect sensitivity and specificity for neurosurgically important lesions. Scenario analyses explored alternative assumptions that all biomarker tests had sensitivities of ≥90% and ≥99%, with corresponding specificities presented in online supplemental tables S1 and S3.

Biomarker concentrations are dynamic and change over time according to their half-life, meaning that diagnostic accuracy may also be time-dependent.[8] Therefore, the diagnostic accuracies of blood biomarker tests were explored in the subgroup of patients whose biomarker samples were taken within 6 hours of ED arrival. This subgroup included 531 patients, of whom 205 (38.6%) were female, with a median age of 49 years (IQR: 31.5 to 65.0) and a median time of taking samples of 3.8 hours (IQR: 3.0 to 4.8). Three additional scenario analyses were conducted to explore the impact of this subgroup data at varying sensitivities of ≥90%, ≥95% and ≥99% (online supplemental tables S4–S6) using the same rule as for the main dataset. As summarised in online supplemental tables S4–S6, the diagnostic accuracy and biomarkers thresholds differ in the subgroup analysis compared with those observed in the whole dataset.

Mortality risks

Patients with neurosurgical lesions were assumed to have a 9.33% probability of death in the initial 6-month period with prompt treatment and increasing to 20.34% probability with delayed treatment. This was informed by the clinical expert input, based on halving the values reported by Grieve *et al*[20] which reported values for 'early' transfer group and for 'no or late' transfer group. The mortality values reported by Grieve *et al* were not considered directly applicable to our model as the study included a higher risk group of patients with moderate and severe as well as mild TBI and all patients were treated in adult critical care units.

For the remaining groups in the short-term model (patients with non-neurosurgical lesions and those with no intracranial lesions) and for all patient groups in the long-term model, a relative risk of 1.83 was applied to the general population mortality risk in England, derived from the ONS life tables for England (2017–2019).[21] The expected probability of death was estimated to be 0.30% (1.83* 0.0016, where 0.0016 represents the 6-month mortality risk of a 52-year-old patient in England). The relative risk of 1.83 was taken from McMillan *et al*,[22] which is a prospective case control and record linkage study estimating the 15-year survival following mild head injury in adults. The study reported an annual mortality of adults admitted to hospital with mild head injury as being 2.45% per year (95% CI 2.32% to 2.58%) compared with the community control mortality of 1.33% per year (95% CI 1.23% to 1.44%), resulting in a relative risk of 1.83 (95% CI 1.66 to 2.00). As McMillan data were based on the 15-year follow-up, a scenario explored the impact of assuming that beyond this period, individuals return to the same mortality risk as the age-matched and sex-matched general population. Another scenario analysis tested the impact of assuming a relative risk of 1, equivalent to the general population mortality, in both short-term model (non-neurosurgical and no intracranial lesions) and long-term model (all groups).

Health-related quality of life

The utilities for patients with intracranial lesions, with and without delayed treatment, were estimated as weighted averages based on the distributions of GOS categories from Holmes *et al*[23] and the GOS category-specific utilities from Fuller *et al*[24] (see table 1). Based on clinical expert input, it was recognised that the non-neurosurgical group in Holmes *et al* included some of the Foks *et al*[4] neurosurgical cohort at risk of life-threatening deterioration but not amenable to neurosurgery, hence the same utility was assumed for patients with non-neurosurgical lesions regardless of treatment timing. For patients with no intracranial lesions, an initial utility value of 0.86 was assumed, which is the weighted utility of the modelled population (age=52 years and female proportion=34%) based on the general population utility in the UK reported by Hernández Alava *et al*.[15] Subsequent utility values were age-adjusted and sex-adjusted using Hernández Alava

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Table 1 Weighted utilities and costs across GOS categories in patient groups with intracranial lesions

GOS score	Utility (Ward Fuller *et al*)[24]	Costs (Williams *et al*)[27]		Distributions of GOS categories in different groups (Holmes *et al*)[23]			
		First year*	Subsequent years*	Neurosurgical lesion: prompt treatment	Neurosurgical lesion: delayed treatment	Non-neurosurgical lesion: prompt treatment	Non-neurosurgical lesion: delayed treatment
1	0	£50 055	£16 321	0.038	0.143	0.009	0.054
2	−0.172	£50 055	£16 321	0.027	0.099	0.000	0.026
3	0.381	£37 696	£9205	0.032	0.120	0.068	0.276
4	0.671	£25 337	£2089	0.093	0.068	0.111	0.082
5	0.888	£354	£32	0.810	0.570	0.812	0.559
Weighted mean utility†				0.79	0.58	0.82	0.82‡
Weighted mean costs–first year				£7103	£18 562	£6114	£6114§
Weighted mean costs–subsequent years (annual costs)				£1575	£5214	£1030	£1030¶
Total lifetime discounted QALYs				8.93	6.57	9.30	9.30
Total lifetime discounted costs				£31 599	£99 655	£22 131	£22 131

*Costs uplifted from 2017/2018 to 2023/2024 price year.
†Applied at the start of the long-term model.
‡The value predicted from the product of the distribution of patients among GOS scores and the utility for each GOS score generated a value of 0.65. However, a value of 0.82 was used assuming that the utility value for delayed treatment was the same as for prompt treatment in patients with non-neurosurgical lesions.
§The value predicted from the product of the distribution of patients among GOS scores and the cost for each GOS score generated a value of £16 684. However, a value of £6114 was used assuming that the cost for delayed treatment was the same as for prompt treatment in patients with non-neurosurgical lesions.
¶The value predicted from the product of the distribution of patients among GOS scores and the cost for each GOS score generated a value of £4035. However, a value of £1030 was used assuming that the cost for delayed treatment was the same as for prompt treatment in patients with non-neurosurgical lesions.
GOS, Glasgow Outcome Scores; QALY, quality-adjusted life-year.

et al. The ranking of average utility values with severity was preserved in the probabilistic sensitivity analysis, by sampling decrements from an anchor state. Thus, the average utility value for a non-neurosurgical lesion is always lower than for no lesion, the average utility associated with delayed treatment of a neurosurgical lesion is always lower than for prompt treatment of a neurosurgical lesion, and the average utility associated with prompt treatment of a neurosurgical lesion is always lower than for non-neurosurgical lesion (online supplemental table S7).

QALY loss due to radiation-related cancers

The economic model accounts for QALY losses associated with radiation-related cancer in patients receiving CT scans. For the modelled population, using estimates from Holmes *et al*,[23] the estimated lifetime cancer risk is 0.01% (calculated as 0.0077 multiplied by age in years$^{-1.076}$) and the corresponding QALY loss is 0.0026 (calculated as 0.0401 multiplied by age in years$^{-1.675}$). The model incorporates QALY losses by multiplying the cancer risk by the associated QALY decrement, discounted over 10 years reflecting the delayed onset of radiation-induced cancer, in line with the assumptions applied in Pandor *et al*.[25]

Resource use and costs

Short-term model

The short-term model includes the costs associated with diagnostic testing strategies (including the initial test and the confirmatory scans), the first and second ED visits, craniotomy and admission to critical care unit and hospital wards, where applicable. The cost of each biomarker test was £30, as provided by the manufacturers, and the costs of ED visits, craniotomy and hospital admissions were taken from NHS Reference Costs 2023/24.[26] Unit cost of first ED visit was assumed to be £503 for patients receiving prompt treatment for neurosurgical or non-neurosurgical lesions (VB05Z—Emergency Medicine, Category 2 Investigation with Category 3 Treatment) and £269 for patients with no intracranial lesions or those receiving delayed treatment (VB08Z—Emergency Medicine, Category 2 Investigation with Category 1 Treatment). It was assumed that only patients with a delayed diagnosis would incur a second time ED visit. The second ED visit was assumed to cost £1180 for neurosurgical lesions (VB01Z—Emergency Medicine, Any Investigation with Category 5 Treatment) and £503 for non-neurosurgical lesions. We have assumed that the costs of CT scans for people with intracranial cranial lesions diagnosed as positive on their first ED visit in the 'CT all' arm are incorporated in the more expensive ED costs. This also applies to the confirmatory CT

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Table 2 Resource use costs by patient groups included in the short-term model

	Proportions of patients requiring resource use	Duration of resource use	Unit cost (per day)	Assumed costs for the model cohort	Source of unit cost (NHS reference costs 2023/2024)[26]
Craniotomy					
Neurosurgical lesions–prompt treatment	25%	N/A	£14 194*	**£3548**	Weighted average cost of very complex intracranial procedures, 19 years and over, with CC score 0–12+, non-elective short stay (codes AA50A-AA50C)
Neurosurgical lesions–delayed treatment	20%	N/A		**£2839**	
Critical care					
Neurosurgical lesions–prompt treatment	50%	4 days	£2406	**£4811**	Weighted average cost of adult critical care, 0–6+organs supported (codes XC01Z-XC07Z)
Neurosurgical lesions–delayed treatment	70%	5 days		**£8420**	
Hospital ward admissions					
Neurosurgical lesions–prompt treatment (patients receiving critical care)	50%	5 days	£873	**£6111**	Weighted average cost of muscular, balance, cranial or peripheral nerve disorders, epilepsy or head injury, with CC score 15+, non-elective short stay (code AA26C)
Neurosurgical lesions–prompt treatment (patients not receiving critical care)	50%	9 days			
Neurosurgical lesions–delayed treatment (patients receiving critical care)	70%	7 days	£604	**£5134**	Weighted average cost of muscular, balance, cranial or peripheral nerve disorders, epilepsy or head injury, with CC score 0–14, non-elective short stay (codes AA26D-AA26H)
Neurosurgical lesions–delayed treatment (patients not receiving critical care)	30%	12 days			

*One-off costs.
CC, complications and comorbidities; N/A, not applicable; NHS, National Health Service.

scans in the biomarker arm either at first ED attendance (TPs) or for those who have returned for a second ED visit after an FN diagnosis. Contrastingly, for patients who are diagnosed with no intracranial lesions on their initial ED visit, the costs of CT scans are added to the 'CT all' arm (TNs), but not to the biomarker arm (TNs or FNs).

Based on the clinical input and Foks *et al*,[4] assumptions were made for the proportions of patients receiving prompt or delayed treatment for neurosurgical lesions who would require craniotomy and admission to critical care and hospital wards. Table 2 summaries the detailed calculations for the costs associated with hospital admissions and treatment. Overall, in the short term, patients with neurosurgical lesions receiving prompt treatment (TPs) are expected to incur resource use costs of £14 471 compared with £16 393 for those receiving delayed treatment (FNs).

Long-term model

As for the calculations of utility values, the long-term costs were estimated as weighted averages, based on the distributions of GOS categories from Holmes *et al*[23] and the GOS category-specific costs by Williams *et al*.[27] Weighted costs are summarised in table 1. Williams *et al* reported the costs separately for the first and subsequent years, and these costs were uplifted from 2017 to 2018 prices. Based on clinical advice, the same cost was assumed for patients with non-neurosurgical lesions, irrespective of treatment timing. Patients with no intracranial lesions were assumed to incur no long-term costs. For the lifetime costs of radiation-induced cancer, a one-off cost of £43 153 was applied in the model, taken from Pandor *et al* which included the costs of glioma treatment (£23 651) and palliative care (£3087). The costs were uplifted from 2003 to 2004 prices.

Model evaluation methods

Estimates of mean life-years gained, QALYs and costs for the base case were estimated using both deterministic and probabilistic versions of the model. The incremental cost-effectiveness of biomarker tests versus 'CT all' was evaluated using fully incremental analysis. Probabilistic

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sensitivity analysis was conducted using Monte Carlo sampling across 1000 iterations to generate distributions of expected health outcomes and costs for each diagnostic strategy. Uncertainty around diagnostic accuracy was handled using distributions of sensitivity and specificity estimated via bootstrapping at specified sensitivity thresholds. A summary of the distributions applied to each model parameter is presented in online supplemental table S7. One-way sensitivity analyses (OWSA) were conducted by varying each parameter across its 95% CI where available, or within a 10% range of its base case value where uncertainty estimates were unavailable, while holding all other parameters constant. All model parameters were included in OWSA, with the exception of the sensitivity of the chosen biomarker test, the diagnostic accuracy of CT, model cycle length and discount rate which were not varied. Among the testing strategies, the OWSA compared the two strategies that generated the highest incremental net monetary benefit (INMB) in the base case analysis. Scenario analyses were also conducted to explore the impact of alternative assumptions: (1) assuming 90% and 99% sensitivities of biomarker tests, (2) stopping the relative risk of 1.83 at 15 years, (3) assuming a relative risk of 1 for non-neurosurgical and no intracranial lesions in the short-term model and for all groups in the long-term model, (4) the age and proportion of female based on the data from Marincowitz *et al* (58.2 years and 33% female) and (5) diagnostic accuracies of biomarker tests based on the data from the subgroup of patients whose biomarker samples were collected within 6 hours of ED arrival (assuming ≥90%, ≥95% and ≥99% sensitivities of biomarker tests).

Model verification and validation

The executable model was verified by one modeller. Model inputs were validated against their original data sources. Outputs were assessed by comparing point estimates with expected values and probabilistic results with deterministic values. Extreme value testing was also performed. Any discrepancies identified were systematically investigated and the model amended as required. Where appropriate, parts of the model were checked by a second modeller.

RESULTS

Table 3 shows the deterministic base case results. Both deterministic and probabilistic results are similar, suggesting that all biomarker tests are dominated by 'CT all', which has the lowest costs and highest health benefits

Table 3 Base-case cost-effectiveness results

Diagnostic strategy	Discounted LYGs	Discounted QALYs*	Discounted costs	ICER
Deterministic results				
'CT all'	17.4778	10.1309	£2876	–
GFAP	17.4761	10.1281	£2905	Dominated
S100B	17.4761	10.1282	£2933	Dominated
NFL	17.4760	10.1280	£2930	Dominated
UCHL1	17.4760	10.1280	£2932	Dominated
Tau	17.4761	10.1281	£2935	Dominated
NSE	17.4760	10.1280	£2948	Dominated
Probabilistic results				
'CT all'	17.6508 (16.8812–18.4214)	10.2092 (9.8778–10.5341)	£2902 (£2535–£3307)	–
GFAP	17.6490 (16.8793–18.4199)	10.2063 (9.8757–10.5319)	£2932 (£2547–£3340)	Dominated (Dominated to Dominated)
S100B	17.6491 (16.8790–18.4199)	10.2065 (9.8752–10.5322)	£2960 (£2575–£3364)	Dominated (Dominated to Dominated)
NFL	17.6490 (16.8795–18.4197)	10.2063 (9.8756–10.5316)	£2957 (£2576–£3363)	Dominated (Dominated to Dominated)
UCHL1	17.6490 (16.8794–18.4200)	10.2063 (9.8757–10.5320)	£2959 (£2577–£3366)	Dominated (Dominated to Dominated)
Tau	17.6490 (16.8767–18.4197)	10.2063 (9.8751–10.5320)	£2961 (£2583–£3359)	Dominated (Dominated to Dominated)
NSE	17.6490 (16.8792–18.4195)	10.2062 (9.8753–10.5318)	£2975 (£2596–£3384)	Dominated (Dominated to Dominated)

*Values differ only at eighth decimal place.
ICER, incremental cost-effectiveness ratio; LYG, life-years gained; NFL, neurofilament light; NSE, neuron-specific enolase; QALY, quality-adjusted life-year; UCHL1, ubiquitin C-terminal hydrolase L1.

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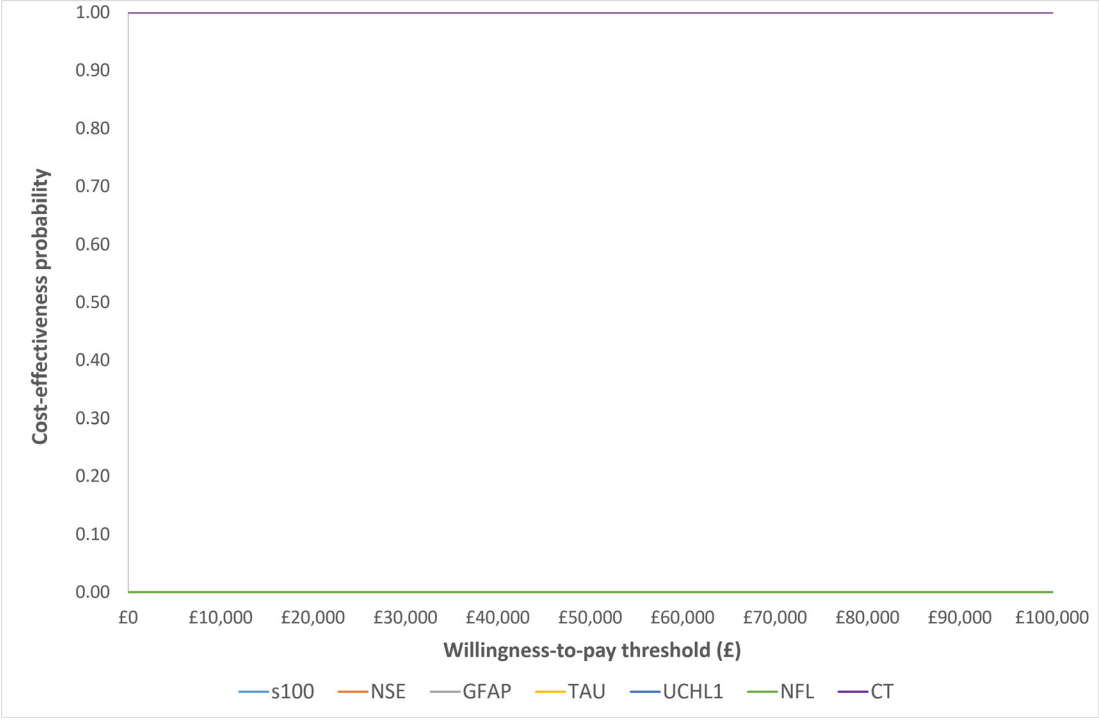


Figure 2 Cost-effectiveness acceptability curves for blood biomarker tests and 'CT all'. GFAP, glial fibrillar acidic protein; NFL, neurofilament light; NSE, neuron-specific enolase; UCHL1, ubiquitin C-terminal hydrolase L1.

among all diagnostic strategies. This finding is consistent across all scenario analyses (online supplemental table S8). The cost-effectiveness acceptability curve, as shown in figure 2, indicates that 'CT all' has a 100% probability of being cost-effective at the willingness-to-pay threshold of £30 000 per QALY gained, while all other biomarker tests have probabilities of zero; this conclusion held for all willingness-to-pay thresholds. The INMB of GFAP compared with 'CT all' was −£114 assuming a threshold of £30 000 per QALY gained; this means that if GFAP were used instead of 'CT all' the NHS would lose £114 per person having translated health losses into money and combining this with additional costs. The OWSA identified the total lifetime discounted QALYs for patients with neurosurgical lesions in the promptly treated group as the parameter with the greatest influence on the INMB. The relative impact of the ten most influential parameters is shown in the tornado diagram (online supplemental figure S1), none of these made the use of GFAP cost-effective.

DISCUSSION

Our economic model suggests current biomarker strategies are expected to be more costly and to generate fewer QALYs than 'CT all' resulting in all biomarker tests being dominated in patients with mTBI who have been identified as needing a CT brain scan using UK NICE Guidelines. The reasons for this result are: (1) biomarker strategies have lower sensitivity than the 'CT all' resulting in more FNs with subsequent delayed treatment which are associated with higher short-term mortality risks and lower long-term utility, both of which produce fewer QALYs, (2) patients requiring a confirmatory CT scan (TP or FP) have both the costs of the biomarker test and the CT scan and (3) the costs of ED attendance increase for FNs who also have estimated longer lengths of hospital stay. However, future biomarkers could be cost-effective and we undertook threshold analyses to determine indicative diagnostic accuracies at which 'CT all' would have a cost per QALY of approximately £30 000 compared with the biomarkers. These diagnostic accuracies were 99% sensitivity with 43% specificity and 97% sensitivity with 80% specificity. At these values, the use of biomarkers may be seen as cost-effective under current NICE guidance[14] and proposed changes to the NICE cost-effectiveness thresholds.[28]

Our findings are different from recent published studies which show cost savings for biomarker strategies when compared with CT. Most of these are costing studies in the short term[29 30] and do not include the costs (or outcomes) in the long term, which is a significant limitation. A recent cost-effectiveness analysis in the French healthcare setting[11] suggested modest cost savings; however, the finding was based on different assumptions from our model. Differences in the previous analysis included (1) employing a much lower prevalence of neurosurgical lesions, (2) using higher sensitivity and specificity estimates of the biomarker strategies, (3) not

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incorporating a high short-term risk of mortality for those with neurosurgical lesions and (4) having more similar GOS profiles between early and delayed treatment of neurosurgical lesions.

Strengths and limitations

Our decision-analytic modelling is based on robust estimates of the diagnostic accuracy of biomarker strategies derived from a large dataset (CENTER-TBI) and draws on clinical expertise to ensure that the model adequately reflects the complexities of the clinical problem while retaining transparency. The estimated model outcomes are based on the lifetime horizon. The CENTER-TBI cohort was used in this analysis as it is the largest available study with detailed CT metrics, biomarkers and outcomes in this population. Age and sex parameters were obtained from Whitehouse *et al*,[16] which used a subset of the CENTER-TBI core dataset. This is the same dataset used to estimate the diagnostic accuracy of the biomarker tests in our analysis, thereby preserving internal validity. We note that the age and sex parameters used in the economic model were broadly representative of the CENTER-TBI core dataset,[17] the CENTER-TBI registry data,[31] and UK data reported by Marincowitz *et al*.[32] We conducted a scenario analysis using the age and sex distributions reported by Marincowitz *et al*, which demonstrated minimal impact on the model results. The prevalence data used in the model were informed by Foks *et al*,[4] which reported a lower CT positivity rate (10.2%) compared with Whitehouse *et al* (45.6%), CENTER-TBI core dataset (57.8%) and registry data (31.10%). This difference is explained by the CENTER-TBI core study having recruited higher rates of patients admitted after TBI after a positive scan (as those with a negative CT scan ready for ED discharge are more reluctant to enrol in studies requiring new blood tests). As our aim was to evaluate the cost impact of biomarkers based on the real-world CT positivity rates we therefore used data from Foks *et al*.[4] To our knowledge, there is no evidence that variation in CT positivity affects the diagnostic accuracy of the biomarkers.[33]

As with all diagnostic modelling studies, our analysis involves some simplifications. We assumed that all patients who tested negative on CT scan or biomarker would be discharged from the hospital. While it is likely that some patients who tested negative on CT scan will need admission (eg, due to intoxication, patients living alone, patients with other illnesses or injuries requiring inpatient care such as sepsis, pneumonia, stroke or patients that were FNs and would require treatment), we did not capture this additional detail in our model. In addition, all patients with FN results were assumed to reattend the ED incurring costs, with no deaths occurring before reattendance. Another limitation relates to uncertainties in the model inputs across patient groups. As the sensitivity and specificity estimates were applied to all lesions, the lesions requiring neurosurgical treatment were assumed to be detected (or missed) at the same rate as other non-neurosurgical lesions. Additionally, due to the limited data, the long-term mortality risk was assumed to be equivalent across all patient groups based on the clinical input. The availability of specific diagnostic accuracy or long-term mortality data for neurosurgical lesions would allow more accurate estimation of model outcomes. In the analysed study (CENTER-TBI), the median time of biomarker sampling was 11.8 hours (IQR 5.4 to 18.6 hours) which is notably higher than the median time to CT scan (2 hours (IQR 1.4 to 3.6 hours)). This does not accurately reflect the clinical scenario where the results of blood biomarkers are available to be used to decide whether a CT is needed. Blood biomarker levels after TBI are dynamic and are affected by the time after injury at which sampling occurs,[19] hence diagnostic performance of biomarkers sampled prior to a CT scan may differ from those we have used from CENTER TBI. Restricting the analysis to patients in whom biomarkers were sampled before a CT would be optimal for informing CT decision making and consistent with manufacturers' recommendations. However, the subgroup meeting this requirement comprised only 6.4% of the overall cohort, decreasing to 4.3% within 4 hours and 3.5% within 2 hours prior to CT. Using this subgroup would substantially reduce the sample size and increase the uncertainty in the estimated results hence the selection of the 'sampled within 6 hours of ED arrival' subgroup. In some cases, a second biomarker test may be required because biomarkers are not always in the detectable range immediately after brain injury. This assumption was not included in the model and incorporating it would increase the incremental costs of biomarkers and make the cost-effectiveness of tests less favourable. Perfect diagnostic accuracy of CT was assumed to reduce the model complexity in this exploratory analysis. Given that CT is included in both arms, any impact on cost-effectiveness is likely limited. Additionally, the value of biomarker tests is not solely confined to prediction of TBI visible on CT scans and may confirm additional prognostic value.[8] Finally, the results produced assume a UK setting; these results may not be generalisable to other jurisdictions.

CONCLUSIONS

This model-based economic evaluation suggests that in patients who have been identified as needing a CT brain scan using UK NICE Guidelines using biomarkers to decide who does get a CT scan is expected to be more costly and less effective compared with the strategy of 'CT all' with indications in the clinical decisions rule—the current NICE Head Injury Guideline recommendation in the UK. However, biomarkers that have very high sensitivity and concurrently high specificity have been estimated to be cost-effective. Further research is needed to reduce the uncertainty around the long-term mortality risks for each underlying health condition.

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