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Gender-specific haemoglobin thresholds in relation to preoperative risk assessment in fast-track total hip and knee arthroplasty.

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Short title:

Preoperative anaemia and recovery in fast-track THA and TKA

Within the last decade there has been an increasing focus on anaemia, iron deficiency and transfusion strategies leading to the concept of "patient blood management" (PBM), aiming at reducing the need for blood transfusions by preoperative optimisation of haemoglobin (Hb) and iron-status and use of intra- and postoperative restrictive transfusion protocols [1].

When diagnosing preoperative anaemia most practitioners have adhered to the WHO guidelines which were developed in 1968 and use gender specific criteria of a Hb of < 130 g.l^{-1} for men and < 12 g.l^{-1} for women [2]. However, these thresholds are based on studies with less sophisticated laboratory end epidemiological techniques than presently available and are consequently under current revision [3].

Furthermore, it has been argued that the WHO definitions of anaemia may not apply to surgical patients, as the relative blood-loss is larger in women, potentially leading to increased risk of allogenic blood transfusions and morbidity when using a gender specific lower preoperative anaemia threshold [4-6].

In total hip (THA) and knee arthroplasty (TKA) it is internationally acknowledged that preoperative iron deficiency anaemia should be corrected by treatment with intravenous (i.v.) iron [7]. However, detailed knowledge of the Hb threshold to increase the risk of postoperative morbidity, indications for treatment and whether it differs in men and women is sparse. The aim of this secondary analysis was to investigate the influence of preoperative Hb level in a comprehensive machine-learning model aimed at identifying patients at "high-risk" of medical complications leading to either a length of hospital stay of >4 days or 30-days readmission after an established fast-track THA and TKA [8]. While the primary study focused on comparing potential benefits of an overall machine-learning model in preoperative risk-prediction [9], this secondary analysis focus specifically on the influence of preoperative Hb level per se and potential differences according to gender and age.

We used a well-defined cohort of elective fast-track THA and TKA patients and evaluated the effect of preoperative Hb-level on the machine-learning model by SHAP-analysis which evaluates the individual effect of the variables included in a machine-learning model [10]. Furthermore, we assessed the distribution of Hb-levels and increases in risk-profile according to gender and age.

From January 2017 to August 2017, we included 3913 patients with a median length of stay of 1 day. Mean preoperative Hb was 154.8 (SD:15.12) but lower in women (149.4 vs. 162 g.l[1]: p<0.001) and there were 30.5% of women vs. 12.0% of men with a Hb of <130 g.l[1] (p<0.001). SHAP-analysis demonstrated an immediate steep increase in the risk-score for medical complications with a preoperative Hb below 147.6 g.l[1], and irrespective of gender and age (figure 1). Finally, the median SHAP-value of Hb-level was 0.35 (IQR:) in the patients with a Hb-level below 147.6 g.l[1]

These results remained consistent regardless of analysing THA and TKA separately (online Supporting Information Figure S1a+b).

Our analysis demonstrates that in a comprehensive machine-learning risk-model, the preoperative Hb threshold was the same in men and women for an increased risk of prolonged length of stay or readmissions due to medical issues after fast-track THA and TKA. The threshold value of 147.6 g.l[1] is remarkably close to the 130 g.l[1] suggested for men in the current WHO guideline. Thus, the results of our study support the current WHO threshold for anaemia in men, but importantly also for removing gender specific Hb criteria for preoperative anaemia in women, at least in elective THA and TKA. Furthermore, the influence of preoperative Hb level < 147.6 g.l[1] was consistent regardless of age, supporting that the removal of gender specific criteria should apply to all patients. Finally, the effect of Hb level on the accumulated risk-score was clinically meaningful. Thus, figure 1, illustrates that preoperative Hb level contributed with SHAP-values of approximately 0.4 in patients with a Hb of

<147.6 g.l[1]. This corresponds with about 50% increased odds of being a high-risk patient. In contrast, in those with Hb-levels >147.6 g.l[1] the odds of being high-risk patients decreased with about 15%.

That gender specific Hb criteria may be inappropriate and need further consideration, has also been demonstrated in cardiac surgery, where women with a preoperative Hb of 120-129 g.l[1] received more blood transfusions and had increased length of hospital stay compared to those with a Hb of >129 g.l[1] [11]. That women with a preoperative Hb level of < 130 g.l[1] may potentially benefit from iron-treatment prior to surgery was illustrated by a large study investigating preoperative Hb levels and iron deficiency in major elective surgery and finding similar incidence of iron deficiency in women with Hb < 130 g.l[1] and < 120 g.l[1] [12]. Our study has some limitations, including lack of information on perioperative blood-transfusions and potential use of preoperative i.v. iron. However, preoperative optimisation with i.v. iron was not standard in the participating departments, and even if some of the outcomes was due to transfusion-related morbidity it would not change the finding of similar SHAP-curves between men and women. Study strengths include well-established fast-track protocols, detailed data on comorbidity and patient outcomes, a complete follow-up, and use of a sophisticated machine-learning model.

In conclusion, from a machine-learning model in fast-track THA and TKA, a Hb threshold of 146.7 g.l[1] was found to increase risk of impaired recovery, regardless of gender or age, thus calling for re-evaluation of preoperative anaemia risk criteria in the elective surgical setting.

Competing Interests

Acknowledgements

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Figure legend:

Figure 1a+b

SHapley Additive exPlanations (SHAP) curves for preoperative haemoglobin level in in relation to preoperative risk-stratification according to the machine-learning algorithm. Each dot indicates a patient with the colour indicating age (increasing from blue to red). Increasing SHAP values indicate increasing risk-score and decreasing values a decreased risk-score. The cut-off for going from a negative to a positive SHAP-value is indicated by the dotted line at a preoperative Hb level of 147.6 g.l[1]
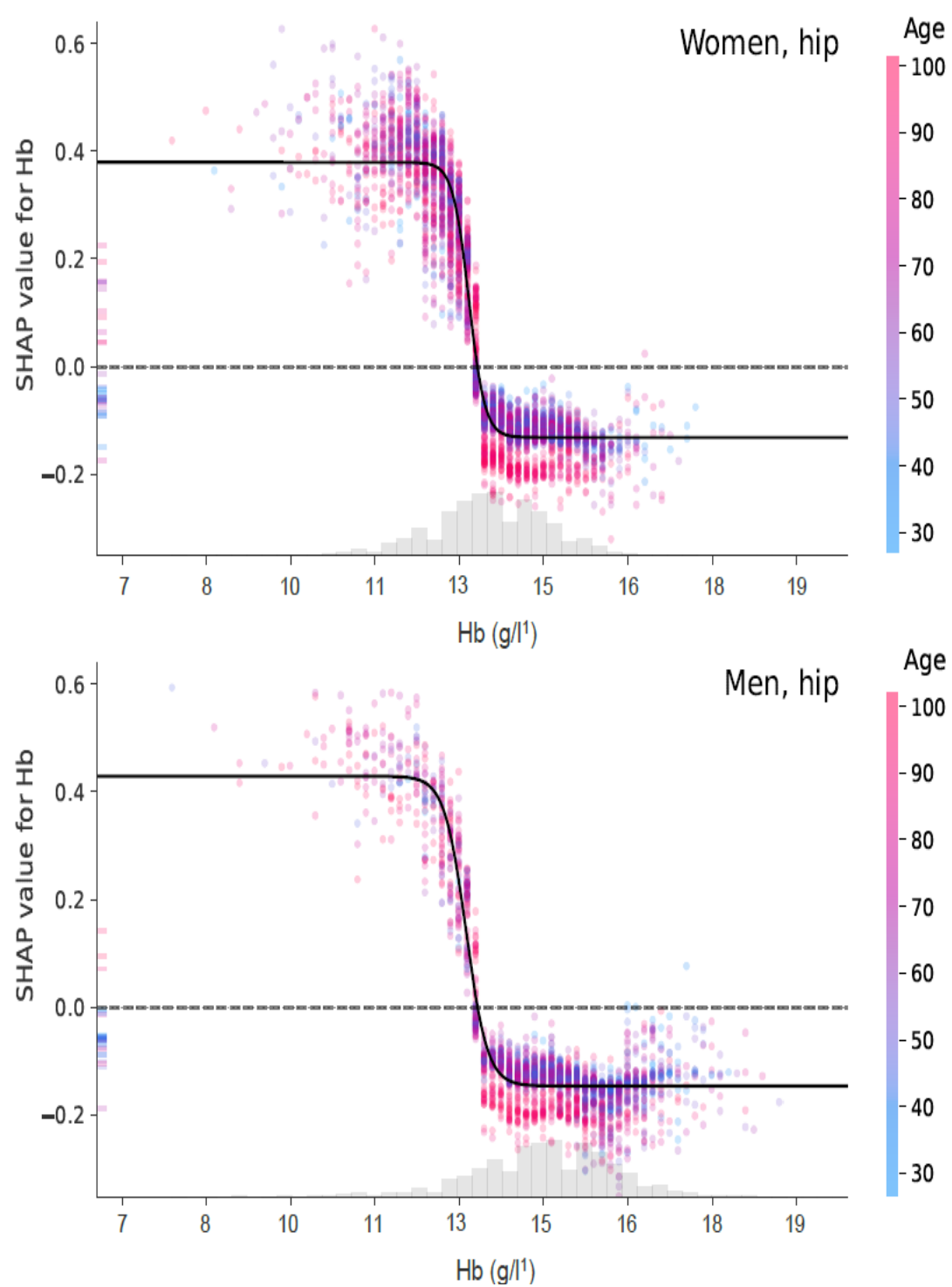
Supplemental material

Figure 1a+b

SHapley Additive exPlanations (SHAP) curves for preoperative haemoglobin level in in relation to preoperative risk-stratification according to the machine-learning algorithm for total hip (1a) and total knee arthroplasty (1b), respectively. Each dot indicates a patient with the colour indicating age (increasing from blue to red). Increasing SHAP values indicate increasing risk-score and decreasing values a decreased risk-score. The cut-off for going from a negative to a positive SHAP-value is indicated by the dotted line at a preoperative Hb level of 147.6 g.l[1]

Figure 1 a+b
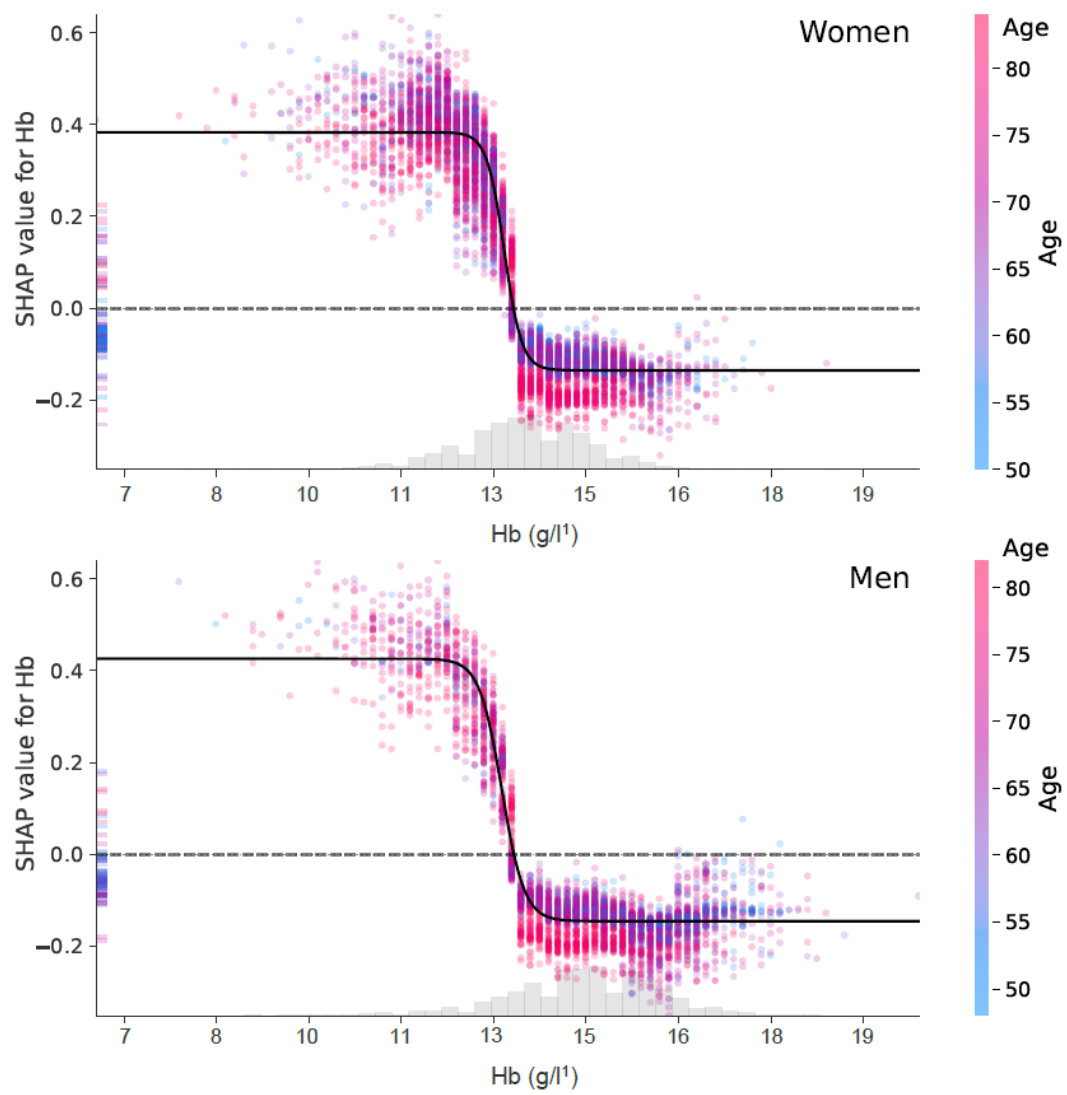
Supplemental figure 1a

Supplemental figure 1b