ESC European Society of Cardiology

European Heart Journal Open (2022) **2**, 1–10
https://doi.org/10.1093/ehjopen/oeac040

ORIGINAL ARTICLE
Coronary artery disease

Relevance of pre-existing anaemia for patients admitted for acute coronary syndrome to an intensive care unit: a retrospective cohort analysis of 7418 patients

**Patricia Wischmann[1], Raphael Romano Bruno[1], Bernhard Wernly[2,3], Georg Wolff [1], Shazia Afzal[1], Richard Rezar[4], Mareike Cramer[1], Nadia Heramvand[1], Malte Kelm [1,5], and Christian Jung[1]*

[1]Division of Cardiology, Pulmonology and Vascular Medicine, Medical Faculty, University Hospital Düsseldorf, Heinrich Heine University Düsseldorf, Moorenstr. 5, 40225 Düsseldorf, Germany; [2]Institute of General Practice, Family Medicine and Preventive Medicine, Paracelsus Medical University, Strubergasse 21, 5020 Salzburg, Austria; [3]Center for Public Health and Healthcare Research, Paracelsus Medical University Salzburg, Strubergasse 21, 5020 Salzburg, Austria; [4]Clinic of Internal Medicine II, Department of Cardiology, Paracelsus Medical University of Salzburg, Strubergasse 21, 5020 Salzburg, Austria; and [5]Cardiovascular Research Institute Düsseldorf (CARID), Heinrich Heine University, Moorenstraße 5, 40225 Duesseldorf, Germany

Received 27 March 2022; revised 30 May 2022; accepted 13 June 2022; online publish-ahead-of-print 15 June 2022

Handling Editor: Magnus Bäck

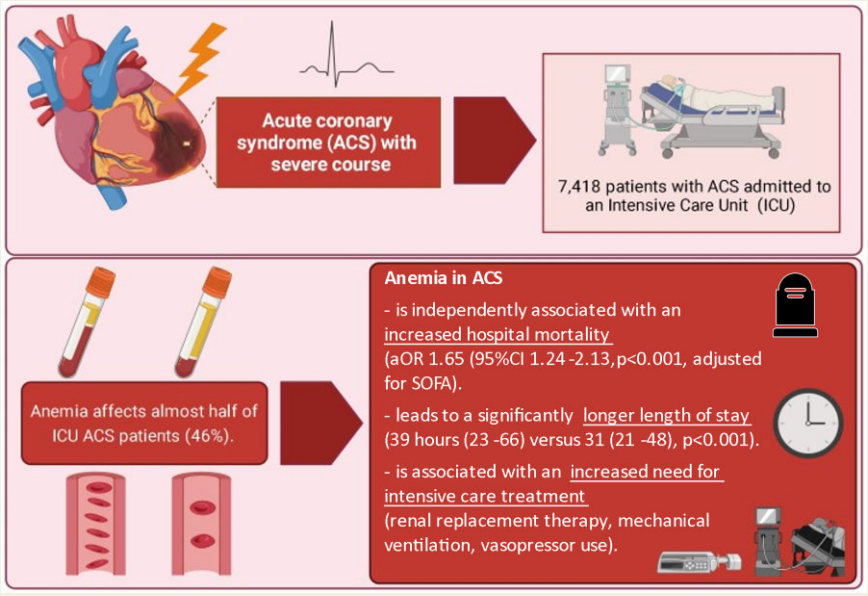
Aims Patients with acute coronary syndrome (ACS) frequently suffer from anaemia, but its role in patients admitted to an intensive care unit (ICU) is unclear. This analysis evaluates the prognostic relevance of different degrees of anaemia and their specific impact on disease severity and the outcome in critically ill ACS patients.

Methods and results and results The multi-centre electronic Intensive Care Unit Collaborative Research Database was used, and all patients admitted with ACS were included in a retrospective analysis. Anaemia and its degrees were defined according to the criteria by the World Health Organization. A multi-level logistic regression analysis was used to fit three sequential regression models for the binary primary outcome of hospital mortality. A total of 7418 patients were included; 3437 patients (46%) had anaemia on admission. Patients with anaemia were significantly older [61 (53–70) vs. 70 (61–78) years, $P < 0.001$], more often female ($P < 0.001$), and required an increased rate of vasopressor use ($P < 0.001$) and mechanical ventilation ($P < 0.001$). With the higher Sequential organ failure assessment score (1 vs. 2; $P < 0.001$) and Acute Physiology And Chronic Health Evaluation (35 vs. 47; $P < 0.001$) scores, a higher degree of anaemia was associated with prolonged ICU stay (2 vs. 5 days, $P < 0.001$). Even patients with mild anaemia needed significantly from more intensive treatment and suffered worse outcome. Intensive care unit and hospital mortality were inversely associated with haemoglobin levels.

Conclusion Nearly half of critically ill patients with ACS suffer from anaemia, which is associated with increased illness severity, complex ICU procedures, and mortality—even in mild anaemia. Haemoglobin on admission is an independent factor for adverse outcome.

* Corresponding author. Tel: +49 211 81 18801, Fax: +49 211 81 18812, Email: christian.jung@med.uni-duesseldorf.de

Graphical Abstract



Designed with biorender®.

Keywords Anaemia • Intensive care • Critically ill • Acute coronary syndrome • Risk stratification • Myocardial infarction

Introduction

Morbidity and mortality of patients with acute coronary syndromes (ACS) decreases due to improved strategies in revascularization and pharmacological treatment, but the incidence and relevance of comorbidities are increasing.[1] There is no convincing evidence for effective dedicated treatment of comorbidities in ACS such as hyperglycaemia, iron deficiency, and anaemia, although they are pivotal for the short- and long-term prognosis.[2–4] In fact, anaemia is a common comorbidity in patients suffering from ACS.[5–8] Under these circumstances, anaemia may reflect its own entity but also might mirror several other comorbidities such as consumptive cancer, malnutrition, and advanced renal failure, among others. In addition, anaemia also directly aggravates tissue hypoxia, as critical anaemia may be more relevant in local perfusion deficits such as in ACS. The incidence of this comorbidity is still rising.[9,10] The estimated prevalence of anaemia on admission in the setting of ACS is between 10 and 43%.[11] Several cohort studies have consistently demonstrated that lower haemoglobin levels at admission are associated with adverse outcomes in patients suffering from chronic coronary syndrome[4,12,13] and in ACS.[14] Wester *et al.*[14] demonstrated in the VALIDATE-SWEDEHEART trial that patients with anaemia had nearly doubled mortality after 180 days. Significantly less information exists about patients with high-risk ACS and anaemia admitted to an intensive care unit (ICU).[15,16] Most of the studies investigating the role of pre-existing anaemia on the impact of critically ill ACS patients were only single-centred and analysed comparatively few patients, although anaemia in cardiovascular ICU patients has a significant number of consequences, including its influence on blood pressure, tissue perfusion, renal function, neurohumoral activation, and its haemodynamic consequences.[17]

However, until now, the role of different degrees of anaemia including mild anaemia, on the one hand, and general disease severity, on the other, has not been investigated for the outcome of critically ill ACS patients. The present retrospective cohort analysis closes this gap using a multi-centre ICU database including over 200 000 admissions from the electronic Intensive Care Unit (eICU) Collaborative Research Database.[18]

Methods

Study subjects

The eICU-Database was initially drawn from the eICU telehealth system. This system complemented on-site ICU teams with remote support. The eICU Collaborative Research Database comprises a multi-centre ICU database that includes over 200 000 admissions from 335 ICUs of 208 hospitals throughout the USA for 2014 and 2015.[18] The database is distributed under the Health Insurance Portability and Accountability Act (HIPAA) safe harbour provision.

Extracted data

We extracted the baseline characteristics and organ support on Day 1 as described previously.[19–21] Acute coronary syndrome was identified using APACHE (Acute Physiology And Chronic Health Evaluation) IV diagnosis to select patients as described previously by Pollard *et al.*[18] The inclusion criterion was a diagnosis of ACS. In this study, patients with ACS were identified via the method established by Pollard *et al.*[18,22,23] The prolonged ICU stay was defined with a duration of >168 h.[23,24] Also, data

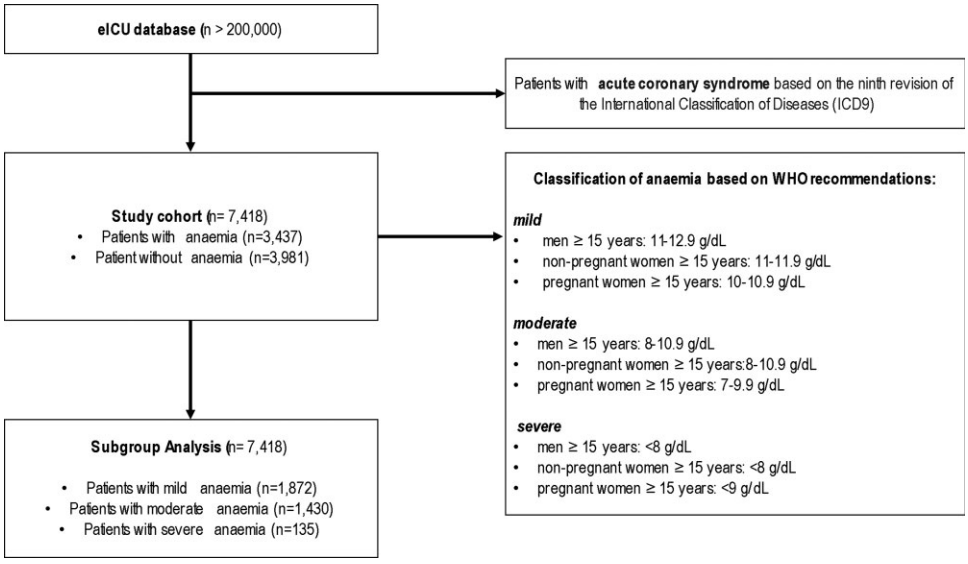


Figure 1 CONSORT diagram.

of further treatments were extracted as well as data on critical illness scores such as SOFA (Sequential organ failure assessment score), APACHE, and pre-existing comorbidities using the Elixhauser comorbidity score as described previously.[25] Scores were calculated with data within the first 24 h. Furthermore, also outcome data were extracted. The primary outcome was hospital mortality; secondary outcomes were the management strategies, mechanical ventilation, and vasopressor use.

Classification of anaemia and illness severity

Patients were classified following the WHO recommendations according to their haemoglobin levels on admission[26] into mild (men ≥ 15 years: 11–12.9 g/dL, non-pregnant women ≥ 15 years: 11–11.9 g/dL, pregnant women ≥ 15 years: 10–10.9 g/dL), moderate (men ≥ 15 years: 8–10.9 g/dL, non-pregnant women ≥ 15 years:8–10.9 g/dL, pregnant women ≥ 15 years: 7–9.9 g/dL), and severe (men ≥ 15 years: <8 g/dL, non-pregnant women ≥ 15 years: <8 g/dL, pregnant women ≥ 15 years: <9 g/dL, *Figure 1*). This classification was used for a subgroup analysis that compared various degrees of anaemia severity. Illness severity was classified according to the initial SOFA score into patients with less and patients with a SOFA ≥ 2.

Stratified sensitivity analysis

Sensitivity analyses, analysing only patients ageing <65 years, 65–79, or >79 years (arbitrary cut-off), Caucasian vs. non-Caucasian ethnicity, lactate ≥/>2.0 mmol/L (arbitrary cut-off), with and without mechanical ventilation, male or female gender, non-teaching and teaching hospital, vasopressor use or no vasopressor use, were performed.

Statistical analysis

Continuous data are expressed as median ± interquartile range. Differences between two independent groups were calculated using the Mann–Whitney U-tests for non-normally distributed data, accordingly. Categorical data are expressed as numbers (percentages), χ^2 tests were applied to calculate univariate differences between groups. We used three sequential random effect multi-level logistic regression models to assess the impact of anaemia on ICU mortality. A baseline model with anaemia as a binary variable as a fixed effect and ICU as a random effect (Model 1) was installed. Second, SOFA (Model 2) was added to Model 1 to correct for illness severity. Third, APACHE 2 was added to Model 1. Adjusted odds ratios (aORs) with respective 95% confidence intervals (CIs) were calculated. Both models were repeated for the three categories of anaemic severity (mild, moderate, severe). Last, the Elixhauser comorbidity score was added to Models 2 and 3, respectively, to correct for illness pre-existing comorbidities (see Supplementary material online, *Tables S1* and *S2*).

All the tests were two-sided, and a *P*-value of <0.05 was considered statistically significant. Stata 16 was used for all the statistical analyses.

Results

Patient characteristics

Baseline characteristics are presented in *Table 1*. In both groups, ACS patients with and without anaemia, male were overrepresented. However, this disproportionality was less pronounced in anaemic patients [71% (2832) vs. 60% (2064)]). Patients with anaemia were, on average, slightly leaner [29 (26–33) vs. 28 (24–32) kg/m^2; $P < 0.001$] and, most importantly, older [61 (53–70) vs. 70 (61–78); $P < 0.001$]. There were no significant differences in laboratory values on admission to the ICU with respect to serum lactate [2.1 (1.4–3.4) vs. 1.8 (1.2–3.1) mmol/L; $P = 0.093$]. Platelets were comparably high [(× 1000/mm^3) 207.0 (172.0–246.0) vs. 205.0 (165.0–254.0); $P = 0.62$], but leucocytes were significantly lower in patients with anaemia [(× 1000/mm^3) 10.3 (8.3–13.0) vs. 9.3 (7.2–12.1); $P < 0.001$]. Overall, scores for disease severity on admission were not high in either group but were significantly higher in anaemic patients by comparison [SOFA 1 (1–3) vs. 2 (1–4); $P < 0.001$; APACHE 35 (27–45) vs. 47 (36–58); $P < 0.001$]. With rising degrees of anaemia, the Elixhauser Comorbidity Score increased as well.

Table 1 Baseline characteristics for patients suffering from acute coronary syndrome with and without anaemia

	No anaemia N = 3981	Anaemia N = 3437	P-value
Male sex	71% (2832)	60% (2064)	<0.001
BMI (kg/m^2)	29 (26–33)	28 (24–32)	<0.001
Age (years)	61 (53–70)	70 (61–78)	<0.001
Elixhauser Comorbidity Score	0.83 (3.3)	2.3 (5.2)	<0.001
Age categories			<0.001
Age <65 years	61% (2439)	35% (1186)	
Age 65 to <80 years	30% (1176)	42% (1458)	
Age ≥80 years	9% (366)	23% (793)	
Ethnicity			<0.001
African American	7% (263)	10% (345)	
Asian	1% (51)	2% (52)	
Caucasian	83% (3220)	78% (2645)	
Hispanic	3% (113)	3% (112)	
Native American	0% (11)	0% (12)	
Other/unknown	6% (243)	6% (204)	
Values at admission			
Maximum serum lactate on Day 1	2.1 (1.4–3.4)	1.8 (1.2–3.1)	0.093
Initial serum lactate > 2 mmol/L	43% (127)	37% (165)	0.083
Platelets × 1000/mm^3	207.0 (172.0–246.0)	205.0 (165.0–254.0)	0.62
WBC × 1000/mm^3	10.3 (8.3–13.0)	9.3 (7.2–12.1)	<0.001
Haemoglobin (g/dL)	13.9 (13.3–14.7)	11.2 (10.1–12.1)	<0.001
Maximum serum creatinine on Day 1	0.9 (0.8–1.1)	1.1 (0.8–1.6)	<0.001
SOFA at admission	1 (1–3)	2 (1–4)	<0.001
APACHE at admission	35 (27–45)	47 (36–58)	<0.001

Table 2 Outcome of patients suffering from acute coronary syndrome with and without with and without anaemia

	No anaemia N = 3981	Anaemia N = 3437	P-value
ICU treatment			
Mechanical ventilation	4% (155)	7% (232)	<0.001
Vasopressor use	6% (225)	9% (319)	<0.001
Outcome			
Length of stay (h)	31 (21–48)	39 (23–66)	<0.001
Length of stay >7 days	2% (95)	5% (187)	<0.001
ICU mortality	1% (59)	4% (128)	<0.001
Hospital mortality	2% (96)	6% (204)	<0.001

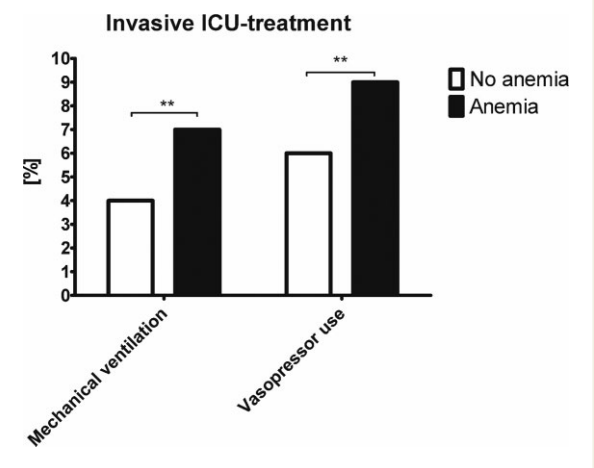


Figure 2 Intensive care treatment in acute coronary syndrome patients with and without anaemia on admission (%). ICU, intensive care unit; *$P < 0.001$.

Intensive care treatment and outcome

During intensive care treatment, invasive ventilation and vasopressors had to be used more frequently in this group (*Figure 2*). Both the total length of stay and the proportion of long-stay patients were higher in the group of patients with anaemia [39 (23–66) vs. 31 (21–48) h, $P < 0.001$]. Patients with anaemia showed significantly higher ICU and hospital mortality (1 vs. 4%, $P < 0.001$ and 6 vs. 2%, $P < 0.001$, respectively). In the multivariate model, the degree of anaemia was associated with an increased risk for hospital mortality [2.55 (1.99–3.27; $P < 0.001$)] and remained significant after the

Table 3 Logarithmic regression models for hospital mortality of patients suffering from acute coronary syndrome with and without with and without anaemia

	Crude events					
	No anaemia $N = 3981$	anaemia $N = 3437$	*P*-value	Model 1 OR (95% CI, *P*-value)	Model 2 aOR (95% CI, *P*-value)	Model 3 aOR (95% CI, *P*-value)
Hospital mortality	2% (96)	6% (204)	<0.001	2.55 (1.99–3.27; $P < 0.001$)	1.62 (1.24–2.13; $P < 0.001$)	1.34 (1.01–1.78; $P = 0.04$)

Model 1.
Model 2—Model 1 plus SOFA.
Model 3—Model 1 plus APACHE.

adjustment for admission disease severity using SOFA [1.62 (1.24–2.13; $P < 0.001$)] and APACHE [1.34 (1.01–1.78; $P = 0.04$), *Table 3* and *Figure 3*].

Stratified sensitivity analysis

The stratified sensitivity analysis revealed that anaemia was significantly associated with adverse outcome in all the assessed subgroups with the exception for critically ill females. There was no difference comparing patients with lower and higher baseline serum lactate and in patients with mechanical ventilation (*Figure 3*).

Subgroup analysis of the various degrees of anaemia severity

With a rising degree of anaemia, the need for mechanical ventilation and vasopressor use rose (*Table 4*). In the subgroup analysis of the various degrees of anaemia severity, only a very small proportion of patients suffered from severe anaemia (*Figures 4* and *5*). Most patients had mild or moderate anaemia. African Americans were over-represented in the severe anaemia group [19% (25); $P < 0.001$]. Disease severity, measured as SOFA, was lowest in patients without anaemia and highest in patients with severe anaemia [1 (1–3) vs. 4 (2–6); $P < 0.001$]. Similar results were found for APACHE [35 (27–45) vs. 53 (43–66); $P < 0.001$]. There were no relevant differences in serum lactate on admission to the ICU [2.1 (1.4–3.4) vs. 2.1 (1.2–6.9) mmol/L; $P = 0.23$], but serum creatinine increases steadily with increasing anaemia severity [0.9 (0.8–1.1) vs. 1.3 (0.9–2.2); $P < 0.001$].

The length of stay in the ICU increased with the severity of anaemia, while mortality grew accordingly. In the adjusted regression analyses, the presence of all grades of anaemia was associated with a significantly increased risk of ICU and hospital mortality (*Table 5*), but severe anaemia evidenced the highest risk (hospital mortality: 12%, $P < 0.001$). The association of moderate and severe anaemia with hospital mortality remained stable in these models even after adjustment for Elixhauser Comorbidity Score (see Supplementary material online, *Table S2*).

In a subgroup analysis on patients with low (<2) SOFA and high (≥2) SOFA, growing degrees of anaemia were associated with worse outcome (*Figure 5*). Even in patients with low SOFA, anaemic patients required more vasopressors and mechanical ventilation. In patients with high SOFA, anaemic patients evidenced worse outcome and required more intensive care therapy than patients without anaemia.

Discussion

The present retrospective analysis examines ACS patients admitted and treated in an ICU. In these particularly vulnerable patients, baseline anaemia was associated with an increased need for intensive care treatment, prolonged ICU length of stay, and significantly higher ICU and hospital mortality—regardless of baseline disease severity. This result is important because almost half of the patients studied suffered from anaemia. Therefore, anaemia is very common in ACS patients in the ICU and is associated with a poor outcome.

Pre-existing anaemia is an independent risk factor for patients with ACS, but it remains unclear whether and how it needs to be treated.[27] In general, there exist different treatment strategies for anaemia—depending on its aetiology: supplementation of iron in case of iron deficiency, administration of erythropoietin α in case of hypo-regenerative anaemias,[28–31] or transfusion of erythrocyte concentrate[9]—regardless of the aetiology.

In general, anaemia might be caused by the impaired production of red blood cells or by an increased loss of red blood cells. Several—often coexisting—conditions affect haematopoiesis, such as iron deficiency, a lack of erythropoietin due to chronic kidney disease or a shortage of folic acid, vitamin B-12. In addition, haemato-oncologic diseases, for example, leukaemia or osteomyelofibrosis, infectious diseases, or drugs such as mycophenolic acid impair haematopoiesis. At last, chronic illness with a pro-inflammatory state is a common finding. Increased blood loss might be caused by gastrointestinal bleeding, haemodialysis, or haemolytic diseases. Thus, the most crucial step in treating anaemia is identifying its aetiology.

Transfusion of erythrocyte concentrates is a common method in critical care medicine to treat anaemia.[32] However, there is growing evidence about the negative consequences of red blood cell transfusion. Transfused erythrocytes have functional defects that might cause harmful effects. These effects seem to be time-dependent because erythrocyte concentrates stored for >14 days are known to contribute to statistically worse outcomes than those receiving 'fresher' erythrocyte concentrates. Low nitric oxide bioavailability might play a critical role that leads to vasoconstriction, decreased microcirculatory blood flow, and insufficient oxygen delivery to end organs.[33] The European Society of Intensive Care Medicine recently published a clinical practice guideline about transfusion strategies in non-bleeding critically ill adults.[34] In patients with ACS, this guideline suggests 'a liberal transfusion threshold (9–10 g/dL) vs. a restrictive transfusion threshold (7 g/dL)'. However, a more recently

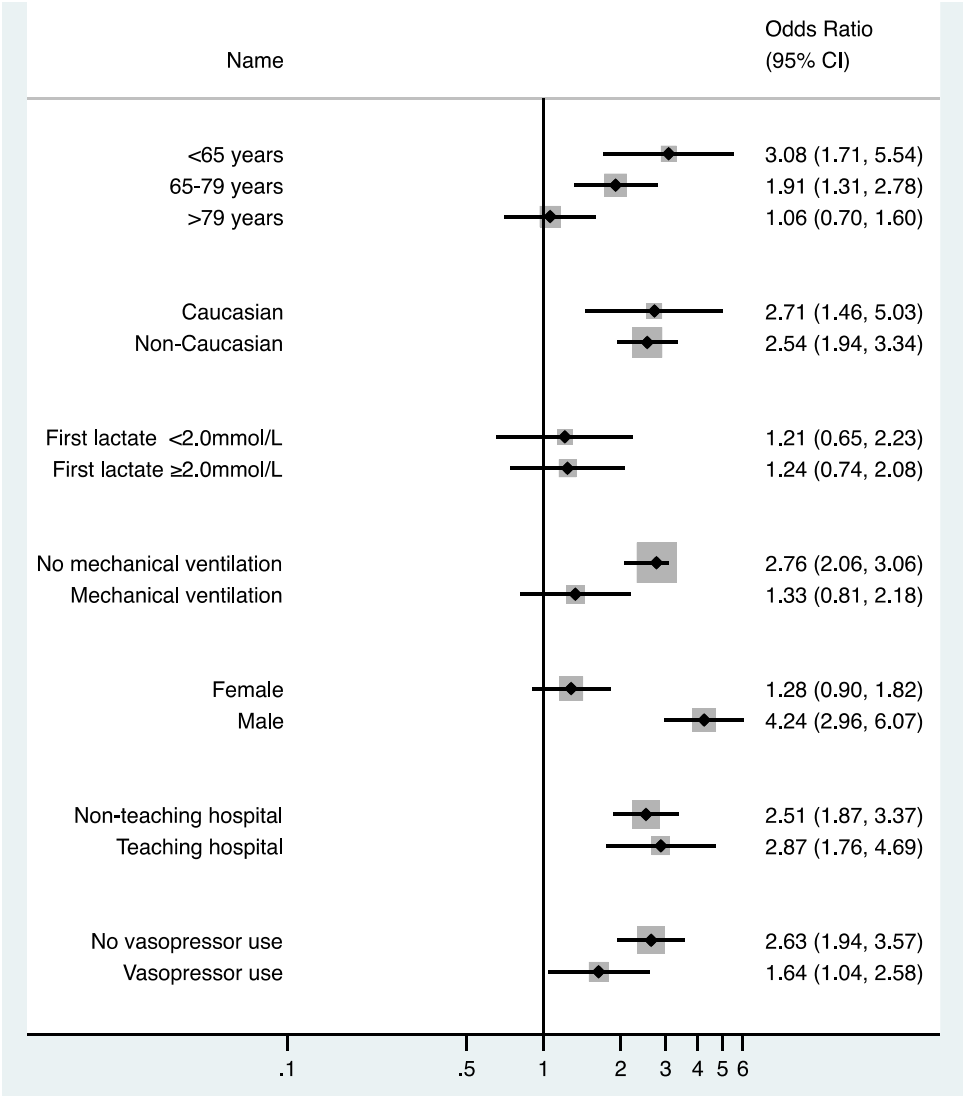


Figure 3 Forest plot of the adjusted odds ratio of anaemic vs. non-anaemic acute coronary syndrome patients for different subgroups according to primary outcome hospital mortality (adjusted odds ratio 95% confidence interval).

published randomized controlled study found no benefit of a liberal regime.[35–37] In sum, transfusion practice is an important factor in anaemic patients, but the eICU does not contain information about transfusion in a sufficient quality. Furthermore, transfusion practice changed over the last decade, and the general approach has become more restrictive compared with the years 2014 and 2015.[38,39]

The present investigation found a high prevalence of pre-existing anaemia (46.3%), which is higher than commonly reported. In a meta-analysis by Liu *et al.*[40] with 241 293 ACS patients, the cumulative prevalence was 24.4%. The meta-analysis by Lawler *et al.*[41] reports a lower percentage of 19.1% from 233 144 patients. A major difference between our retrospective cohort analysis is the gender distribution: we found significantly more anaemic males than females (60 vs. 40%, $P < 0.001$), although this imbalance was more pronounced in non-anaemic patients. In contrast, Lawler *et al.*[41] found significantly more anaemic females than males, but the baseline demographic data reveal a considerable heterogeneity of gender distribution across all included studies.

In the present study, patients with anaemia were significantly older; age rose with declining haemoglobin. Currently, the incidence of anaemia in older patients with acute myocardial infarction still rises.[9,10] Anaemia affects elderly patients with critical illness in particular.[4,42] This is in line with the present analysis: in the subgroup of ACS patients with moderate anaemia, 72% were ≥65 years. The same observation was true for patients with severe anaemia (73.3%).

Regarding mortality, our results are in line with the literature: Lawler *et al.* observed increased all-course mortality (both early and late) in anaemic ACS patients. Notably, anaemia was associated with a higher re-infarction rate than non-anaemic ACS patients (relative risk 1.25, 95% CI 1.02–1.53).[41] Another interesting finding by Lawler *et al.* was that anaemic ACS patients evidenced higher rates

Table 4 Baseline characteristics for patients suffering from acute coronary syndrome with different degrees of anaemia according to their haemoglobin

Degrees of anaemia according to WHO	No anaemia *N* = 3981	Mild anaemia *N* = 1872	Moderate anaemia *N* = 1430	Severe anaemia *N* = 135	*P*-value
Male sex	71% (2832)	71% (1334)	46% (661)	51% (69)	<0.001
BMI (kg/m^2)	29 (26–33)	28 (24–32)	27 (24–32)	27 (23–32)	<0.001
Age (years)	61 (53–70)	67 (59–76)	72 (63–81)	71 (64–81)	<0.001
Elixhauser Comorbidity Score	0.8 (3.3)	1.6 (4.3)	3.2 (6.0)	3.3 (5.5)	<0.001
Age categories					
Age <65 years	61% (2439)	40% (750)	28% (400)	27% (36)	<0.001
Age 65 to <80 years	30% (1176)	41% (768)	44% (629)	45% (61)	
Age ≥80 years	9% (366)	19% (354)	28% (401)	28% (38)	
Ethnicity					<0.001
African American	7% (263)	9% (160)	11% (160)	19% (25)	
Asian	1% (51)	2% (28)	2% (22)	1% (2)	
Caucasian	83% (3220)	79% (1453)	78% (1096)	72% (96)	
Hispanic	3% (113)	4% (67)	3% (42)	2% (3)	
Native American	0% (11)	0% (5)	0% (6)	1% (1)	
Other/unknown	6% (243)	6% (118)	6% (79)	5% (7)	
Values at admission					
Maximum serum lactate on Day 1	2.1 (1.4–3.4)	1.7 (1.2–3.0)	1.8 (1.3–3.5)	2.1 (1.2–6.9)	0.23
Initial serum lactate > 2 mmol/L	43% (127)	34% (66)	38% (88)	50% (11)	0.14
Platelets × 1000/mm^3	207.0 (172.0–246.0)	201.0 (168.0–246.0)	211.0 (162.0–265.0)	215.0 (155.0–291.0)	0.020
WBC × 1000/mm^3	10.3 (8.3–13.0)	9.3 (7.4–12.0)	9.3 (7.1–12.1)	9.4 (6.6–13.1)	<0.001
Haemoglobin (g/dL)	13.9 (13.3–14.7)	12.0 (11.6–12.6)	10.0 (9.2–10.6)	7.4 (7.0–7.7)	<0.001
Maximum serum creatinine on Day 1	0.9 (0.8–1.1)	1.0 (0.8–1.3)	1.2 (0.9–2.0)	1.3 (0.9–2.2)	<0.001
SOFA at admission	1 (1–3)	2 (1–4)	3 (1–5)	4 (2–6)	<0.001
APACHE at admission	35 (27–45)	43 (34–53)	51 (41–64)	53 (43–66)	<0.001

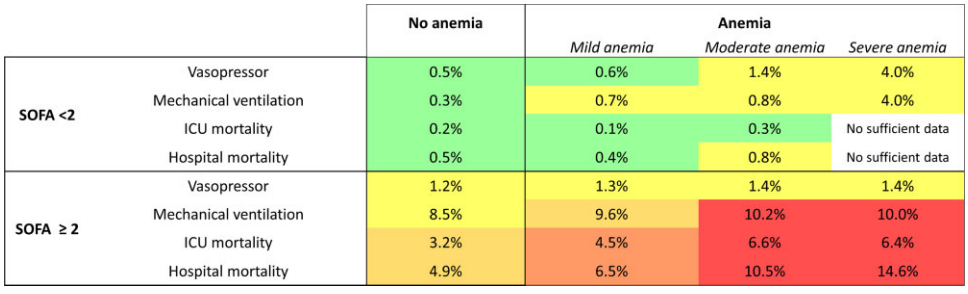


Figure 4 Distribution of intensive care treatment and outcome according to anaemia and illness severity (Sequential organ failure assessment score).

of other comorbidities like diabetes mellitus, congestive heart failure, cerebrovascular disease, and history of major bleeding.[41] Another meta-analysis by Liu *et al.* reported an increased risk for early [odds ratio (OR) 2.77; 95% CI 2.09, 3.65] and late mortality (OR 2.03; 95% CI 1.52, 2.71) in anaemic patients with myocardial infarction. Again, anaemic patients suffered significantly more often from other comorbidities such as heart failure (OR 1.96; 95% CI 1.47, 2.62), cardiogenic shock (OR 1.95; 95% CI 1.04, 2.64), and major bleeding (OR 4.28; 95% CI 1.05, 17.14).[40] The Elixhauser Comorbidity Score contains many comorbidities like congestive heart failure, renal failure, liver disease, peptic ulcer disease, bleeding, AIDS/HIV, coagulopathy, blood loss anaemia, and deficiency anaemia. Thus, adjusting the model on anaemic patients for SOFA, and APACHE, and the Elixhauser Comorbidity Score results in a significant 'over fitting' regarding the impact of anaemia. However, despite these adjustments, moderate and severe anaemia remained

independent risk factors for adverse outcome in the SOFA model (see Supplementary material online, *Tables S1* and *S2*).

Interestingly, there were no differences in maximum serum lactate on Day 1 between anaemic and non-anaemic patients in the present study. It is tempting to speculate that obviously red blood cell dysfunction occurs independently from microcirculatory hypoxia or disturbances. Recently, Lorente *et al.*[43] investigated the impact of anaemia on the outcome of 629 patients suffering from non-ST segment elevation ACS admitted to an ICU. In their cohort, almost one-third of the patients evidenced pre-existing anaemia. Even after adjusting for confounders, anaemia was significantly associated with a combined endpoint of mortality and readmission after 6 months ($P = 0.031$).

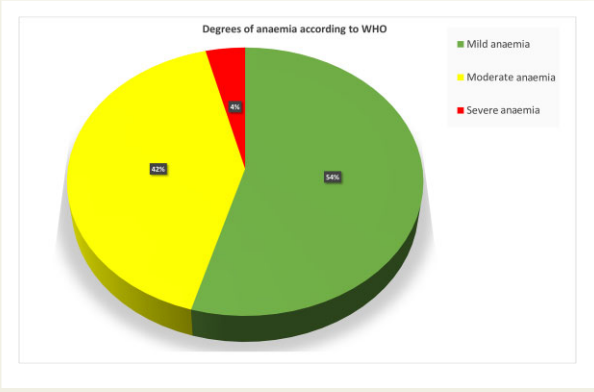


Figure 5 Distribution of the different degrees of anaemia according to WHO classification[26] in critically ill acute coronary syndrome patients (%). Intensive care treatment in patients with and without anaemia on admission (%).

Anaemia is one of ACS patients' most common—and rising—comorbidities. Pre-existing anaemia independently contributes to significantly worse short- and long-term prognoses. Although the pathophysiologic link to adverse outcome seems to be logical and established, there are still no effective evidence-based treatment options. Thus, the identification of its aetiology is the most essential cornerstone. Future studies are urgently needed to identify effective treatment options for this dangerous and common comorbidity.

Limitations

This retrospective analysis suffers from some limitations. First, it was not possible to extract data about the aetiology of the anaemia from the database. Consequently, we do not know the iron deficiency, chronic bleeding, impaired production, or increased destruction. We have no information on serum ferritin, transferrin saturation, vitamin B12 and folic acid levels, reticulocytes, and erythropoietin levels. Another important lack of information regards invasive ACS management. Complicated percutaneous coronary intervention procedures might influence both bleeding events and the outcome. Furthermore, need for anticoagulation might result in an increased incidence of gastrointestinal bleedings. Unfortunately, eICU does not contain sufficient information about these complications including transfusion practice. However, this is contrasted by the high number of patients included. In fact, we see a very robust association—even after adjustment—that anaemia is a strong predictor of adverse outcomes. Finally, this study contains data from 2014 and 2015, which were pre-defined by the database.

Conclusion

Anaemia is common in patients suffering from ACS who were admitted to an ICU. Nearly half of the ICU patients with ACS suffer from anaemia. In most of the cases, patients are affected by a mild or

Table 5 Outcome of patients suffering from acute coronary syndrome with and without with different degrees of anaemia

	No anaemia *N* = 3981	Mild anaemia *N* = 1872	Moderate anaemia *N* = 1430	Severe anemia *N* = 135	*P*-value
ICU treatment					
Mechanical ventilation	4% (155)	6% (108)	8% (112)	9% (12)	<0.001
Vasopressor use	6% (225)	8% (145)	11% (158)	12% (16)	<0.001
Outcome					
LOS (h)	31 (21–48)	36 (23–60)	41 (25–72)	50 (28–85)	<0.001
Length of stay >7 days	2% (95)	4% (82)	7% (97)	6% (8)	<0.001
ICU mortality	1% (59)	3% (49)	5% (72)	5% (7)	<0.001
Hospital mortality	2% (96)	4% (72)	8% (116)	12% (16)	<0.001
Logistic regression for hospital mortality					
Model 1	OR (95% CI, *P*-value)	1.62 (1.19–2.21; $P = 0.002$)	3.57 (2.71–4.72; $P < 0.001$)	5.44 (3.11–2.21; $P < 0.001$)	
Model 2	aOR (95% CI, *P*-value)	1.18 (0.84–1.66; $P = 0.352$)	1.99 (1.47–2.71; $P < 0.001$)	2.51 (1.36–4.65. $P = 0.003$)	
Model 3	aOR (95% CI, *P*-value)	1.05 (0.73–1.49; $P = 0.80$)	1.51 (1.10–2.07; $P = 0.011$)	2.51 (1.35–4.65; $P = 0.004$)	

Logarithmic regression models for hospital mortality of patients suffering from acute coronary syndrome with and without different degrees of anaemia.
ICU, intensive care unit; LOS, length of stay; OR, odds ratio; aOR, adjusted odds ratio.
Model 2—Model 1 plus SOFA.
Model 3—Model 1 plus APACHE.

moderate degree, but even mild degrees of anaemia are already associated with a higher need for intensive care treatment, a longer length of stay, and higher hospital mortality. With growing anaemia, these effects increase further—independently from the general illness severity. After adjustment for SOFA or APACHE, anaemia on ICU admission remained an independent risk factor for adverse outcomes.

Authors' contributions

R.R.B., B.W., and C.J. analysed the data and wrote the first draft of the manuscript. N.H. contributed to statistical analysis and improved the paper. P.W., S.A., R.R.B., M.C., and M.K. gave guidance, contributed data, and improved the paper. All authors read and approved the final manuscript.

Ethics

This was a population-based cohort study conducted under pre-existing institutional review board (IRB) approval. The database was released under the Health Insurance Portability and Accountability Act (HIPAA) safe harbour provision.

Lead author biography

Christian Jung is residency and habilitation at the University Hospital of Jena, Germany. PhD at Karolinska Institute (Stockholm, Sweden). Currently, Professor Jung heads the Section for Coronary Vascular Cardiology and Conservative Intensive Care Medicine (University Hospital Düsseldorf; Germany). Research interests include the relevance of comorbidities in acute myocardial infarction, diagnosis and treatment of shock, interventional cardiology and translational research.

Data availability

All data relevant for this study will be given by the authors upon specific request. Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Supplementary material

Supplementary material is available at *European Heart Journal Open* online.

Funding

This work was supported by the Forschungskommission of the Medical Faculty of the Heinrich Heine University (No. 2018-32 to G.W. and No. 2020-21 to R.R.B.) for a Clinician Scientist Track. Furthermore, institutional support has been received by the German Research Council (SFB 1116, B06) as well as the State of North Rhine Westphalia (Giga for Health: 5GMedizincampus. NRW, Project number 005-2008-0055 and PROFILNRW-2020-107-A, TP4).

Conflict of interest: None declared .

References

1. Bruno RR, Kelm M, Jung C. Spotlight on comorbidities in STEMI patients. *Endocrinol Diabetes Metab* 2020;**3**:e00102.
2. Marechaux S, Barrailler S, Pincon C, Decourcelle V, Guidez T, Braun S, Bouabdallaoui N, Bauchart JJ, Auffray JL, Juthier F, Banfi C, Susen S, Jude B, Asseman P, Van Belle E, Ennezat PV. Prognostic value of hemoglobin decline over the GRACE score in patients hospitalized for an acute coronary syndrome. *Heart Vessels* 2012;**27**:119–127.
3. Vicente-Ibarra N, Marin F, Pernias-Escrig V, Sandin-Rollan M, Nunez-Martinez L, Lozano T, Macias-Villaniego MJ, Carrillo-Aleman L, Candela-Sanchez E, Guzman E, Esteve-Pastor MA, Orenes-Pinero E, Valdes M, Rivera-Caravaca JM, Ruiz-Nodar JM. Impact of anemia as risk factor for major bleeding and mortality in patients with acute coronary syndrome. *Eur J Intern Med* 2019;**61**:48–53.
4. Mamas MA, Kwok CS, Kontopantelis E, Fryer AA, Buchan I, Bachmann MO, Zaman MJ, Myint PK. Relationship between anemia and mortality outcomes in a national acute coronary syndrome cohort: insights from the UK myocardial ischemia national audit project registry. *J Am Heart Assoc* 2016;**5**:e003348.
5. Formiga F, Ariza-Solé A. Elderly patients with acute coronary syndromes: a continuous tsunami. *J Geriatr Cardiol* 2019;**16**:100–102.
6. Lanser L, Fuchs D, Scharnagl H, Grammer T, Kleber ME, Marz W, Weiss G, Kurz K. Anemia of chronic disease in patients with cardiovascular disease. *Front Cardiovasc Med* 2021;**8**:666638.
7. Ogiso M, Yamaguchi J, Otsuki H, Arashi H, Sekiguchi H, Ogawa H, Hagiwara N. Association between anemia and mortality in patients with acute coronary syndrome treated with percutaneous coronary intervention and contemporary lipid-lowering therapy. *Heart Vessels* 2021;**36**:1626–1634.
8. Grammer TB, Kleber ME, Silbernagel G, Pilz S, Scharnagl H, Tomaschitz A, Konig W, Marz W. Hemoglobin, iron metabolism and angiographic coronary artery disease (The Ludwigshafen Risk and Cardiovascular Health Study). *Atherosclerosis* 2014;**236**:292–300.
9. Wu W-C, Rathore SS, Wang Y, Radford MJ, Krumholz HM. Blood transfusion in elderly patients with acute myocardial infarction. *N Engl J Med* 2001;**345**:1230–1236.
10. Chesebro JH, Knatterud G, Roberts R, Borer J, Cohen LS, Dalen J, Dodge HT, Francis CK, Hillis D, Ludbrook P. Thrombolysis in Myocardial Infarction (TIMI) Trial. Phase I: a comparison between intravenous tissue plasminogen activator and intravenous streptokinase. Clinical findings through hospital discharge. *Circulation* 1987;**76**:142–154.
11. Stucchi M, Cantoni S, Piccinelli E, Savonitto S, Morici N. Anemia and acute coronary syndrome: current perspectives. *Vasc Health Risk Manag* 2018;**14**:109–118.
12. González-Ferrer JJ, García-Rubira JC, Balcones DV, Gil IN, Barrio RC, Fuentes-Ferrer M, Fernández-Ortiz A, Macaya C. Influence of hemoglobin level on in-hospital prognosis in patients with acute coronary syndrome. *Rev Esp Cardiol* 2008;**61**:945–952.
13. Younge JO, Nauta ST, Akkerhuis KM, Deckers JW, van Domburg RT. Effect of anemia on short- and long-term outcome in patients hospitalized for acute coronary syndromes. *Am J Cardiol* 2012;**109**:506–510.
14. Wester A, Attar R, Mohammad MA, Andell P, Hofmann R, Jensen J, Szummer K, Erlinge D, Koul S. Impact of baseline anemia in patients with acute coronary syndromes undergoing percutaneous coronary intervention: a prespecified analysis from the VALIDATE-SWEDEHEART trial. *J Am Heart Assoc* 2019;**8**:e012741.
15. Uscinska E, Sobkowicz B, Lisowska A, Sawicki R, Dabrowska M, Szmitkowski M, Musial WJ, Tycinska AM. Predictors of long-term mortality in patients hospitalized in an intensive cardiac care unit. *Int Heart J* 2016;**57**:67–72.
16. Uscinska E, Sobkowicz B, Sawicki R, Kiluk I, Baranicz M, Stepek T, Dabrowska M, Szmitkowski M, Musial WJ, Tycinska AM. Parameters influencing in-hospital mortality in patients hospitalized in intensive cardiac care unit: is there an influence of anemia and iron deficiency? *Intern Emerg Med* 2015;**10**:337–344.
17. Docherty AB, Walsh TS. Anemia and blood transfusion in the critically ill patient with cardiovascular disease. *Crit Care* 2017;**21**:61.
18. Pollard TJ, Johnson AEW, Raffa JD, Celi LA, Mark RG, Badawi O. The eICU collaborative research database, a freely available multi-center database for critical care research. *Sci Data* 2018;**5**:180178.
19. Wernly B, Bruno RR, Mamandipoor B, Jung C, Osmani V. Sex-specific outcomes and management in critically ill septic patients. *Eur J Intern Med* 2020;**83**:74–77.
20. Bruno RR, Wernly B, Binneboessel S, Baldia P, Duse DA, Erkens R, Kelm M, Mamandipoor B, Osmani V, Jung C. Failure of lactate clearance predicts the outcome of critically ill septic patients. *Diagnostics* 2020;**10**:1105.
21. Bruno RR, Wernly B, Mamandipoor B, Rezar R, Binnebossel S, Baldia PH, Wolff G, Kelm M, Guidet B, De Lange DW, Dankl D, Kokofer A, Danninger T, Szczeklik W, Sigal S, van Heerden PV, Beil M, Fjolner J, Leaver S, Flaatten H, Osmani V, Jung C. ICU-mortality in old and very old patients suffering from sepsis and septic shock. *Front Med* 2021;**8**:697884.
22. Su G, Zhang Y, Xiao R, Zhang T, Gong B. Systemic immune-inflammation index as a promising predictor of mortality in patients with acute coronary syndrome: a real-world study. *J Intern Med Res* 2021;**49**:3000605211016274.

23. Tan L, Xu Q, Li C, Liu J, Shi R. High-normal serum magnesium and hypermagnesemia are associated with increased 30-day in-hospital mortality: a retrospective cohort study. *Front Cardiovasc Med* 2021;**8**:625133.
24. Moitra VK, Guerra C, Linde-Zwirble WT, Wunsch H. Relationship between ICU length of stay and long-term mortality for elderly ICU survivors. *Crit Care Med* 2016;**44**:655–662.
25. Elixhauser A, Steiner C, Harris DR, Coffey RM. Comorbidity measures for use with administrative data. *Med Care* 1998;**36**:8–27.
26. World Health Organization. Haemoglobin Concentrations for the Diagnosis of Anaemia and Assessment of Severity. Geneva: World Health Organization; 2011. WHO Reference Number: WHO/NMH/NHD/MNM/11.1
27. Lasocki S, Pène F, Ait-Oufella H, Aubron C, Ausset S, Buffet P, Huet O, Launey Y, Legrand M, Lescot T, Mekontso Dessap A, Piagnerelli M, Quintard H, Velly L, Kimmoun A, Chanques G. Management and prevention of anemia (acute bleeding excluded) in adult critical care patients. *Ann Intensive Care* 2020;**10**:97.
28. Kang J, Park J, Lee JM, Park JJ, Choi D-J. The effects of erythropoiesis stimulating therapy for anemia in chronic heart failure: a meta-analysis of randomized clinical trials. *Int J Cardiol* 2016;**218**:12–22.
29. Swedberg K, Young JB, Anand IS, Cheng S, Desai AS, Diaz R, Maggioni AP, McMurray JJ, O'Connor C, Pfeffer MA, Solomon SD, Sun Y, Tendera M, van Veldhuisen DJ. Treatment of anemia with darbepoetin alfa in systolic heart failure. *N Engl J Med* 2013;**368**:1210–1219.
30. Besarab A, Bolton WK, Browne JK, Egrie JC, Nissenson AR, Okamoto DM, Schwab SJ, Goodkin DA. The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. *N Engl J Med* 1998;**339**:584–590.
31. Hai-Tao Y, Wen-Juan X, Ying-Ying Z, Yi-Tong M, Xie X. Effects of erythropoietin on the clinical outcomes of patients with acute ST segment elevation myocardial infarction after percutaneous coronary intervention: a meta-analysis. *Int J Clin Pharmacol Ther* 2018;**56**:277–279.
32. Vlaar AP, Oczkowski S, de Bruin S, Wijnberge M, Antonelli M, Aubron C, Aries P, Duranteau J, Juffermans NP, Meier J, Murphy GJ, Abbasciano R, Muller M, Shah A, Perner A, Rygaard S, Walsh TS, Guyatt G, Dionne JC, Cecconi M. Transfusion strategies in non-bleeding critically ill adults: a clinical practice guideline from the European society of intensive care medicine. *Intensive Care Med* 2020;**46**:673–696.
33. Roback JD, Neuman RB, Quyyumi A, Sutliff R. Insufficient nitric oxide bioavailability: a hypothesis to explain adverse effects of red blood cell transfusion. *Transfusion* 2011; **51**:859–866.
34. Jolicœur EM, O'Neill WW, Hellkamp A, Hamm CW, Holmes DR Jr, Al-Khalidi HR, Patel MR, Van de Werf FJ, Pieper K, Armstrong PW, Granger CB, APEX-AMI Investigators. Transfusion and mortality in patients with ST-segment elevation myocardial infarction treated with primary percutaneous coronary intervention. *Eur Heart J* 2009;**30**:2575–2583.
35. Ducrocq G, Gonzalez-Juanatey JR, Puymirat E, Lemesle G, Cachanado M, Durand-Zaleski I, Arnaiz JA, Martinez-Selles M, Silvain J, Ariza-Sole A, Ferrari E, Calvo G, Danchin N, Avendano-Sola C, Frenkiel J, Rousseau A, Vicaut E, Simon T, Steg PG, Investigators R. Effect of a restrictive vs liberal blood transfusion strategy on major cardiovascular events among patients with acute myocardial infarction and anemia: the REALITY randomized clinical trial. *JAMA* 2021;**325**:552–560.
36. Hébert PC, Wells G, Blajchman MA, Marshall J, Martin C, Pagliarello G, Tweeddale M, Schweitzer I, Yetisir E. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. *N Engl J Med* 1999;**340**:409–417.
37. Carson JL, Brooks MM, Abbott JD, Chaitman B, Kelsey SF, Triulzi DJ, Srinivas V, Menegus MA, Marroquin OC, Rao SV, Noveck H, Passano E, Hardison RM, Smitherman T, Vagaonescu T, Wimmer NJ, Williams DO. Liberal versus restrictive transfusion thresholds for patients with symptomatic coronary artery disease. *Am Heart J* 2013;**165**:964–971.e1.
38. Sadana D, Kummangal B, Moghekar A, Banerjee K, Kaur S, Balasubramanian S, Tolich D, Han X, Wang X, Hanane T, Mireles-Cabodevila E, Quraishy N, Duggal A, Krishnan S. Adherence to blood product transfusion guidelines—an observational study of the current transfusion practice in a medical intensive care unit. *Transfus Med* 2021;**31**: 227–235.
39. Cable CA, Razavi SA, Roback JD, Murphy DJ. RBC transfusion strategies in the ICU: a concise review. *Crit Care Med* 2019;**47**:1637–1644.
40. Liu Y, Yang YM, Zhu J, Tan HQ, Liang Y, Li JD. Anaemia and prognosis in acute coronary syndromes: a systematic review and meta-analysis. *J Intern Med Res* 2012;**40**: 43–55.
41. Lawler PR, Filion KB, Dourian T, Atallah R, Garfinkle M, Eisenberg MJ. Anemia and mortality in acute coronary syndromes: a systematic review and meta-analysis. *Am Heart J* 2013;**165**:143–53.e5.
42. Willis P, Voeltz MD. Anemia, hemorrhage, and transfusion in percutaneous coronary intervention, acute coronary syndromes, and ST-segment elevation myocardial infarction. *Am J Cardiol* 2009:**104**:34c–8c.
43. Lorente V, Aboal J, Garcia C, Sans-Rosello J, Sambola A, Andrea R, Tomas C, Bonet G, Vinas D, El Ouaddi N, Montero S, Cantalapiedra J, Pujol M, Hernandez I, Perez-Rodriguez M, Llao I, Sanchez-Salado JC, Gual M, Ariza-Solé A. Anemia in patients with high-risk acute coronary syndromes admitted to intensive cardiac care units. *J Geriatr Cardiol* 2020;**17**:35–42.