Article

Association of Postoperative Nadir Haemoglobin Levels With Long-term Adverse Events After Elective Noncardiac Surgery

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AIM: Preoperative anaemia is a well-established risk factor for poor outcomes. However, the impact of postoperative haemoglobin (Hb) levels on long-term outcomes, including mortality and cardiovascular events, remains uncertain. This study aims to assess the independent association between postoperative nadir Hb levels and long-term outcomes, considering the potential interaction with preoperative anaemia status.

METHODS: This study is a secondary analysis of data from the Myocardial Injury in Noncardiac Surgery in Sweden study, which included patients aged ≥50 years undergoing elective noncardiac surgery. Postoperative Hb levels were measured daily for up to 3 days or until discharge, and the lowest recorded value was used as the primary exposure variable. Multivariable logistic regression analysis was employed to explore the independent association of postoperative nadir Hb with the primary outcome of a composite endpoint comprising all-cause mortality and cardiovascular complications over a one-year period, adjusting for a range of perioperative risk factors, including preoperative anaemia. To account for a potential interaction with preoperative anaemia, an interaction term was added to the model. Secondary outcomes were one-year mortality and one-year cardiovascular morbidity.

RESULTS: A total of 1284 patients were included, of whom 521 (40.6%) had preoperative anaemia. The median postoperative nadir Hb level was 102 $g \cdot L^{-1}$ (interquartile range 92–114). Postoperative nadir Hb was not independently associated with the composite primary outcome; however, it showed a weak but statistically significant association with one-year mortality (adjusted odds ratio [aOR] 0.98, 95% confidence interval [CI] 0.95–0.99). No significant interaction was found between preoperative anaemia and postoperative nadir Hb. Independent predictors of the primary outcome included university hospital status (aOR 2.83, 95% CI 1.96–4.10), age (aOR 1.05, 95% CI 1.03–1.07), and unplanned postoperative intensive care (aOR 3.17, 95% CI 1.08–9.28).

CONCLUSIONS: Postoperative nadir Hb levels, within the observed range well above 70 $g \cdot L^{-1}$, were not independently associated with the long-term composite outcome. However, they were weakly associated with one-year mortality. No significant interaction was found between preoperative anaemia and postoperative nadir Hb. These findings highlight the need for further investigation into the clinical significance of postoperative Hb levels in high-risk patients.

Keywords: long-term outcomes; noncardiac surgery; anaemia; haemoglobin

Introduction

Haemoglobin (Hb) levels often decline during the perioperative period due to multiple factors, primarily bleeding [1]. Since tissue oxygen delivery is critically dependent on Hb levels, maintaining adequate Hb is crucial to prevent adverse outcomes [2,3]. Preoperative anaemia is prevalent in the surgical population and poses a potential threat to surgical success [4–7], prompting various clinical interventions to optimise Hb levels before surgery [8]. Blood transfusion, traditionally employed to increase Hb levels [9,10], has consistently been linked to higher complication rates [11–13]. The lowest postoperative Hb level, referred to as nadir Hb, typically occurs around the third postoperative day, after which it tends to stabilize [14,15]. Practising clinicians react differently to low or declining Hb levels, both of which have been linked to poorer short-term outcomes and an increased risk of postoperative complications [16–18], especially adverse cardiovascular events [19–21]. However, whether the nadir Hb is a reliable indicator of long-term outcomes is not well studied.

Physiological adaptations in anaemic patients may alter their tolerance to low postoperative Hb levels [22], raising the question of whether the impact of postoperative nadir

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Hb on long-term morbidity and mortality differs based on preoperative anaemia status or other clinical factors. To address the importance of numerical values of Hb level, we aimed to investigate the independent association of postoperative nadir Hb levels with one-year mortality and cardiovascular morbidity, considering a possible interaction of preoperative anaemia, as it may affect postoperative Hb recovery and, most importantly, the long-term outcomes.

Methods

This study is a pre-planned secondary analysis of data collected for the Myocardial Injury in Noncardiac Surgery in Sweden (MINSS) study and was included in the MINSS registration at ClinicalTrials.gov (Identifier: NCT03436238) [23]. It is reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [24], and it complies with the Declaration of Helsinki. Ethical approval for the MINSS study and all sub-studies, including this sub-study, was granted by the Regional Ethical Committee in Linköping, Sweden, on March 29, 2017 (No. 2017/23-31). Patient enrolment occurred between April 2017 and December 2020. Upon inclusion, participants were provided with information about the MINSS study and its sub-studies, after which written informed consent was obtained, with explicit assurance of their right to withdraw from the study.

The study population included patients aged $\geq$50 years who underwent elective major or complex noncardiac surgeries requiring postoperative overnight hospitalisation [25]. Patients with missing preoperative or postoperative Hb measurements in the MINSS dataset were not eligible for this study. Preoperative Hb levels, measured up to 24 hours before surgery, were used to determine preoperative anaemia status, adopting the World Health Organisation definition of anaemia [26,27]. Daily Hb level measurements for up to 3 days postoperatively or until discharge were collected by research group members [15]. The lowest recorded value of Hb levels from up to 3 consecutive daily measurements (nadir Hb) was considered the primary exposure and treated as a continuous variable. Independent covariates were coded either as dichotomous (hospital status, sex, smoking, metastatic cancer, preoperative anaemia, and intraoperative erythrocyte transfusion), continuous (age, body mass index, number of chronic comorbidities, duration of surgery, and intraoperative blood loss), or categorical variables (American Society of Anesthesiologist Physical Status [ASA PS] and direct postoperative destination). Follow-up data on patient status and cardiovascular events at 30 days for the MINSS study were extended to include 1 year follow-up data as well.

The primary outcome was a composite of all-cause mortality and cardiovascular morbidity occurring within one-year post-surgery, i.e., from postoperative day 1 as earliest through day 365 as latest [28]. Morbidity was defined as adverse cardiovascular events and included perioperative myocardial injury defined as an increase in postoperative high-sensitivity Troponin T (hs-TnT) level of $\geq$14 ng$\cdot$L^{-1} over preoperative level (in any sample collected within three days post-surgery) [23], myocardial infarction, congestive heart failure, new arrhythmia, angina pectoris, cerebrovascular incident, transient ischaemic attack, or nonfatal cardiac arrest (registered within 1 year after surgery) [29–31]. Secondary outcomes were one-year mortality and one-year cardiovascular morbidity as defined above.

Statistical Analysis

All eligible patients were included in the analysis; therefore, no a priori sample size calculation was performed. Perioperative risk factors considered for the explanatory model were selected based on previously demonstrated associations in the literature or on plausible theoretical and clinical relevance. However, variance inflation factor (VIF) measurements for these factors were conducted to assess multicollinearity and singularity. Factors with VIF $\leq$4 were considered for the analysis. The Box-Tidwell test was used to evaluate the logit linearity assumption for continuous variables and to address no violation if it returned non-significant.

Adhering to the recommendations for dealing with missing follow-up data, patients with complete outcome data up to one-month post-surgery but missing one-year morbidity and/or mortality data were included in the analysis if the individual component missingness was $\leq$5% or collectively comprised $\leq$1% of the whole cohort [32]. Missing one-year follow-up data were assessed with a non-significant Little's Missing Completely at Random (MCAR) test result and completed using the Expectation–Maximization (EM) method [32]. Descriptive statistics were selected according to variable type and distribution. Continuous variables with approximately normal distributions were summarised as mean $\pm$ standard deviation (SD), whereas skewed continuous variables were presented as median with interquartile range (IQR). Categorical variables were reported as counts (n) with corresponding percentages (%).

A multivariable logistic regression model was used to assess the independent effect of nadir Hb on the outcomes. An interaction term (preoperative anaemia $\times$ postoperative nadir Hb) was inserted to explore potential effect modification, along with all other perioperative risk factors as covariates without stepwise selection or exclusion based on *p*-values [33]. Adjusted odds ratios (aORs) with 95% confidence intervals (CIs) were reported for all independent variables and the interaction term. Model fit was evaluated using the Hosmer-Lemeshow test [34]. The influence of outliers was ruled out by measuring Cook's distance to confirm the model's robustness. All statistical analyses were performed using SPSS version 30 (SPSS Inc., Chicago, IL, USA), with two-sided tests and a significance level set at 0.05.

Results

A total of 1284 patients were included in this sub-study after exclusion of seven patients (0.5%) from the MINSS cohort of 1291 patients due to either a missing preoperative (6 patients) or postoperative (1 patient) Hb measurement (Fig. 1). Patients' perioperative data and outcome measures are presented in Table 1.

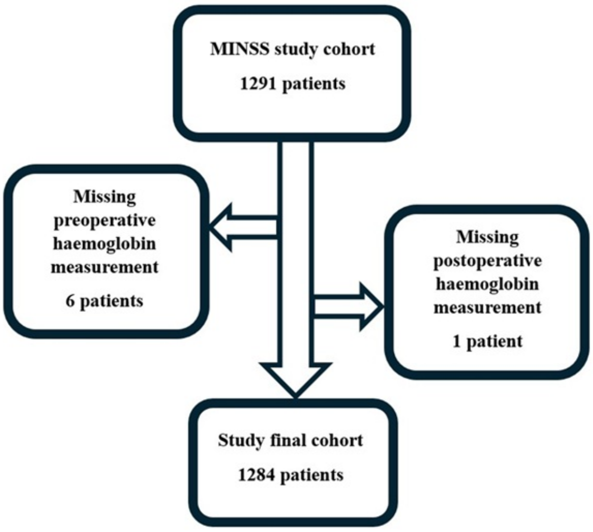

Fig. 1. Study flow diagram. MINSS, Myocardial Injury in Noncardiac Surgery in Sweden.

The median preoperative Hb level was 128 g·L^{-1} (IQR 115–138), declining to 116 g·L^{-1} (IQR 104–127) after surgery. Postoperative haemoglobin levels continued to decline during the three-day follow-up but remained above 70 g·L^{-1} except in a single outlier, with a measured Hb level of 66 g·L^{-1}. Median Hb levels on day 1–3 were 110 (IQR 100–121), 105 (IQR 95–116), and 104 (IQR 95–113) g·L^{-1}, respectively (Fig. 2). Nadir Hb was recorded on day 0 through 3 in 15%, 21%, 26%, and 38% of cases respectively. The median postoperative nadir Hb level was 102 g·L^{-1} (IQR 92–114). Little´s MCAR test resulted in a *p*-value of 0.743, and after adopting the EM method to obtain complete primary outcome data, we could confirm it in 271 patients (21.1% of the whole cohort).

Univariable logistic regression revealed the significant but unadjusted associations of several perioperative variables and the primary outcome (see **Supplementary Table 1**). In multivariable analysis (Table 2), neither preoperative anaemia nor postoperative nadir Hb showed an independent association with the primary outcome. No interaction was observed between preoperative anaemia status and postoperative nadir Hb level, due to a non-significant interaction term that also caused a wide confidence interval for its component (preoperative anaemia). Independent predictors of the primary outcome were surgery in a university hospital (aOR 2.83, 95% CI 1.96–4.10), advancing age (aOR 1.05 per year, 95% CI 1.03–1.07), and unplanned postoperative intensive care (aOR 3.17, 95% CI 1.08–9.28). Results of the logistic regression analysis for the primary composite outcome were consistent in the sensitivity analysis conducted after stratification by the significant dichotomous university hospital status variable to rule out an overshadowing effect of surgical complexity (see **Supplementary Table 2**).

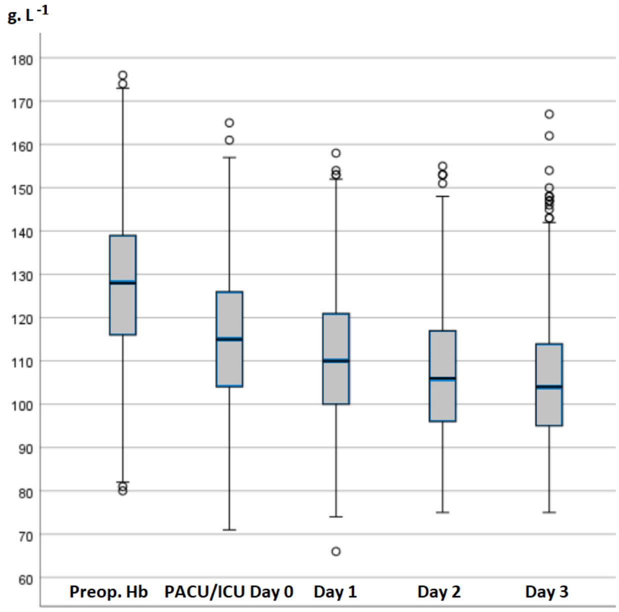

Fig. 2. Box-and-whisker plot representing the preoperative and postoperative haemoglobin levels (Day 0 to Day 3). Hb, haemoglobin; PACU/ICU, post-anaesthesia or intensive care unit.

Multivariable analyses of the secondary outcomes demonstrated slightly different patterns (Table 3). Age and university hospital surgery remained significant predictors for both outcomes. Metastatic cancer was independently associated with one-year mortality (aOR 2.34, 95% CI 1.45–3.78), while the number of preoperative comorbidities was associated with postoperative cardiovascular events (aOR 1.29, 95% CI 1.11–1.49). Postoperative nadir Hb was weakly associated with one-year mortality (aOR 0.98, 95% CI 0.95–0.99), but no significant association with cardiovascular morbidity was observed (Table 3).

Discussion

No statistically significant independent association was observed between postoperative nadir Hb levels within the observed range and the composite outcome of one-year cardiovascular events and mortality. This may reflect the relatively safe postoperative Hb level range maintained across participating centres in the MINSS study, which aligns with current evidence-based recommendations [35,36]. Unplanned postoperative ICU admission, advancing age, and hospital type emerged as stronger and more consistent predictors of adverse outcomes, highlighting the importance of

Table 1. Characteristics of the study population and the outcome measures.

Perioperative data and outcome measures	n = 1284
Surgery in university hospital, n (%)	863 (67.2%)
Age (year), median (IQR)	70 (63–76)
Sex, male, n (%)	696 (54.2%)
Smoking, n (%) [(a)]	128 (10.0%)
Body mass index ($kg \cdot m^{-2}$), mean (±SD)	26.6 (±4.7)
American Society of Anesthesiologists Physical Status (ASA PS)	
ASA PS I, n (%)	155 (12.1%)
ASA PS II, n (%)	723 (56.3%)
ASA PS III, n (%)	397 (30.9%)
ASA PS IV, n (%)	9 (0.7%)
Comorbidities, n (%)	
Hypertension [(b)]	636 (49.6%)
Hyperlipidaemia	217 (16.9%)
Chronic obstructive pulmonary disease	167 (13.0%)
Ischaemic heart disease	168 (13.1%)
Atrial fibrillation	123 (9.6%)
Cerebrovascular incident or stroke	107 (8.3)
Insulin-dependent diabetes mellitus	101 (7.9%)
Heart failure	69 (5.4%)
Chronic kidney failure	14 (1.1%)
Liver cirrhosis	7 (0.5%)
Metastatic cancer [(c)], n (%)	163 (12.7%)
Number of comorbidities (excluding cancer) [(d)], median (IQR)	1 (0–2)
Preoperative anaemia [(e)], n (%)	521 (40.6%)
Surgical category (%) [(f)]	
Colorectal	466 (36.3%)
Hepatobiliary	241 (18.8%)
Pancreas	193 (15.1%)
Renal	115 (9.0%)
Upper gastrointestinal	108 (8.4%)
Gynaecology	72 (5.6%)
Urology (not renal)	66 (5.1%)
Other	21 (1.6%)
Duration of surgery (minutes), median (IQR)	206 (135–327)
Intraoperative blood loss (mL), median (IQR)	150 (50–400)
Intraoperative erythrocyte transfusion, n (%)	131 (10.2%)
Postoperative destination directly after surgery	
Post-Anaesthesia Care Unit, n (%)	1253 (97.6%)
Intensive Care Unit, planned admission, n (%)	13 (1.0%)
Intensive Care Unit, unplanned admission, n (%)	18 (1.4%)

Table 1. Continued.

Perioperative data and outcome measures	n = 1284
Postoperative nadir haemoglobin level ($g{\cdot}L^{-1}$), median (IQR)	102 (92–114)
Primary outcome [(g)], n (%) [complete data for 1273 (99.1%)]	271 (21.1%)
Secondary outcome 1 [(h)], n (%) [data for 1273 (99.1%)]	119 (9.3%)
Secondary outcome 2 [(i)], n (%)	194 (15.1%)

IQR, interquartile range; SD standard deviation.
(a) Data for 1280 (99.7% of the cohort).
(b) Data for 1282 (99.8% of the cohort).
(c) Metastatic cancer as a separate comorbidity.
(d) Number of comorbidities in total, encompassing ischaemic heart disease, heart failure, insulin-dependent diabetes mellitus, chronic renal failure, cerebrovascular incident or stroke, hyperlipidaemia, hypertension, atrial fibrillation, chronic obstructive pulmonary disease, and liver cirrhosis.
(e) According to the World Health Organisation definition of anaemia as haemoglobin levels below 130 $g{\cdot}L^{-1}$ for men and 120 $g{\cdot}L^{-1}$ for women.
(f) Data for 1282 (99.8% of the cohort).
(g) Primary outcome is a composite of morbidity and all-cause mortality occurring after the day of nadir Hb and within one year after surgery. Morbidity encompasses perioperative myocardial injury within 3 days of surgery (i.e. increase in high-sensitivity Troponin T level $\geq$14 $ng{\cdot}L^{-1}$ over the preoperative level), myocardial infarction, congestive heart failure, new arrhythmia, angina pectoris, cerebrovascular incident, transient ischaemic attack, or nonfatal cardiac arrest within 1 year after surgery.
(h) Secondary outcome 1 is one-year all-cause mortality.
(i) Secondary outcome 2 is one-year morbidity (cardiovascular events occurring after nadir haemoglobin day) as defined in (g).

patient frailty and surgical complexity, and possibly overshadowing the impact of postoperative nadir haemoglobin level for the composite outcome in this cohort. Advancing age remains a significant factor in the sensitivity analysis after stratifying by the hospital type. However, a weak negative but statistically significant association of nadir Hb with one-year mortality has also been noted, with a notable significance of cancer for this secondary outcome. For the long-term cardiovascular morbidity outcome, preoperative multimorbidity and advancing age emerged as the significant factors, in line with the clinical expectations, but with no association with postoperative nadir Hb. The lack of interaction between preoperative anaemia and postoperative nadir Hb suggests that, while preoperative anaemia is a well-established surgical risk factor [5,7], nadir Hb level association with the composite outcome was not influenced by preoperative anaemia status.

The previous study has highlighted an association between lower postoperative Hb levels and in-hospital or short-term myocardial injury, increased risk of ischaemic complications, and early mortality after noncardiac surgery [37]. Postoperative anaemia has also been identified as a modifiable risk factor for non-fatal myocardial infarction and all-cause mortality within 3 days post-surgery [21]. Hb variation rather than absolute nadir values has been suggested as a more relevant predictor of adverse outcomes [38,39]. For instance, a $\geq$50% decline in Hb following gastrointestinal surgery, even when nadir Hb remained above 70 $g{\cdot}L^{-1}$, has been linked to increased ischaemic complications [40]. In our cohort and only for simple comparison, the percentage of decline of median Hb level was 18% (IQR 11–25) with a maximum decrease of 45% from the preoperative level, yet postoperative Hb values generally remained above critical transfusion thresholds [41,42], except for a single outlier. Evaluation of the perioperative percentage of decline of Hb level was not within the scope of this study.

Long-term surgical outcomes are sparsely studied in a similar case-mix with attention on postoperative nadir Hb level or on a possible interaction with preoperative anaemia, our findings remain novel and need larger cohorts with extensive perioperative data to confirm their validity and applicability in clinical settings. Although they may contrast with prior research emphasizing postoperative anaemia as a predictor of poor outcomes, particularly in cardiac and critically ill patients [40,43–45], they may align with research highlighting individualised transfusion thresholds and patient-specific tolerance to low Hb levels [46–48]. Literature confirms that preoperative Hb level is a significant

Table 2. Multivariable logistic regression analysis for the primary outcome [(1)].

Perioperative factors	aOR (95% CI)	p
Surgery in university hospital	2.83 (1.96–4.10)	<0.001
Age (per year)	1.05 (1.03–1.07)	<0.001
Sex, male	1.14 (0.84–1.54)	0.410
Smoking [(a)]	1.07 (0.66–1.76)	0.779
Body mass index (per 1 $kg{\cdot}m^{-2}$)	0.99 (0.95–1.02)	0.448
American Society of Anesthesiologists Physical Status (ASA PS)		
ASA PS I (reference)	1	
ASA PS II	1.37 (0.24–7.72)	0.721
ASA PS III	1.28 (0.25–6.63)	0.769
ASA PS IV	1.85 (0.36–9.48)	0.458
Metastatic cancer [(b)]	1.38 (0.93–2.06)	0.114
Number of comorbidities (excluding cancer) [(c)]	1.12 (0.98–1.29)	0.089
Preoperative anaemia [(d)]	1.93 (0.16–23.60)	0.607
Duration of surgery (per hour)	1.06 (0.99–1.13)	0.095
Intraoperative blood loss (per Liter)	0.90 (0.74–1.11)	0.323
Intraoperative erythrocyte transfusion	1.04 (0.64–1.68)	0.876
Postoperative destination directly after surgery		
Post–Anaesthesia Care Unit (reference)	1	
Intensive Care Unit, planned admission	1.86 (0.55–6.26)	0.317
Intensive Care Unit, unplanned admission	3.17 (1.08–9.28)	0.036
Postoperative nadir haemoglobin level (per $g{\cdot}L^{-1}$)	0.99 (0.97–1.01)	0.123
Interaction Term (Preoperative anaemia × Nadir Hb)	1.00 (0.98–1.03)	0.989

(1) Primary outcome is a composite of morbidity and all-cause mortality occurring after the day of nadir Hb and within one year after surgery. Morbidity encompasses perioperative myocardial injury within 3 days of surgery (i.e., increase in high-sensitivity Troponin T level $\geq$14 $ng{\cdot}L^{-1}$ over the preoperative level), myocardial infarction, congestive heart failure, new arrhythmia, angina pectoris, cerebrovascular incident, transient ischaemic attack, or nonfatal cardiac arrest within 1 year after surgery.

aOR, adjusted odds ratio; CI, confidence interval.

(a) Data for 1280 (99.7% of the cohort).

(b) Metastatic cancer as a separate comorbidity.

(c) Number of comorbidities in total, encompassing ischaemic heart disease, heart failure, insulin-dependent diabetes mellitus, chronic renal failure, cerebrovascular incident or stroke, hyperlipidaemia, hypertension, atrial fibrillation, chronic obstructive pulmonary disease, and liver cirrhosis.

(d) According to the World Health Organisation definition of anaemia as haemoglobin levels below 130 $g{\cdot}L^{-1}$ for men and 120 $g{\cdot}L^{-1}$ for women.

predictor of long-term cardiovascular events, independent of perioperative erythrocytes transfusions [13,49], therefore, absence of a statistical effect modification of preoperative anaemia on the association of postoperative nadir Hb and the composite outcome can be explained either by an individualised patient care in the participating centres, acceptable yet declining postoperative Hb levels in this cohort, or the physiological adaptation of anaemic patients.

Blood transfusion is usually considered to manage a low or declining Hb level in the early postoperative period, but the complex relationship between postoperative Hb level or its threshold and outcomes is rooted in the conflicting findings in the literature. While some studies associate nadir Hb levels below 90 $g{\cdot}L^{-1}$ with increased adverse events [43,50], others suggest that transfusion at Hb levels above 80 $g{\cdot}L^{-1}$ offers no benefit and may even be harmful [48]. This paradox underscores the need for caution when considering red cell transfusion, as transfusion itself has been linked to poorer short- and long-term surgical outcomes [18]. Our findings go in line with a cautious approach, reinforcing the view that Hb concentration alone is not the most informative marker of transfusion need and emphasizing the need for individualised patient care [41]. In our cohort, anaemic patients received more blood transfusions despite less surgical bleeding intraoperatively and had generally lower nadir Hb, and this possibly may reflect part of the individualised patient management. Furthermore, the strong association between unplanned ICU admission and poor outcomes highlights the importance of early perioperative risk stratification and optimised postoperative care pathways [51,52].

Table 3. Multivariable logistic regression analysis for the secondary outcomes. Secondary outcome 1 is the one-year all-cause mortality (1), and secondary outcome 2 is the one-year cardiovascular morbidity (2).

	Secondary outcome 1 (1)		Secondary outcome 2 (2)	
Perioperative factors	aOR (95% CI)	p	aOR (95% CI)	p
Surgery in university hospital	3.53 (1.98–6.29)	<0.001	2.22 (1.48–3.32)	<0.001
Age (per year)	1.04 (1.01–1.06)	0.008	1.06 (1.03–1.08)	<0.001
Sex, male	0.96 (0.63–1.45)	0.841	1.26 (0.88–1.78)	0.204
Smoking (a)	1.57 (0.84–2.92)	0.156	0.97 (0.54–1.72)	0.903
Body mass index (per 1 kg·m^{-2})	0.98 (0.94–1.03)	0.489	0.99 (0.95–1.03)	0.593
American Society of Anesthesiologists Physical Status (ASA PS)				
ASA PS I (reference)		1		1
ASA PS II	0.93 (0.46–1.88)	0.841	0.75 (0.39–1.42)	0.378
ASA PS III	1.16 (0.51–2.63)	0.725	1.23 (0.60–2.52)	0.574
ASA PS IV	1.48 (0.15–14.60)	0.740	0.80 (0.14–4.68)	0.801
Metastatic cancer (b)	2.34 (1.45–3.78)	<0.001	0.84 (0.51–1.38)	0.482
Number of comorbidities (excluding cancer) (c)	0.92 (0.76–1.11)	0.388	1.29 (1.11–1.49)	<0.001
Preoperative anaemia (d)	0.36 (0.01–11.80)	0.564	2.67 (0.15–47.90)	0.504
Duration of surgery (per hour)	1.06 (0.97–1.16)	0.180	1.09 (1.02–1.17)	0.016
Intraoperative blood loss (per Liter)	0.94 (0.75–1.17)	0.569	0.86 (0.66–1.14)	0.301
Intraoperative erythrocyte transfusion	1.51 (0.85–2.67)	0.163	0.98 (0.57–1.69)	0.936
Postoperative destination directly after surgery				
Post–Anaesthesia Care Unit (reference)		1		1
Intensive Care Unit, planned admission	2.30 (0.56–9.47)	0.249	2.42 (0.66–8.86)	0.183
Intensive Care Unit, unplanned admission	1.54 (0.37–6.34)	0.553	3.70 (1.23–11.14)	0.020
Postoperative nadir haemoglobin level (per g·L^{-1})	0.98 (0.95–0.99)	0.029	1.00 (0.98–1.01)	0.541
Interaction Term (Preoperative anaemia × Nadir Hb)	1.02 (0.98–1.05)	0.380	1.00 (0.97–1.02)	0.717

(1) Secondary outcome 1 is all-cause mortality occurring after the day of nadir Hb and within one year after surgery.

(2) Secondary outcome 2 is a composite of morbidities and encompasses perioperative myocardial injury within 3 days of surgery (i.e. increase in high-sensitivity Troponin T level $\geq$14 ng·L^{-1} over the preoperative level), myocardial infarction, congestive heart failure, new arrhythmia, angina pectoris, cerebrovascular incident, transient ischaemic attack, or nonfatal cardiac arrest within 1 year after surgery.

(a) Data for 1280 (99.7% of the cohort).

(b) Metastatic cancer as a separate comorbidity.

(c) Number of comorbidities in total, encompassing ischaemic heart disease, heart failure, insulin-dependent diabetes mellitus, chronic renal failure, cerebrovascular incident or stroke, hyperlipidaemia, hypertension, atrial fibrillation, chronic obstructive pulmonary disease, and liver cirrhosis.

(d) According to the World Health Organisation definition of anaemia as haemoglobin levels below 130 g·L^{-1} for men and 120 g·L^{-1} for women.

For one-year all-cause mortality, in addition to the weak effect of nadir Hb, metastatic cancer demonstrated an independent association, consistent with clinical expectations given the limited life expectancy of these patients [50]. In contrast, multiple chronic comorbidities were independently associated with one-year postoperative cardiovascular events but not with all-cause mortality. These distinctions highlight that mortality is primarily driven by high-burden, isolated conditions such as metastatic cancer, whereas cardiovascular events are more closely linked to the cumulative impact of chronic comorbidities. Our decision to sum up comorbidities in one continuous variable and treat metastatic cancer as a separate perioperative risk factor allowed for better reflection of the cumulative burden of comorbidity while maintaining granularity in the analysis. In a further sensitivity analysis for the one-year mortality and after stratifying for the significant dichotomous metastatic cancer variable, only preoperative anaemia was a significant factor for patients with cancer.

Several limitations should be acknowledged. First, residual confounding cannot be entirely ruled out despite rigorous adjustments [34], because apart from the number of chronic comorbidities and ASA PS, we did not include other indices commonly used to predict poorer surgical outcomes, as this could have complicated the model without an obvious benefit. Second, our analysis focused on the numerical value of nadir Hb, not on the shift in it or the percentage of decline, and only within the first three postoperative days, because Hb fluctuations beyond this period may also influence long-term outcomes [14]. Third, the limited sample size, the fewer secondary outcome events, and the number of variables in the regression model could have resulted in overfitting and uncertain results. Finally, our cohort consisted exclusively of patients undergoing major noncardiac surgeries, which may limit the generalisability of our findings to other surgical populations. Moreover, neither perioperative anaemia management nor surgical category was considered in the analysis.

Future research should explore the impact of postoperative nadir Hb on patient-centred outcomes, including functional recovery, quality of life, and long-term complications beyond one year. Additionally, randomized trials comparing different transfusion strategies in this population could further elucidate optimal perioperative Hb thresholds for improving patient outcomes while minimizing unnecessary transfusions [35,44,46,49].

Conclusions

In conclusion, among patients undergoing major noncardiac surgery, postoperative nadir Hb levels within the observed range over 70 g·L^{-1} were not independently associated with long-term mortality and cardiovascular events. Preoperative anaemia did not modify this relationship. Instead, factors such as advancing age, unplanned ICU admission, and hospital type emerged as stronger predictors of adverse outcomes. These findings suggest that restrictive transfusion strategies maintaining Hb above critical levels are generally appropriate. Future research should focus on the clinical implications of Hb variability, individualised transfusion approaches, and the long-term impact of perioperative anaemia management.

Availability of Data and Materials

The data supporting the findings of this sub-study are available from the corresponding author upon reasonable request and following approval by the steering committee of the Myocardial Injury after Noncardiac Surgery in Sweden study.

Author Contributions

MJ and AB designed the research study. MJ performed the research. AB contributed to the statistical methods. MJ analyzed the data and drafted the manuscript. Both authors contributed to the critical revision of the manuscript for important intellectual content. Both authors read and approved the final manuscript. Both authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This sub-study complies with the Declaration of Helsinki. Ethical approval for the Myocardial Injury after Noncardiac Surgery in Sweden (MINSS) study and all sub-studies, including this sub-study, was granted by the Regional Ethical Committee in Linköping, Sweden, on March 29, 2017 (No. 2017/23-31). Upon inclusion, participants were provided with information about the MINSS study and its substudies, after which written informed consent was obtained, with explicit assurance of their right to withdraw from the study.

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Conflict of Interest

Monir Jawad is serving as one of the Editorial Board Members of this journal. We declare that Monir Jawad had no involvement in the peer review of this article and has no access to information regarding its peer review. The other author declares no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.62713/aic.4416.

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