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Low haemoglobin and postoperative outcomes in patients aged ≥80 years: effect modification by haemodynamic and renal vulnerability in a retrospective cohort study

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Research Article

Keywords: older adults, anaemia, physiological reserve, intraoperative hypotension, acute kidney injury, major adverse cardiac events, spinal anaesthesia, perioperative medicine

Posted Date: November 18th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11308217/v1

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Additional Declarations: No competing interests reported.

Abstract

Background

Adults aged ≥ 80 years have limited physiological reserve and are vulnerable to postoperative complications, yet modest preoperative haemoglobin reductions are common and do not by themselves define a treatment threshold. We examined whether the association of haemoglobin < 10 g/dL with postoperative outcomes differed according to concurrent haemodynamic or renal vulnerability.

Methods

This retrospective single-centre cohort included 836 patients aged ≥ 80 years who underwent surgery under spinal anaesthesia between 2017 and 2021. Major adverse cardiac events (MACE) and creatinine-based Kidney Disease: Improving Global Outcomes (KDIGO) acute kidney injury (AKI; stage ≥ 1) were assessed during the index admission. Multivariable logistic-regression interaction terms tested haemoglobin < 10 g/dL with a baseline-referenced intraoperative mean arterial pressure decrease (ΔMAP) > 40 mmHg for MACE and with preoperative creatinine > 1.5 mg/dL for AKI.

Results

MACE occurred in 69/836 patients (8.3%) and AKI in 249/836 (29.8%). MACE incidence was 5.7% in the reference group, 8.9% with ΔMAP > 40 mmHg alone, 9.1% with low haemoglobin alone, and 36.1% when both exposures coexisted; the adjusted Hb × ΔMAP interaction was significant (OR 3.89, 95% CI 1.08–13.98; p = 0.037). AKI incidence was 26.3% in the reference group, 40.0% with creatinine > 1.5 mg/dL alone, 30.8% with low haemoglobin alone, and 65.2% when both coexisted; the adjusted Hb×creatinine interaction was significant (OR 8.26, 95% CI 3.00–22.76; p < 0.001). Conditional effects from the adjusted models were weak when the corresponding co-factor was absent and substantially larger when it was present. Combined-exposure groups were small (n = 36 for MACE; n = 23 for AKI), and Firth analyses yielded similar interaction estimates.

Conclusions

In adults aged ≥ 80 years, the association of modest preoperative haemoglobin reduction with postoperative outcomes was strongly dependent on accompanying haemodynamic or renal vulnerability. These findings support a geriatric vulnerability–stressor framework for risk assessment, but do not establish a transfusion threshold or blood-pressure target and require prospective multicentre validation.

1. Background

Adults aged ≥ 80 years constitute a growing surgical population in whom postoperative risk reflects not only the procedure itself but also reduced physiological reserve and multimorbidity. Frailty, a clinical expression of diminished reserve, is independently associated with postoperative mortality across noncardiac surgical specialties [1]. This makes very old surgical patients particularly relevant for studying whether combinations of otherwise modest physiological abnormalities identify vulnerability more effectively than isolated risk factors.

Anaemia is common in older surgical patients. Large cohort studies have shown that even mild preoperative anaemia is associated with increased 30-day mortality and morbidity after noncardiac surgery, including in older adults [2, 3]. However, a haemoglobin concentration below 10 g/dL is not itself a contemporary transfusion trigger, and values in this range frequently require individualised interpretation. In older people with reduced cardiovascular or renal reserve, the clinical relevance of a modest haemoglobin reduction may therefore depend on the presence of an additional physiological stressor.

Intraoperative haemodynamic disturbance is one such stressor. Lower intraoperative mean arterial pressure and increasing duration of hypotension have been associated with myocardial injury and AKI after noncardiac surgery [4, 5]. Spinal anaesthesia is frequently used in older adults; although the REGAIN randomised trial found no superiority of spinal over general anaesthesia for survival and recovery of ambulation after hip-fracture surgery [6], sympathetic blockade can produce arterial and venous vasodilation and clinically important hypotension [7, 8]. Age-related arterial and ventricular stiffness, diastolic dysfunction, and reduced β-adrenergic responsiveness may further limit compensation for reductions in preload and arterial pressure [9, 10].

Renal vulnerability represents a second, clinically distinct limitation of physiological reserve. AKI is a common perioperative complication defined by standardised criteria [11], and pre-existing kidney disease, anaemia, emergency surgery, and perioperative haemodynamic disturbances are recognised contributors to perioperative AKI risk [12]. In very old adults, serum creatinine must also be interpreted cautiously because reduced muscle mass may mask impaired renal function.

Although anaemia, intraoperative hypotension, and renal impairment are individually associated with adverse perioperative outcomes, their joint effects in adults aged ≥ 80 years remain less well characterised. The clinically relevant question is therefore not only whether a modest haemoglobin reduction is associated with risk, but whether its association changes when haemodynamic or renal reserve is simultaneously compromised. Such effect modification would support a geriatric vulnerability–stressor framework in which risk arises from the interaction between limited reserve and an acute perioperative challenge.

We therefore hypothesised that the association of preoperative haemoglobin < 10 g/dL with postoperative outcomes would differ according to the presence of a second physiological stressor: a marked intraoperative decrease in mean arterial pressure for MACE and elevated preoperative creatinine

for AKI. We tested these prespecified interactions in a retrospective cohort restricted to patients aged ≥ 80 years undergoing spinal anaesthesia.

2. Methods

The study was approved by the Ethics Committee of Witten/Herdecke University. The requirement for informed consent was waived because of the retrospective study design.

This study is reported in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement for cohort studies. Clinical trial number is not applicable

2.1 Study design and setting

We conducted a retrospective, single-centre cohort study at Klinikum Dortmund. All patients aged ≥ 80 years who underwent surgery under spinal anaesthesia between 2017 and 2021 were considered for inclusion.

2.2 Participants

Of 1,114 patients screened for eligibility, 836 met inclusion criteria and were included in the final analytic cohort. Exclusion criteria were failed spinal anaesthesia (n = 39), surgery exceeding two hours requiring conversion to general anaesthesia (n = 46), incomplete data records required for the prespecified analyses (n = 141), and more than one operation during the same hospital admission (n = 52), for a total of 278 exclusions (Fig. 1).

2.3 Outcome definitions

The primary cardiac outcome, MACE, was defined as a composite of postoperative heart failure, myocardial infarction, and cardiac arrest occurring during the index hospital admission. The primary renal outcome, AKI, was defined according to Kidney Disease: Improving Global Outcomes (KDIGO) criteria (stage ≥ 1) [11]. In-hospital mortality (all-cause, during the index admission) was additionally recorded and is reported descriptively in relation to both primary outcomes (Section 3.7); it was not itself a prespecified outcome and was not modelled multivariably.

2.4 Exposures and covariate definitions

Low haemoglobin was defined as a preoperative haemoglobin concentration < 10 g/dL. This cut-point was used as an operational exposure definition rather than as a transfusion trigger: actual intraoperative transfusion decisions were made at the treating clinicians' discretion and were captured separately as a binary covariate. Published guidance and recent reviews describe restrictive thresholds around 7–8 g/dL and emphasize individualised decisions in older or cardiovascular patients [13, 14]. In the present cohort, however, low-haemoglobin values were concentrated near the upper end of this range: the median (IQR) was 9.2 (8.7–9.6) g/dL; only 7 patients (0.8% of the cohort) had haemoglobin between 7 and 8 g/dL

(mean 7.71 g/dL, range 7.19–7.97 g/dL), and none had haemoglobin below 7 g/dL. The low-haemoglobin exposure should therefore not be interpreted as representing the full 7–10 g/dL spectrum. Marked intraoperative haemodynamic stress was defined as ΔMAP > 40 mmHg, where ΔMAP was the last MAP recorded on the ward before surgery minus the lowest invasively measured intraoperative MAP. A baseline-referenced measure was deliberately selected to capture patient-specific haemodynamic deviation rather than impose a uniform absolute pressure threshold; >40 mmHg was used as an operational threshold for a pronounced perturbation, not as a universally validated definition of hypotension or a treatment target. Elevated preoperative creatinine was defined as > 1.5 mg/dL and was treated as a marker of renal vulnerability rather than a diagnostic threshold for CKD. Cardiac burden was defined as the presence of at least one of coronary artery disease, heart failure, or atrial fibrillation. CKD was defined as a pre-existing diagnosis documented in the medical record before surgery; CKD was not retrospectively assigned from a single preoperative eGFR value. ASA physical status, emergency versus elective surgery, operative duration, and intraoperative allogeneic red blood cell transfusion (yes/no) were recorded from the anaesthesia record. Preoperative beta-blocker and ACE-inhibitor use (yes/no) and intraoperative vasopressor requirement (yes/no) were used only in post-hoc sensitivity models.

2.5 Statistical analysis

Categorical variables are presented as n (%) and continuous variables as mean (SD) or median (IQR), as appropriate. Formal between-group comparisons for categorical variables in stratified tables used the chi-square test; continuous variables were presented descriptively. Unadjusted associations between exposure groups and outcomes were summarized as odds ratios (OR) with 95% confidence intervals (CI), calculated from the underlying 2×2 cell counts. Because the multivariable interaction terms quantify departure from a multiplicative (odds-ratio) null, we additionally assessed departure from an additive null using the unadjusted stratum-specific odds ratios: the relative excess risk due to interaction (RERI = OR11 − OR10 − OR01 + 1) and the attributable proportion due to interaction (AP = RERI / OR11), with 95% confidence intervals obtained by parametric bootstrap (100,000 resamples) of the stratum-specific binomial event counts.

Multivariable logistic regression was used to evaluate associations with MACE and AKI. For each outcome, we prespecified an interaction term testing whether low haemoglobin modified the association of the corresponding second physiological stressor with the outcome: hypotension (ΔMAP) for MACE and elevated creatinine for AKI. The primary MACE model included low haemoglobin, ΔMAP > 40 mmHg, creatinine > 1.5 mg/dL, the Hb × ΔMAP interaction, emergency surgery, and cardiac burden; the primary AKI model included low haemoglobin, creatinine > 1.5 mg/dL, the Hb×creatinine interaction, CKD, and emergency surgery. Cardiac burden was initially operationalised as an ordinal count (0–3 diagnoses); this specification showed a non-monotonic association with MACE across its three non-reference categories and used three degrees of freedom, and was therefore replaced with a binary indicator (≥ 1 vs. 0 diagnoses), which resolved the non-monotonicity and improved events-per-variable from ≈ 8.6 to ≈ 11.5 (69 events / 6 parameters), above the conventional threshold of 10. Given the limited number of MACE events (n = 69) relative to the number of candidate covariates, age, sex, ASA class, and operative

duration were not included jointly in the primary MACE model, consistent with the conventional recommendation of at least 10 events per variable in logistic regression [15]; baseline comparisons of these variables across exposure groups were examined descriptively, and each was additionally tested individually in post-hoc sensitivity models (Section 3.6). Because the larger number of AKI events (n = 249) did not impose the same constraint, additional post-hoc sensitivity models for both outcomes incorporated ASA class, intraoperative blood transfusion, and — for AKI — ΔMAP, to evaluate the stability of the primary findings and to explore whether blood transfusion materially altered the core interaction estimates (see Section 3.6).

Given the small combined-exposure groups and the possibility of small-sample bias or separation, Firth bias-reduced logistic regression was used as an additional sensitivity analysis for each primary interaction model. Model discrimination was assessed using the area under the receiver operating characteristic curve (AUC), and calibration using the Hosmer-Lemeshow test. E-values were calculated as a sensitivity analysis for potential unmeasured confounding [16], with values reported in the Supplementary Material. Additional post-hoc sensitivity models evaluated beta-blocker use, ACE-inhibitor use, intraoperative vasopressor requirement, blood transfusion, and ΔMAP as appropriate (Section 3.6). These post-hoc sensitivity analyses were considered exploratory, and no adjustment for multiple comparisons was applied. Statistical analyses were performed using jamovi version 2.7.23 (The jamovi project, Sydney, Australia). Multicollinearity was assessed directly within the logistic regression models using variance inflation factors (VIF) and tolerance. Maximum VIFs were 1.65 for the primary MACE model, 1.77 for the primary AKI model, and 1.83 for the fully adjusted AKI sensitivity model, indicating no relevant multicollinearity. A two-sided p-value < 0.05 was considered statistically significant.

3. Results

3.1 Patient population

The final analytic cohort comprised 836 patients aged ≥ 80 years undergoing spinal anaesthesia between 2017 and 2021 (Fig. 1). MACE occurred in 8.3% (n = 69) and AKI in 29.8% (n = 249).

3.2 Baseline characteristics

Table 1
Baseline characteristics by MACE and AKI exposure groups

Panel A: MACE exposure groups

Characteristic	Reference (n = 487)	Hypotension only (n = 247)	Low Hb only (n = 66)	Combined (n = 36)	Overall p-value
Age, mean (SD), years	85.5 (4.58)	86.8 (5.00)	85.7 (4.34)	86.9 (3.70)	—
Male, n (%)	254 (52.2%)	90 (36.4%)	38 (57.6%)	15 (41.7%)	< 0.001
ASA I, n (%)	5 (1.0%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	< 0.001
ASA II, n (%)	80 (16.4%)	32 (13.0%)	5 (7.6%)	2 (5.6%)	—
ASA III, n (%)	300 (61.6%)	153 (61.9%)	33 (50.0%)	13 (36.1%)	—
ASA IV, n (%)	102 (20.9%)	61 (24.7%)	28 (42.4%)	21 (58.3%)	—
Operative duration, mean (SD), min	76.8 (37.9)	99.4 (37.4)	79.8 (39.0)	116 (53.6)	—

Panel B: AKI exposure groups

Characteristic	Reference (n = 615)	Cr > 1.5 only (n = 120)	Low Hb only (n = 78)	Combined (n = 23)	Overall p-value
Age, mean (SD), years	85.8 (4.74)	86.7 (4.81)	86.3 (4.30)	85.7 (3.71)	—
Male, n (%)	261 (42.4%)	84 (70.0%)	39 (50.0%)	13 (56.5%)	< 0.001
ASA I, n (%)	5 (0.8%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	< 0.001
ASA II, n (%)	103 (16.7%)	9 (7.5%)	5 (6.4%)	2 (8.7%)	—
ASA III, n (%)	380 (61.8%)	74 (61.7%)	35 (44.9%)	10 (43.5%)	—
ASA IV, n (%)	127 (20.7%)	36 (30.0%)	38 (48.7%)	11 (47.8%)	—
Operative duration, mean (SD), min	85.0 (39.2)	81.0 (39.2)	92.3 (50.7)	94.1 (36.9)	—

Overall p-values are shown in Table 1 for variables with formal between-group testing in each panel; the ASA p-value refers to the overall ASA distribution.

Age was similar across MACE exposure groups (85.5–86.9 years). Sex and ASA class differed significantly across groups (both p<.001), with ASA IV prevalence rising from 20.9% in the reference group to 58.3% in the combined-exposure group. Operative duration was descriptively longer in the two groups with marked ΔMAP (99–116 minutes) than in the two groups without (77–80 minutes). Within

the low-haemoglobin group, preoperative haemoglobin was concentrated near the < 10-g/dL threshold (median 9.2 g/dL, IQR 8.7–9.6); only 7 patients had haemoglobin between 7 and 8 g/dL, and none had haemoglobin below 7 g/dL.

Baseline characteristics by AKI exposure group are shown in Table 1, Panel B. Age was similar across groups, whereas sex and ASA class differed significantly (both p<.001). Operative duration is presented descriptively because no formal between-group test was used for this continuous variable.

3.3 Unadjusted associations between exposure groups and outcomes

Unadjusted MACE incidence rose from 5.7% (28/487) in the reference group (Hb ≥ 10 g/dL, ΔMAP ≤ 40 mmHg) to 8.9% (22/247; OR 1.60, 95% CI 0.90–2.86, p = 0.111) with marked hypotension alone and 9.1% (6/66; OR 1.64, 95% CI 0.65–4.12, p = 0.293) with low haemoglobin alone — neither significantly different from reference — but to 36.1% (13/36; OR 9.27, 95% CI 4.25–20.21, p < 0.0001) when both were present (χ^2=41.1, df = 3, p<.001 overall; Additional file 1: Supplementary Table S1). Unadjusted AKI incidence showed a related but distinct pattern: 26.3% (162/615) at reference (Hb ≥ 10 g/dL, creatinine ≤ 1.5 mg/dL), rising to 40.0% (48/120; OR 1.86, 95% CI 1.24–2.80, p = 0.0027) with elevated creatinine alone, 30.8% (24/78; OR 1.24, 95% CI 0.74–2.08, p = 0.4065) with low haemoglobin alone, and 65.2% (15/23; OR 5.24, 95% CI 2.18–12.60, p = 0.0002) when both were present (χ^2=23.3, df = 3, p<.001 overall; Additional file 1: Supplementary Table S1). Figure 2 illustrates both patterns; the adjusted multiplicative interaction terms were significant for MACE and AKI (Tables 2–3). On the additive scale, MACE showed evidence of superadditivity (RERI 7.02, 95% CI 1.73–17.40; AP 0.76, 95% CI 0.36–0.93). For AKI, the point estimates also suggested positive additive interaction (RERI 3.14, 95% CI − 0.03–12.21; AP 0.60, 95% CI − 0.01–0.87), but both confidence intervals included the null; additive interaction for AKI was therefore not statistically established.

3.4 Multivariable models

Table 2
Multivariable logistic regression model for MACE

Predictor	OR	95% CI	p-value
Hb < 10 g/dL	1.29	0.50–3.35	0.598
ΔMAP > 40 mmHg	1.14	0.63–2.09	0.659
Creatinine > 1.5 mg/dL	1.91	1.05–3.47	0.033
Emergency surgery	6.75	2.37–19.22	< 0.001
Hb × ΔMAP (interaction)	3.89	1.08–13.98	0.037
Cardiac burden (≥ 1 vs. 0)	3.48	1.87–6.46	< 0.001

Age, sex, ASA class, and operative duration were not included in the primary MACE model because of the limited number of events; each was added individually in sensitivity analyses (Section 3.6). Cardiac burden was modelled as a binary indicator (≥ 1 vs. 0 of coronary artery disease, heart failure, or atrial fibrillation), yielding approximately 11.5 events per model parameter [15]. Neither low haemoglobin nor hypotension was independently associated with MACE; the interaction, creatinine, emergency surgery, and cardiac burden were significant (Fig. 3A). Model AUC was 0.79 (Additional file 1: Supplementary Table S2).

Table 3
Multivariable logistic regression model for AKI

Predictor	OR	95% CI	p-value
Hb < 10 g/dL	1.00	0.58–1.73	0.987
Creatinine > 1.5 mg/dL	1.11	0.66–1.85	0.693
Hb × Creatinine (interaction)	8.26	3.00–22.76	< 0.001
CKD (pre-existing documented diagnosis)	2.46	1.63–3.71	< 0.001
Emergency surgery	4.51	2.90–7.02	< 0.001

Neither low haemoglobin nor elevated creatinine alone was independently associated with AKI; the interaction, CKD, and emergency surgery were significant (Fig. 3B). Model AUC was 0.71 (Additional file 1: Supplementary Table S2).

3.5 Model discrimination and calibration

Discrimination was acceptable to good for both endpoints (Additional file 1: Supplementary Table S2): AUC 0.732 for the reduced MACE model, 0.785 for the full MACE model including cardiac burden, and 0.714 for the AKI model. There was no statistical evidence of poor calibration for the primary models (Hosmer-Lemeshow χ^2=11.65, df = 14, p = 0.63 for the reduced MACE model; χ^2=4.02, df = 8, p = 0.855 for the full MACE model; χ^2=7.64, df = 15, p = 0.94 for the AKI model). Sensitivity models likewise showed no evidence of poor calibration (Additional file 1: Supplementary Table S2). E-value analyses were performed to assess the potential impact of unmeasured confounding [16]; detailed results are reported in the Supplementary Material.

3.6 Simple effects and blood transfusion (post-hoc analyses)

The interaction coefficients in Tables 2 and 3 are mathematically symmetric and do not by themselves indicate whether haemoglobin or the co-factor (ΔMAP or creatinine) contributes more to the interaction. To characterise the fitted interactions, conditional (“simple”) effects were computed (Additional file 1: Supplementary Table S3) directly from the adjusted models using per-patient data. For MACE (holding creatinine, emergency surgery, and cardiac burden status fixed), the adjusted effect of ΔMAP was OR

1.14 when Hb was ≥ 10 g/dL and OR 4.46 when Hb was < 10 g/dL; the adjusted effect of low Hb was OR 1.29 when ΔMAP was ≤ 40 mmHg and OR 5.03 when ΔMAP was > 40 mmHg. For AKI (holding CKD and emergency surgery status fixed), the adjusted effect of creatinine > 1.5 mg/dL was OR 1.11 when Hb was ≥ 10 g/dL and OR 9.16 when Hb was < 10 g/dL; the adjusted effect of low Hb was OR 1.00 when creatinine was ≤ 1.5 mg/dL and OR 8.30 when creatinine was > 1.5 mg/dL. These conditional estimates illustrate the multiplicative effect modification but do not establish which factor is causal or dominant. Because the combined-exposure subgroups were small (n = 36 for MACE and n = 23 for AKI), the corresponding effect sizes are imprecisely estimated and should be interpreted cautiously.

Intraoperative blood transfusion rate differed significantly by exposure group for both endpoints (Additional file 1: Supplementary Table S4): for MACE, from 17.0% (83/487) at reference to 50.0% (18/36) in the combined-exposure group (χ^2=35.3, df = 3, p<.001); for AKI, from 21.3% (131/615) at reference to 43.5% (10/23) in the combined-exposure group (χ^2=21.4, df = 3, p<.001), with the transfusion rate tracking haemoglobin status rather than creatinine status (19.2% in the “creatinine only” group vs. 41.0–43.5% in the two low-haemoglobin groups).

In post-hoc sensitivity models additionally accounting for blood transfusion (Additional file 1: Supplementary Table S4 and Supplementary Figure S3), both core interactions were reproduced: OR 3.91 (95% CI 1.09–14.04, p = 0.037) for Hb × ΔMAP in the MACE model, re-fitted without ASA class after an earlier specification including it showed numerically unstable coefficients consistent with quasi-complete separation given the limited number of events (69); and OR 12.41 (p < 0.001; 95% CI not reported for this specification) for Hb×creatinine in the AKI model without ΔMAP, rising to OR 12.69 (95% CI 5.19–31.01, p < 0.001) once ΔMAP was added. Blood transfusion itself was not independently associated with MACE (OR 1.07, 95% CI 0.60–1.88, p = 0.827) but was independently associated with AKI both without ΔMAP (OR 2.25, p < 0.001) and with ΔMAP added (OR 2.23, 95% CI 1.53–3.25, p < 0.001), at a magnitude comparable to CKD and below the dominant haemoglobin×creatinine interaction. Because the AKI model did not initially include a haemodynamic covariate, we explored whether the transfusion association might reflect intraoperative haemodynamic disturbance by adding ΔMAP: the transfusion association was materially unchanged while ΔMAP itself was not a significant predictor (OR 1.02, 95% CI 0.72–1.45, p = 0.900), which did not support ΔMAP as an explanation for the transfusion association, although residual confounding remains possible (see Discussion). CKD was no longer statistically significant once ΔMAP was added (OR 1.25, 95% CI 0.84–1.86, p = 0.274, vs. OR 2.27, p < 0.001 without ΔMAP; see Discussion).

To further address possible residual confounding by factors excluded from the primary MACE model owing to the limited number of events, three post-hoc sensitivity models individually added age, sex, and operative duration (Additional file 1: Supplementary Table S5). The Hb × ΔMAP interaction remained significant in all three: OR 3.87 (95% CI 1.08–13.91, p = 0.038) with sex added, OR 4.01 (95% CI 1.11–14.49, p = 0.034) with age added, and OR 3.77 (95% CI 1.05–13.58, p = 0.043) with operative duration added, each closely consistent with the primary model (OR 3.89). Age itself was independently associated with MACE (OR 1.07 per year, 95% CI 1.02–1.13, p = 0.012); sex and operative duration were

not. Given the limited combined-exposure group (n = 36), Firth's penalized logistic regression was additionally used to assess robustness to small-sample bias and potential separation. The Hb × ΔMAP interaction remained materially unchanged (Firth OR 3.64, 95% CI 1.07–13.22). Firth analysis of the primary AKI model likewise reproduced the Hb×creatinine interaction (OR 7.75, 95% CI 2.94–21.77).

Additional medication and haemodynamic sensitivity analyses are reported in Additional file 1: Supplementary Table S5. Adjustment for beta-blocker use did not materially change the MACE interaction (OR 3.85, 95% CI 1.07–13.85), and adjustment for ACE-inhibitor use did not materially change the AKI interaction (OR 9.39, 95% CI 3.56–24.79). An additional fully adjusted AKI sensitivity model intentionally excluded CKD while simultaneously including ACE-inhibitor use, ΔMAP, vasopressor requirement, and blood transfusion; the Hb×creatinine interaction remained strong (OR 10.51, 95% CI 4.00–27.58, $p < 0.001$), and transfusion remained independently associated with AKI (OR 2.12, 95% CI 1.47–3.08, $p < 0.001$). Direct logistic-regression collinearity diagnostics showed no relevant multicollinearity (maximum VIF 1.83; Additional file 1: Supplementary Table S5).

3.7 Association with in-hospital mortality

Both outcomes were strongly associated with in-hospital mortality in unadjusted cross-tabulations (the Supplementary Material mortality section). Mortality was 55.1% (38/69) among patients with MACE versus 0.13% (1/767) among those without ($\chi^2=430$, df = 1, $p < 0.001$), and 8.8% (22/249) among patients with AKI versus 2.9% (17/587) among those without ($\chi^2=13.9$, df = 1, $p < 0.001$). Overall in-hospital mortality in the cohort was 4.7% (39/836). These are purely descriptive, unadjusted cross-tabulations: mortality was not a prespecified outcome, and no multivariable model was fitted for it, in part because only 1 of 767 patients without MACE died, which precludes stable multivariable estimation (near-complete separation on the MACE variable). The associations are reported as descriptive context rather than as an independent, causally interpretable finding, given the likelihood of confounding by underlying illness severity common to both the exposures examined here and death (see Limitations).

4. Discussion

4.1 Principal findings

In this cohort restricted to 836 adults aged ≥ 80 years undergoing spinal anaesthesia, the central finding was a context-dependent pattern rather than a uniform association of haemoglobin < 10 g/dL with MACE or AKI. Low-haemoglobin values were concentrated near 10 g/dL (median 9.2 g/dL, IQR 8.7–9.6), indicating that the study primarily examined modest haemoglobin reduction rather than severe anaemia. Significant multiplicative effect modification was observed between low haemoglobin and ΔMAP > 40 mmHg for MACE (adjusted OR 3.89, 95% CI 1.08–13.98) and between low haemoglobin and creatinine > 1.5 mg/dL for AKI (adjusted OR 8.26, 95% CI 3.00–22.76). This pattern is clinically relevant to geriatric medicine because it suggests that a modest laboratory abnormality may acquire different prognostic meaning when physiological reserve is simultaneously challenged. The combined-exposure groups were small (n = 36 and n = 23), however, and the wide confidence intervals make the magnitude of the

interactions uncertain. The findings therefore support statistical effect modification and a vulnerability–stressor hypothesis, not causal amplification.

A relevant comparison is the post hoc POISE-2 analysis by Turan et al. of 7,940 adults aged ≥ 45 years with known or suspected cardiovascular disease. In that study, the lowest postoperative haemoglobin concentration and the average daily duration of systolic blood pressure < 90 mmHg during the first four postoperative days were each associated with myocardial infarction or death and with AKI, but no significant multiplicative interaction was detected [25]. The authors interpreted the absence of multiplicative interaction as suggesting additive rather than multiplicative effects. Our study differs in several important respects: the cohort was restricted to patients aged ≥ 80 years undergoing spinal anaesthesia, haemoglobin was measured preoperatively, and haemodynamic stress was defined intraoperatively relative to the individual preoperative MAP. We also formally assessed departure from an additive null using RERI and AP, finding evidence of positive additive interaction for MACE but not statistically establishing additive interaction for AKI. These differences in population, timing, and exposure definition preclude direct comparison and reinforce the hypothesis-generating interpretation of our findings.

4.2 Geriatric interpretation: vulnerability and physiological reserve

The MACE interaction is physiologically plausible within a vulnerability–stressor framework. Reduced haemoglobin lowers arterial oxygen-carrying capacity and therefore narrows oxygen-delivery reserve; contemporary perioperative cardiovascular guidance recognizes limited tissue oxygen delivery as an important mechanism of adverse outcomes in anaemia and notes that anaemia may contribute to myocardial ischaemia [17]. A pronounced fall in arterial pressure can simultaneously challenge coronary and systemic perfusion. In very old patients, in whom cardiovascular compensatory reserve is often limited, the concurrence of these two stressors may therefore increase susceptibility to myocardial oxygen supply–demand imbalance. We deliberately used a baseline-referenced ΔMAP to capture the magnitude of haemodynamic deviation experienced by the individual patient. In a retrospective septic-shock cohort, AKI incidence was lowest when post-resuscitation MAP was closest to or higher than the patient's pre-admission MAP [18]; however, that setting does not validate a > 40-mmHg perioperative cut-off. Our threshold should therefore be interpreted as an operational marker of pronounced haemodynamic perturbation rather than a universal definition of hypotension.

The renal interaction may reflect the same vulnerability principle through a different physiological pathway. Preoperative creatinine > 1.5 mg/dL was used as a conservative marker of renal vulnerability, not as a CKD definition. Serum creatinine can underestimate impaired renal function in older adults: in a population study of adults aged ≥ 65 years, 80.6% of individuals with stage 3 CKD had creatinine ≤ 1.5 mg/dL [19]. Thus, a value > 1.5 mg/dL identifies a relatively overt abnormality rather than excluding renal impairment below that threshold. The choice is also clinically relevant to this very old cohort because creatinine > 1.5 mg/dL is incorporated in the Geriatric-Sensitive Perioperative Cardiac Risk Index,

whereas the original Revised Cardiac Risk Index uses ≥ 2.0 mg/dL [20]. Mechanistically, anaemia reduces renal oxygen-carrying capacity and increases susceptibility of the renal medulla to hypoxic injury [12], while perioperative hypotension can further compromise renal medullary oxygenation [21]. Coexistence of reduced oxygen-carrying capacity and impaired renal reserve therefore provides a plausible explanation for the strong Hb×creatinine effect modification observed here. These mechanisms remain hypothesis-generating and were not directly measured in this study.

Individual and combined exposure patterns. The four exposure groups provide additional clinical context for the interaction analyses. For MACE, event rates were similar among patients with marked MAP reduction alone (8.9%) and those with low haemoglobin alone (9.1%), compared with 5.7% in the reference group; neither individual exposure was significantly associated with MACE in the unadjusted comparisons (OR 1.60, 95% CI 0.90–2.86, p = 0.111, and OR 1.64, 95% CI 0.65–4.12, p = 0.293, respectively). In contrast, MACE occurred in 36.1% of patients with both exposures (OR 9.27, 95% CI 4.25–20.21, p < 0.0001). The pattern differed for AKI. Elevated creatinine alone was associated with higher unadjusted AKI incidence than the reference condition (40.0% vs. 26.3%; OR 1.86, 95% CI 1.24–2.80, p = 0.0027), whereas low haemoglobin alone was not (30.8%; OR 1.24, 95% CI 0.74–2.08, p = 0.4065). AKI incidence was highest when low haemoglobin and elevated creatinine coexisted (65.2%; OR 5.24, 95% CI 2.18–12.60, p = 0.0002). Thus, the descriptive four-group comparisons suggest somewhat different patterns for the two outcomes: neither isolated exposure clearly characterised the MACE signal, whereas preoperative renal vulnerability was already informative for AKI before considering its coexistence with low haemoglobin.

The adjusted simple-effects analyses further illustrate the context dependence of these associations (Additional file 1: Supplementary Table S3). For MACE, the association of ΔMAP > 40 mmHg was weak when haemoglobin was ≥ 10 g/dL (OR 1.14, 95% CI 0.63–2.09) but stronger when haemoglobin was < 10 g/dL (OR 4.46, 95% CI 1.44–13.79). Conversely, the association of low haemoglobin was weak when ΔMAP was ≤ 40 mmHg (OR 1.29, 95% CI 0.50–3.35) but stronger when ΔMAP was > 40 mmHg (OR 5.03, 95% CI 2.15–11.79). A similar pattern was observed for AKI: creatinine > 1.5 mg/dL was weakly associated with AKI when haemoglobin was ≥ 10 g/dL (OR 1.11, 95% CI 0.66–1.85) but strongly associated when haemoglobin was < 10 g/dL (OR 9.16, 95% CI 3.74–22.44); correspondingly, low haemoglobin was not associated with AKI when creatinine was ≤ 1.5 mg/dL (OR 1.00, 95% CI 0.58–1.73) but was associated when creatinine was > 1.5 mg/dL (OR 8.30, 95% CI 3.48–19.80). These conditional estimates represent different contrasts within the same fitted interaction models and should therefore not be interpreted as a formal ranking of the relative importance of haemoglobin, haemodynamic stress, and renal vulnerability. Together with the four-group analyses, they instead support the interpretation that the association of modest haemoglobin reduction with postoperative outcomes in this cohort was strongly dependent on the accompanying physiological context.

4.3 The role of blood transfusion

Blood transfusion status differed markedly across exposure groups, but its relationship with the two outcomes was distinct. For MACE, transfusion was not independently associated with the outcome (OR

1.07, 95% CI 0.60–1.88), while adjustment for transfusion left the Hb × ΔMAP interaction essentially unchanged (OR 3.91 vs. 3.89 in the primary model). This suggests that transfusion exposure alone does not explain the cardiac interaction. Published cardiovascular evidence is context-dependent: observational vascular-surgery data have associated perioperative transfusion with increased MACE [22], whereas the REALITY randomised trial in patients with acute myocardial infarction and haemoglobin 7–10 g/dL found a restrictive transfusion strategy noninferior to a liberal strategy for 30-day MACE, while its confidence interval still allowed clinically important harm [23]. Our null transfusion–MACE association should therefore not be interpreted as evidence that transfusion is universally cardiovascularly neutral. In contrast, transfusion was independently associated with AKI in our sensitivity analyses (OR 2.23, 95% CI 1.53–3.25), consistent with perioperative literature linking red blood cell transfusion with postoperative AKI [12, 24]. Importantly, the Hb×creatinine interaction remained strong after transfusion adjustment (OR 12.69, 95% CI 5.19–31.01), indicating that transfusion did not account for the observed renal effect modification. Because detailed blood-loss volume and transfusion timing were unavailable, confounding by indication and the temporal direction of the transfusion–AKI association cannot be resolved, and no causal interpretation is warranted.

4.4 Strengths

Strengths include a physiologically motivated, prespecified interaction hypothesis, assessment on both multiplicative and additive scales, Firth bias-reduced regression, and direct logistic-regression collinearity diagnostics showing no relevant multicollinearity (maximum VIF 1.83). E-value analysis provided an additional assessment of sensitivity to unmeasured confounding, with values reported in the Supplementary Material. The persistence of the core multiplicative interaction terms across sensitivity specifications supports the internal consistency of the observed effect-modification pattern, while not establishing causality.

4.5 Limitations

Several limitations should be considered. First, the retrospective, single-centre design limits causal inference and generalisability, and residual or unmeasured confounding cannot be excluded despite multivariable adjustment, sensitivity analyses, Firth regression, and E-value assessment. Second, 141 screened patients were excluded because of incomplete data records required for the prespecified analyses; this may have introduced selection bias. Third, age, sex, ASA class, and operative duration were not jointly included in the primary MACE model because of the limited number of MACE events; individual sensitivity models reproduced the interaction, but joint residual confounding remains possible. Fourth, the combined-exposure groups were small (n = 36 for MACE and n = 23 for AKI), producing wide confidence intervals; the direction of effect modification was consistent across analyses, but its magnitude is imprecisely estimated. Fifth, cardiac burden was simplified to a binary indicator after an initial categorical specification showed non-monotonic estimates; this improved model parsimony but discarded information on graduated burden. Sixth, haemodynamic stress was operationalised as the maximal decrease in MAP from the individual preoperative baseline (ΔMAP); alternative measures, including absolute MAP thresholds, relative percentage reductions, duration below threshold, and time-

weighted or area-under-threshold hypotension burden, were not evaluated. The > 40-mmHg threshold is therefore an operational study definition requiring external validation and should not be interpreted as a treatment target. Seventh, detailed blood-loss volume and transfusion timing were unavailable, limiting causal interpretation of the observed transfusion–AKI association and leaving the possibility of confounding by indication. Eighth, low haemoglobin was operationalised as < 10 g/dL, and values were concentrated near this threshold; the cohort contained very few patients at 7–8 g/dL and none below 7 g/dL, so the findings should not be generalized to the entire 7–10 g/dL range. Ninth, AKI was defined using creatinine-based KDIGO criteria because urine-output data were unavailable, potentially underestimating AKI. Finally, the numerous post-hoc sensitivity analyses were exploratory and were not adjusted for multiple comparisons, and mortality analyses were descriptive and unadjusted. Prospective multicentre validation is required.

4.6 Clinical implications

For older surgical patients, these findings argue for contextual rather than isolated interpretation of haemoglobin. They do not show that patients with haemoglobin < 10 g/dL should be transfused earlier or more often, and they do not establish a new blood-pressure target. Instead, modest haemoglobin reduction may be more informative when considered alongside haemodynamic and renal vulnerability, particularly in adults aged ≥ 80 years with limited physiological reserve. If validated prospectively, this vulnerability–stressor framework could complement conventional geriatric and perioperative assessment by identifying patients who may benefit from closer haemodynamic surveillance and renal monitoring without implying a change in transfusion threshold.

4.7 Future research

Prospective, ideally multicentre, validation should test both interactions with adequate power for broader covariate adjustment. Future studies should compare baseline-referenced ΔMAP with absolute MAP thresholds, relative percentage reductions, duration below threshold, and time-weighted hypotension burden; collect detailed blood-loss volume and transfusion timing; incorporate urine-output criteria for AKI; and evaluate haemoglobin as a continuous exposure as well as prespecified clinically relevant ranges. Mortality should be examined as a prespecified outcome in appropriately powered models.

5. Conclusions

Among adults aged ≥ 80 years undergoing spinal anaesthesia, the association of preoperative haemoglobin < 10 g/dL with postoperative outcomes was context-dependent. For MACE, low haemoglobin alone and marked ΔMAP alone showed similarly modest unadjusted event rates, whereas the combined-exposure group had a substantially higher event rate. For AKI, elevated preoperative creatinine was already informative as an isolated marker, while low haemoglobin alone was not; the highest event rate again occurred when both exposures coexisted. Adjusted interaction and simple-effects analyses supported the interpretation that the association of modest haemoglobin reduction differed according to accompanying haemodynamic or renal vulnerability. The small combined-exposure

groups and retrospective single-centre design limit precision and causal interpretation. Prospective multicentre validation is required before these operational thresholds are used for clinical decision-making.

Abbreviations

AKI
acute kidney injury
AP
attributable proportion due to interaction
ASA
American Society of Anesthesiologists physical status
AUC
area under the receiver operating characteristic curve
CI
confidence interval
CKD
chronic kidney disease
ΔMAP
decrease in mean arterial pressure from the last preoperative ward measurement to the lowest invasive intraoperative measurement
Hb
haemoglobin
KDIGO
Kidney Disease:Improving Global Outcomes
MACE
major adverse cardiac events
MAP
mean arterial pressure
OR
odds ratio
RERI
relative excess risk due to interaction
VIF
variance inflation factor.

Declarations

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Competing interests

The authors declare that they have no competing interests.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Witten/Herdecke University .The requirement for informed consent was waived because of the retrospective study design.

Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available because they contain potentially identifiable clinical information and are subject to institutional data-protection requirements, but de-identified data may be available from the corresponding author on reasonable request and subject to applicable institutional, ethical, and data-protection approvals.

Authors' contributions

NF contributed to conceptualisation, methodology, investigation, data curation, formal analysis, validation, visualisation, writing the original draft, review and editing, and project administration. BB and UG contributed to investigation and data curation. SH and RKE contributed to supervision and review and editing. All authors read and approved the final manuscript.

Acknowledgements

Not applicable.

Consent for publication

Not applicable.

Use of generative AI and AI-assisted technologies in the writing process

During manuscript preparation, ChatGPT (OpenAI) and Claude (Anthropic) were used to assist with language editing, organisation and restructuring, formatting, and checks of internal textual and numerical consistency. These tools were not used to generate or modify study data, determine outcomes, perform the primary statistical analyses, make autonomous scientific decisions, or qualify for authorship. References and scientific claims were reviewed and verified by the authors. The authors reviewed and edited all AI-assisted content and take full responsibility for the accuracy, integrity, and originality of the manuscript.

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Figures

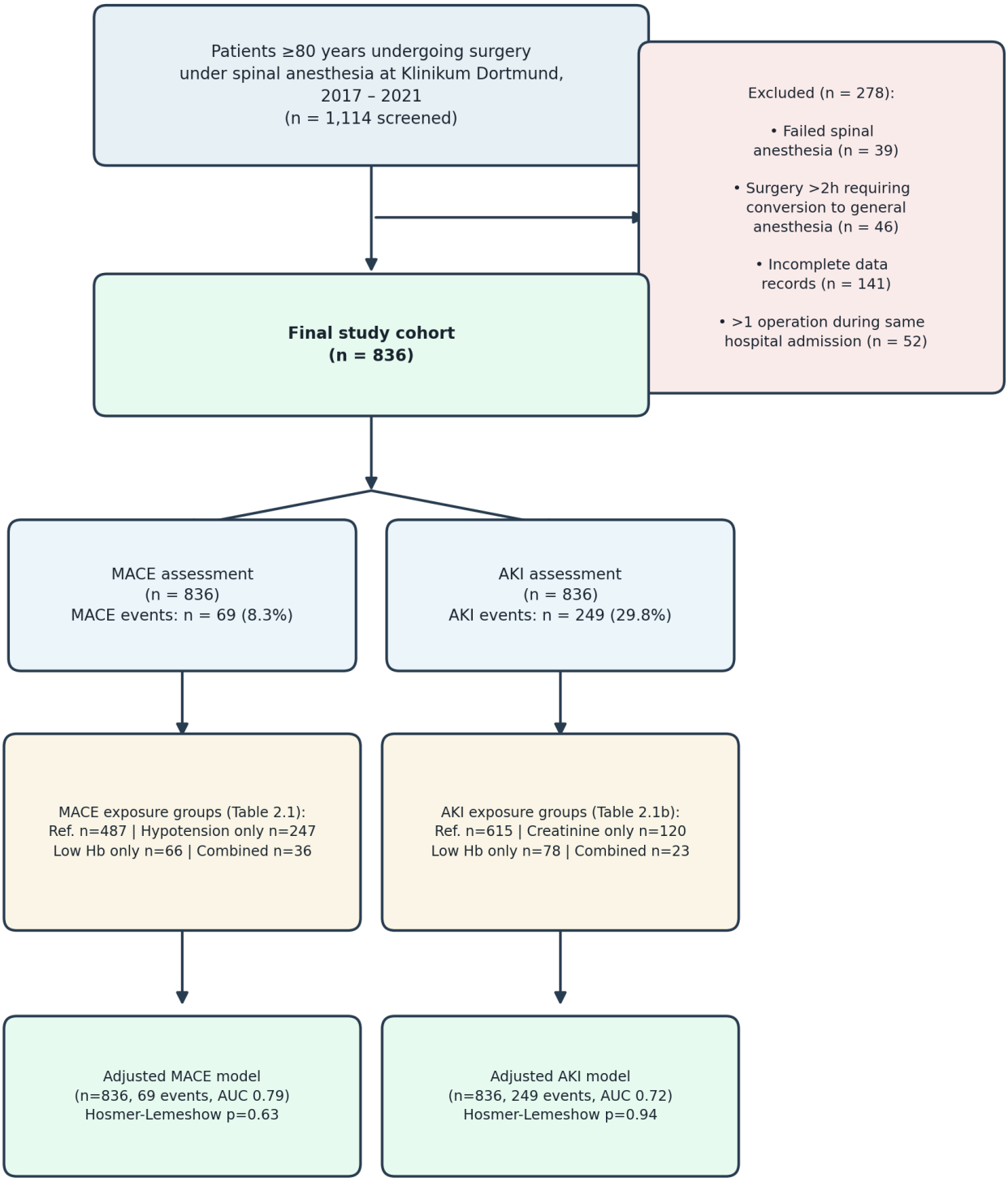


Figure 1

STROBE flow diagram of patient screening, exclusion, and inclusion, 2017–2021.

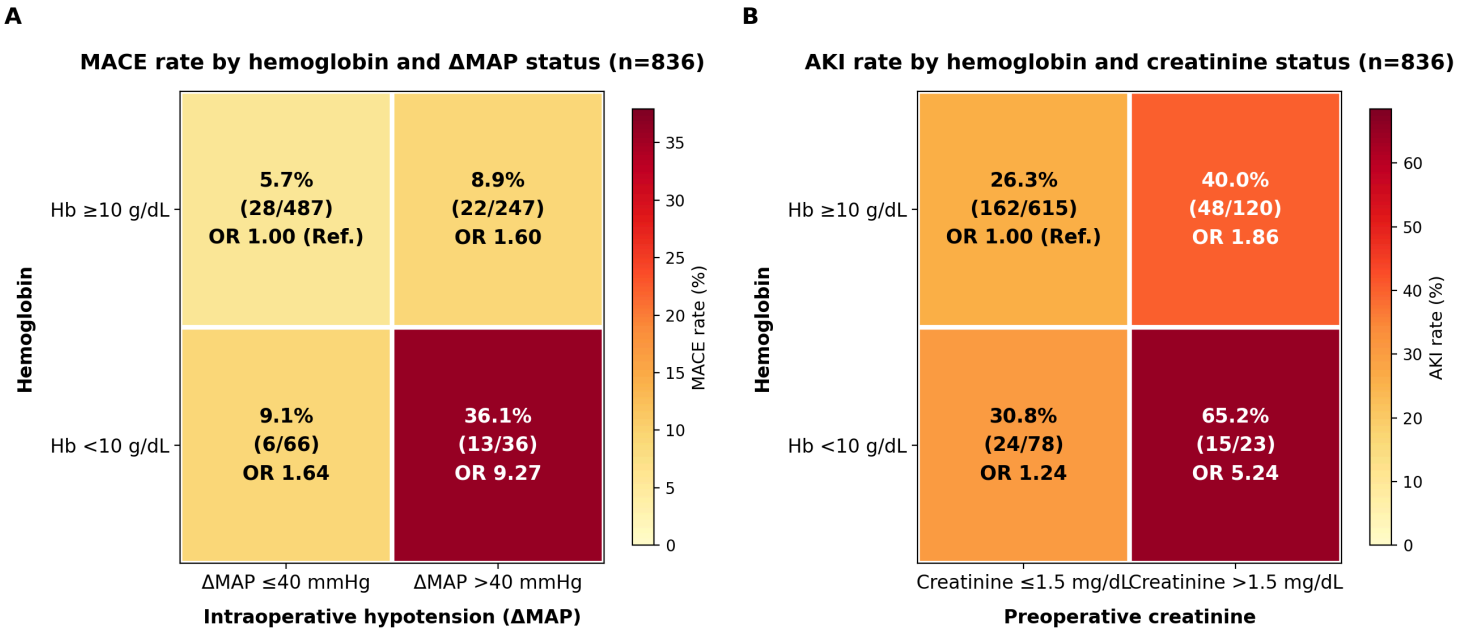


Figure 2

Unadjusted MACE and AKI rates by haemoglobin and second-stressor status (n=836 for each panel). (A) MACE by haemoglobin and ΔMAP status. (B) AKI by haemoglobin and creatinine status. The combined-exposure groups had the highest observed event rates; adjusted multiplicative interaction p=0.037 for MACE and p<0.001 for AKI (Tables 2–3).

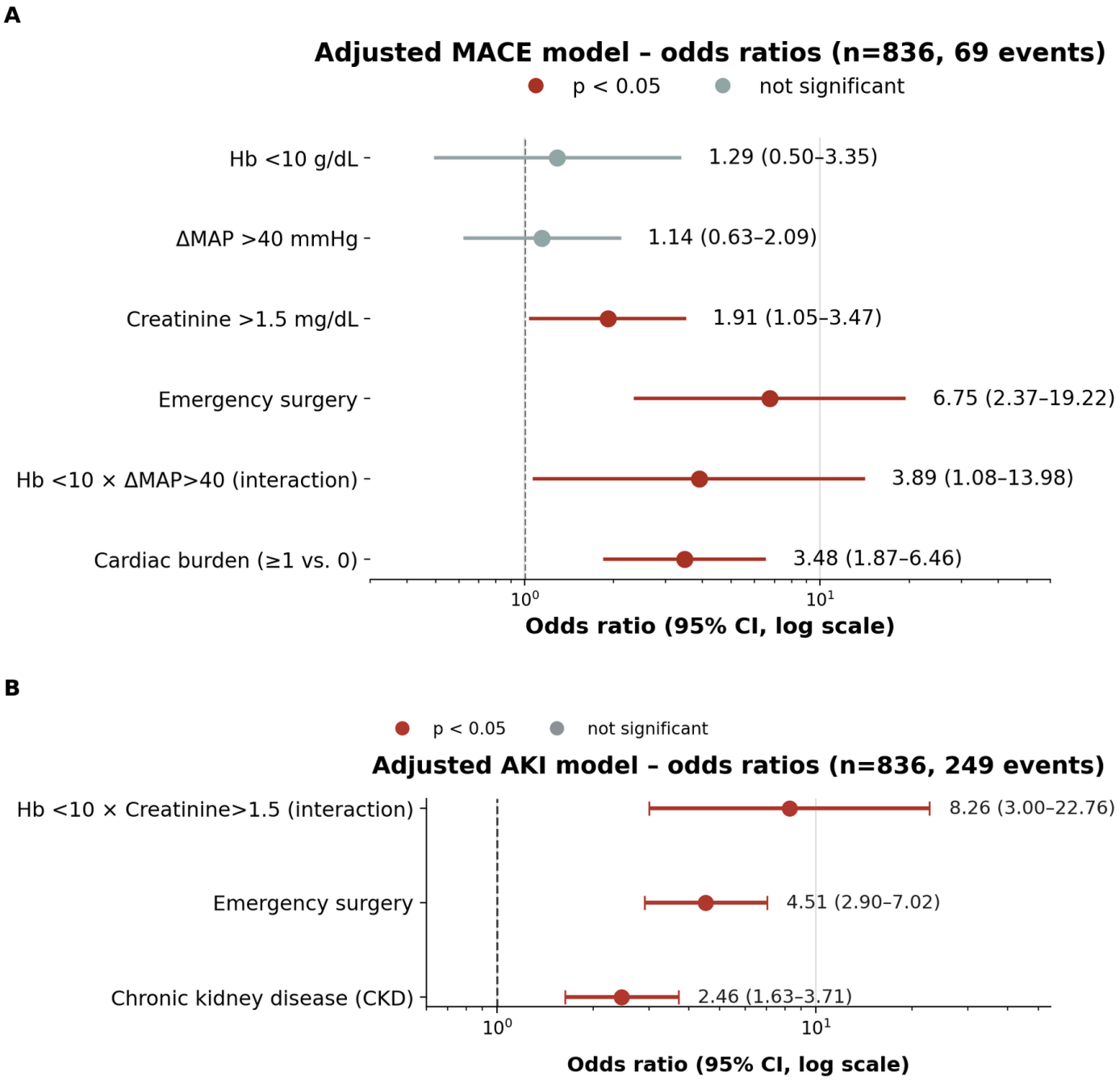


Figure 3

Adjusted multivariable models. (A) MACE model (n=836, 69 events; AUC 0.79): creatinine, emergency surgery, the haemoglobin×ΔMAP interaction, and cardiac burden (≥1 vs. 0) were significant. The haemoglobin and ΔMAP coefficients represent conditional effects at the reference level of the interacting factor and were not significant. (B) AKI model (n=836, 249 events; AUC 0.71): the haemoglobin×creatinine interaction, chronic kidney disease, and emergency surgery were significant. The haemoglobin and creatinine coefficients likewise represent conditional effects at the reference level of the interacting factor and were not significant.

Supplementary Files

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