Are there patients with an intracapsular fracture of the hip who may benefit from an uncemented hemiarthroplasty?

A CAUSAL FOREST ANALYSIS OF THE WHITE 5 RANDOMIZED CLINICAL TRIAL

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Aims
Cemented hemiarthroplasty is an effective form of treatment for most patients with an intracapsular fracture of the hip. However, it remains unclear whether there are subgroups of patients who may benefit from the alternative operation of a modern uncemented hemiarthroplasty – the aim of this study was to investigate this issue. Knowledge about the heterogeneity of treatment effects is important for surgeons in order to target operations towards specific subgroups who would benefit the most.

Methods
We used causal forest analysis to compare subgroup- and individual-level treatment effects between cemented and modern uncemented hemiarthroplasty in patients aged > 60 years with an intracapsular fracture of the hip, using data from the World Hip Trauma Evaluation 5 (WHiTE 5) multicentre randomized clinical trial. EuroQol five-dimension index scores were used to measure health-related quality of life at one, four, and 12 months postoperatively.

Results
Our analysis revealed a complex landscape of responses to the use of a cemented hemiarthroplasty in the 12 months after surgery. There was heterogeneity of effects with regard to baseline characteristics, including age, pre-injury health status, and lifestyle factors such as alcohol consumption. This heterogeneity was greater at the one-month mark than at subsequent follow-up timepoints, with particular regard to subgroups based on age. However, for all subgroups, the effect estimates for quality of life lay within the confidence intervals derived from the analysis of all patients.

Conclusion
The use of a cemented hemiarthroplasty is expected to increase health-related quality of life compared with modern uncemented hemiarthroplasty for all subgroups of patients aged > 60 years with a displaced intracapsular fracture of the hip.

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Introduction
Fractures of the hip in elderly patients compromise health-related quality of life and impose a considerable economic strain on healthcare systems worldwide.[1-3] The most common treatment for a displaced intracapsular fracture is a hemiarthroplasty. A meta-analysis of randomized controlled trials (RCTs) published in 2010 indicated that fixation with bone cement leads to less pain and improved mobility postoperatively, compared with early versions of uncemented 'press-fit' implants.[4] However, the use of cement has also been linked with adverse factors such as perioperative hypotension, occasional cardiovascular collapse, and death.[5]

The World Hip Trauma Evaluation 5 (WHiTE 5) RCT found that cemented hemiarthroplasty resulted in a modest but statistically significantly better quality of life, a lower risk of periprosthetic fracture, and a lower cost compared with a

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Table I. Baseline characteristics.

Covariate	Overall	Uncemented	Cemented	p-value
Total, n	956	484	472	
Median age, yrs (IQR)	86.0 (81.0 to 90.0)	86.0 (81.0 to 89.0)	86.0 (80.0 to 90.0)	0.990*
Median EQ-5D index (IQR)	0.64 (0.38 to 0.80)	0.63 (0.38 to 0.79)	0.65 (0.40 to 0.80)	0.260*
Median EQ-5D VAS (IQR)	60.0 (50.0 to 80.0)	65.0 (50.0 to 80.0)	60.0 (50.0 to 80.0)	0.640*
Type of consent, n (%)				0.104†
Individual consent	494 (51.7)	238 (49.2)	256 (54.2)	
Proxy consent	40 (4.2)	19 (3.9)	21 (4.4)	
Missing	422 (44.1)	227 (46.9)	195 (41.3)	
Sex, n (%)				
Male	651 (68.1)	326 (67.4)	325 (68.9)	0.668†
Female	305 (31.9)	158 (32.6)	147 (31.1)	
Current smoker, n (%)				0.064†
No	80 (8.4)	32 (6.6)	48 (10.2)	
Yes	2 (0.2)	2 (0.4)	0 (0)	
Missing	874 (91.4)	450 (93.0)	424 (89.8)	
Chronic renal failure, n (%)				0.808†
No	80 (8.4)	42 (8.7)	38 (8.1)	
Yes	3 (0.3)	2 (0.4)	1 (0.2)	
Missing	873 (91.3)	440 (90.9)	433 (91.7)	
Diabetes, n (%)				0.882†
No	165 (17.3)	82 (16.9)	83 (17.6)	
Yes	4 (0.4)	3 (0.6)	3 (0.6)	
Missing	787 (82.3)	399 (82.4)	388 (82.2)	
Alcohol consumption, n (%)				0.616†
0 to 7 units/wk	45 (4.7)	20 (4.1)	25 (5.3)	
8 to 14 units/wk	16 (1.7)	9 (1.9)	7 (1.5)	
15 to 21 units/wk	20 (2.1)	8 (1.7)	12 (2.5)	
> 21 units/wk	6 (0.6)	5 (1.0)	1 (0.2)	
Missing	869 (90.9)	442 (91.3)	427 (90.5)	
Residence status before injury, n (%)				0.116†
Own home/sheltered housing	116 (12.1)	59 (12.2)	57 (12.1)	
Residential care	116 (12.1)	69 (14.3)	47 (10.0)	
Nursing care	3 (0.3)	2 (0.4)	1 (0.2)	
Missing	721 (75.4)	354 (73.1)	367 (77.8)	

*Kruskal-Wallis test.
†Chi-squared test.
EQ-5D, EuroQol five-dimension index; IQR, interquartile range; VAS, visual analogue scale.

modern, hydroxyapatite-coated, uncemented hemiarthroplasty, in patients aged > 60 years with an intracapsular fracture of the hip.[6,7] However, whether a cemented hemiarthroplasty may give a better outcome in some patients more than others – thus, whether the treatment effect is heterogeneous – remains unknown. The value of investigating heterogeneous treatment effects to support clinicians and policy-makers has been acknowledged for a long time, but these studies still mainly focus on average treatment effects.[1-3,6,8] The aim of this study was to assess the heterogeneity of treatment effects on the health-related quality of life of cemented versus uncemented hemiarthroplasty for patients aged > 60 years with an intracapsular fracture of the hip, using data from the WHiTE 5 trial.

Methods

WHiTE 5 was a multicentre RCT, the protocol and main results of which have been published,[7,8] and the results have also been reported in the *New England Journal of Medicine* (trial registration number ISRCTN18393176).[6] Briefly, this trial compared cemented with modern uncemented hemiarthroplasty in patients aged > 60 years with an intracapsular fracture of the hip. The primary outcome measure was health-related quality of life, assessed using the EuroQol five-dimension (EQ-5D)[9] index scores at one, four, and 12 months post-randomization. The EQ-5D visual analogue scale (VAS) score was also reported, where participants reported their perceived health status with a grade ranging from 0 (the worst possible health status) to 100 (the best possible health status). A total of 1,225 patients were enrolled, with 876 (71.6%) providing follow-up data at four months. Outcome data were also available at one month (n = 927) and 12 months (n = 876). The demographic spread and baseline characteristics are consistent with patients typically affected by this fracture.[10] The authors found that a cemented hemiarthroplasty resulted in a modest but significantly better quality of life and a lower risk of periprosthetic fracture than an uncemented hemiarthroplasty, at a significantly lower cost.

Statistical analysis. We evaluated the balance of covariates across the treatment arms for the following variables: age group,

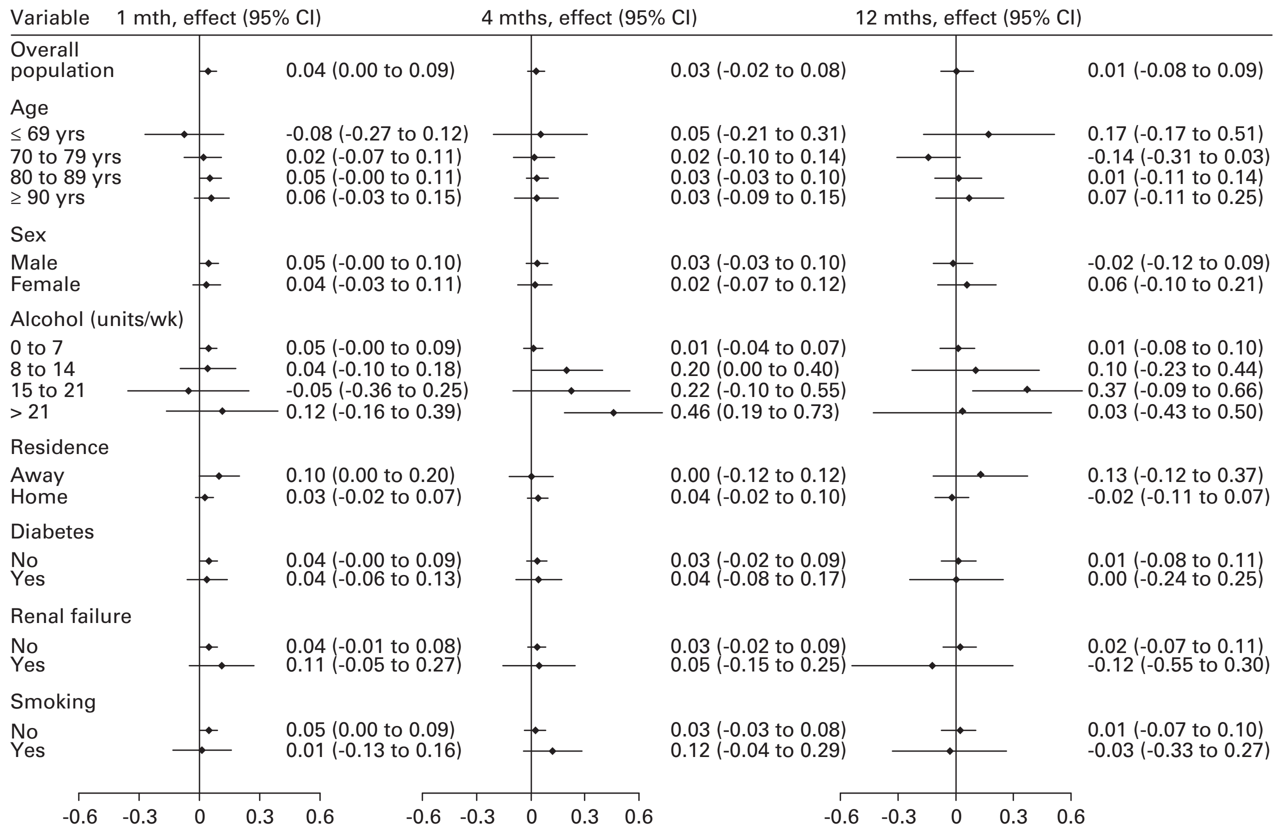

Fig. 1

Graphs showing the conditional treatment effects on Euro-Qol five-dimension health questionnaire (EQ-5D) index scores at a) one, b) four, and c) 12 months for the subgroups. CI, confidence interval; var, variable.

sex, proxy consent as a marker of cognitive impairment, smoking status, chronic renal failure, diabetes, alcohol consumption, residence status before injury, home ownership, residential care status, nursing care status, and EQ-5D index and VAS scores. Specifically, the Student's *t*-test for independent samples was used to analyze differences in means, while the Kruskal-Wallis test assessed differences in medians between treatment arms. The chi-squared test for categorical variables evaluated differences in distributions across treatment arms.

We used the causal forest (CF) algorithm,[11] a machine-learning technique, to estimate patient-level treatment effects and to identify factors which determine the heterogeneity of these effects in relation to the trial intervention. The CF method is a generalization of random forest tailored to the estimation of treatment effects.[12] A random forest comprises an ensemble of decision trees which iteratively split the dataset based on the response variable such that the groups' outcomes are as different as possible until a set stopping criterion is met. This procedure is repeated many times over random subsets of data, which mitigates the risk of 'overfitting' which plagues single decision trees. In CFs, splits are determined based on expected effects rather than outcomes.

The use of random forests has been popular in economics, as well as health and environmental science, due to their robust predictive capabilities and their robustness against potential confounding effects.[13] Comparative studies have demonstrated that random forests can yield similar or superior predictions compared with traditional methods such as ordinary least squares and logistic regression.[14] This advantage stems from the model's flexibility in handling both linear and non-linear relationships and intricate inter-variable interactions, all without the need for predefined model structures. This method is implemented in the generalized random forest R package *grf*.[15] We estimated conditional average treatment effects (CATEs) for our pre-specified subgroups by taking the estimated patient-level treatment effects and plugging them into an augmented inverse propensity weighted estimator of group average treatment effects.[16,17] The Supplementary Material provides additional details about the CF and its implementation in this study.

The heterogeneity of treatment effects was assessed using existing data, informed by relevant literature and clinical judgement.[8] We considered the following pre-specified subgroup variables: sex (male, female); age group (≤ 69, 70 to 79, 80 to 89, and ≥ 90 years) ; age group (≤ 80 and > 90 years); smoking status; chronic renal failure; diabetes; and alcohol consumption. Statistical analysis was implemented using R software v. 4.4.0 (R Foundation for Statistical Computing, Austria). We provide details of the calibration and tuning parameters in the implementation of CF in the Supplementary Material.

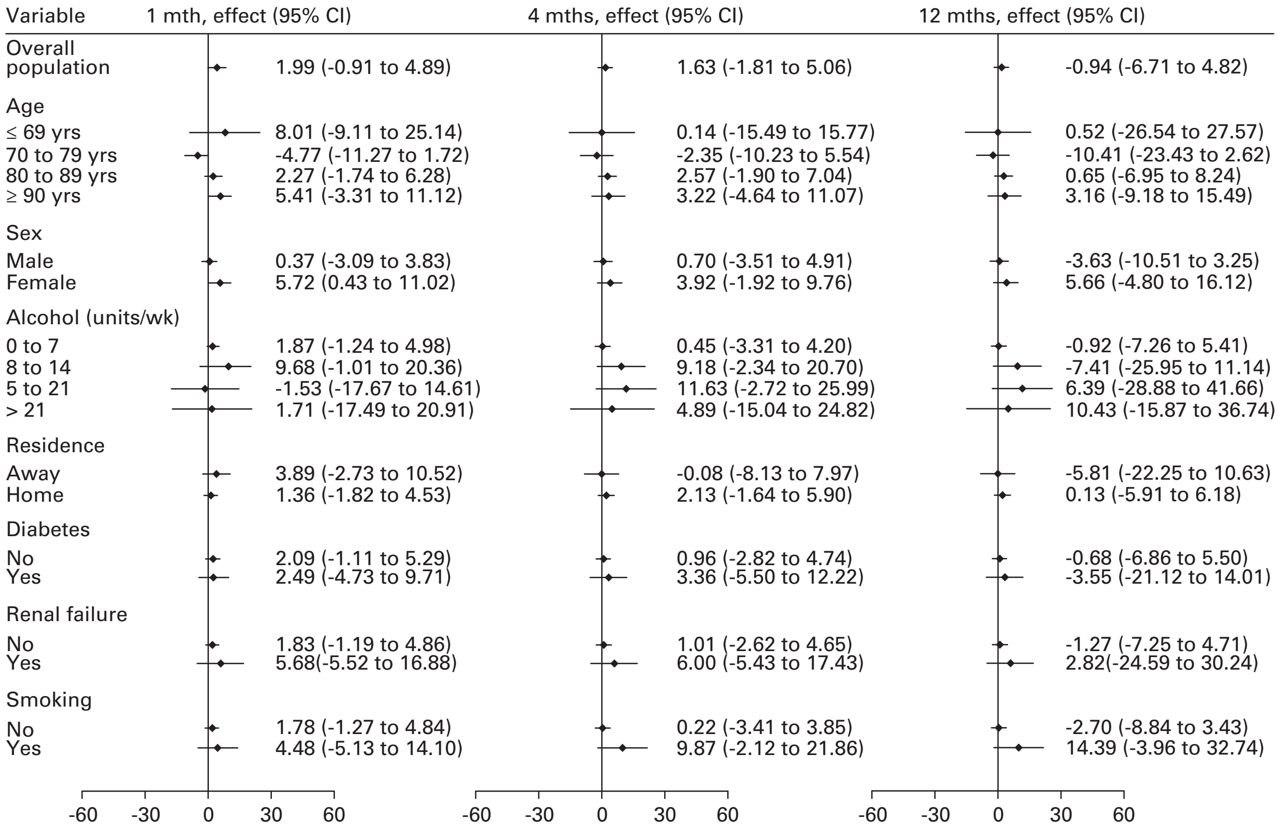

Fig. 2

Graphs showing the conditional treatment effects on Euro-Qol five-dimension health questionnaire (EQ-5D) visual analogue scale at a) one, b) four, and c) 12 months for the subgroups. CI, confidence interval; var, variable.

Results

Table I shows that the baseline characteristics were balanced between patients allocated to cemented versus uncemented hemiarthroplasty. The median age was 86 years (interquartile range (IQR) 9.0). The median pre-injury EQ-5D index score for the uncemented group was 0.64 (IQR 0.42), compared with 0.65 (0.41) for the cemented group (p = 0.260, Kruskal-Wallis test). There was no significant difference in baseline median EQ-5D VAS (p = 0.64, Kruskal-Wallis test), smoking status (p = 0.064), chronic renal failure (p = 0.808), diabetes (p = 0.882), alcohol consumption (p = 0.616), or residence status before injury (p = 0.116, all chi-squared test). Supplementary Tables ii to v show the EQ-5D index and VAS scores and covariates at outcomes at three timepoints (one, four, and 12 months). Covariate balance across treatment arms was achieved at months one and four. At 12 months, there were significant differences between the treatment arms for chronic renal failure and proxy consent (Supplementary Table v).

Supplementary Figure b illustrates the estimated treatment effects for both the EQ-5D index and VAS scores at the three timepoints, ordered by their magnitude. The sample at each timepoint differs due to loss to follow-up, most notably at 12 months. The caterpillar plots suggest some heterogeneity for the VAS scores, while there is less heterogeneity for the EQ-5D index scores. Figures 1 and 2 illustrate the effects for the subgroups and over time. Generally, the estimates suggest weak variation in effects, with the confidence intervals (CIs) of the estimates including the overall effect in most cases. Notably, there is little evidence of differences in effects among sex, diabetes, and smoking subgroups at each timepoint. While there is some evidence of heterogeneity in the age and alcohol consumption subgroups, it varies by timepoint and outcome. Multiple testing concerns and the absence of clear relationships suggest that caution is warranted in viewing this as representing truly heterogeneous effects. Treatment effects on the EQ-5D index for the age subgroups at one month suggest a differential response to treatment in the short term, with older subgroups (≥ 90 years) deriving greater benefit from cemented hemiarthroplasty compared with younger subgroups (80 to 90 years, 70 to 79 years, and ≤ 69 years). By four months, the distribution of treatment effects by age group converged towards the overall effect, indicating a more uniform response to the treatment across the age subgroups. At 12 months, a similar pattern of variation re-emerged to some degree, albeit with greater benefit for patients aged < 69 years. Again, attrition means that the estimates are not directly comparable. The results for alcohol consumption in the subgroups showed some evidence of heterogeneity in effects at four months on EQ-5D index score, but the pattern of heterogeneity differs in other timepoints and for the VAS score. Overall, the results do not provide a strong justification for making different treatment decisions for the subgroups considered.

Discussion

In this study, we used novel machine-learning methods to investigate the heterogeneity of treatment effects in patients randomized to cemented versus modern uncemented hemiarthroplasty for the treatment of an intracapsular fracture of the hip. We used CF models to examine how different patients respond to treatment. Our analysis did not reveal significant differences across age groups, providing reassurance to clinicians and policy-makers that cemented hemiarthroplasty is the preferred operation for all subgroups of patients aged > 60 years with this fracture.

At 12 months postoperatively, there appeared to be more variation in effect sizes across age groups compared with earlier timepoints. The effect size for the youngest age group (< 69 years) at 12 months showed a markedly larger positive effect compared with earlier timepoints, although the CI was wide and crossed zero. This suggests that younger patients might derive greater benefit from a cemented hemiarthroplasty over time, which could be clinically relevant as these patients are likely to live longer than older patients. The older subgroups (70 to 79 years, 80 to 89 years, and ≥ 90 years) did not show a consistent trend, with effect sizes fluctuating around zero.

Females tended to benefit more from cemented hemiarthroplasty compared with males, at all follow-up timepoints. However, again, the CIs were wide and included zero, so the effects are not significant. Nevertheless, the consistent direction of the effect might suggest that significant effects by sex may be detected with a larger sample size. Overall, with regard to cemented versus uncemented hemiarthroplasty for these patients, treatment effects appeared to be homogeneous by subgroup and timepoint.

Previously, several theoretical frameworks have been suggested to evaluate heterogeneous treatment effects. However, each framework has its limitations. Traditional parametric methods which use interaction terms provide a direct way to estimate heterogeneous effects. However, these methods are limited because of the interdependence of variables, especially when several interaction terms are used. This issue can reduce the depth and use of the analysis.[18] The robustness of results obtained from interaction analysis can be compromised by the mis-specification of the model.[19–21] Subgroup analysis may produce inaccurate conclusions due to being underpowered,[22] and is susceptible to the misinterpretation of random variation as significant treatment effects.[19,22–24] Finally, the practice of retrospective 'effect fishing' across several subgroups typically results in spurious findings,[25–27] leading to a proliferation of false-positive subgroup results, and sampling bias.[28,29]

The CF was designed to address the drawbacks of traditional modelling as an approach grounded in machine learning for causal inference.[11] The CF's key strengths in estimating heterogeneous treatment effects include managing complex, high-dimensional interactions among many input variables without necessitating parametric assumptions by the researcher.[11] It algorithmically segments data according to variation in treatment effects between individuals,[28,29] and can generate CIs for the effects.[11] Furthermore, it uses cross-fitting, or 'honesty', as a critical element of sound statistical inference, incorporating a safeguard against overfitting through the estimation of treatment effects using out-of-bag samples.[11,30] The use of CFs has been demonstrated in diverse fields and they are increasingly being used in healthcare decision-making.[31–33] This study further highlights the potential of CF analysis to investigate different treatment effects in subgroups of patients and at different timepoints. However, the use of CF analysis, as in this study, is still limited by the number of patients available for analysis.

In conclusion, the WHiTE 5 trial found that, on average, cemented hemiarthroplasty is expected to increase health-related quality of life compared with modern uncemented hemiarthroplasty. Our CF analysis of individual-level treatment effects, suggests that this benefit is likely to be present in all subgroups of patients, irrespective of age or other baseline characteristics.

Take home message

- The study concludes that cemented hemiarthroplasty generally improves health-related quality of life for all subgroups of patients aged over 60 years with a displaced intracapsular hip fracture, regardless of age or other baseline characteristics.

Supplementary material

A comprehensive explanation of the causal forest method used to estimate treatment effects and description of how the causal forest approach was specifically applied to the WHiTE 5 trial data, as well as tables detailing the outcome characteristics and details of the covariates at one, four, and 12 months.

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The datasets generated and analyzed in the current study are not publicly available due to data protection regulations. Access to data is limited to the researchers who have obtained permission for data processing. Further inquiries can be made to the corresponding author.

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