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Outcomes of anemic patients presenting with acute coronary syndrome: An analysis of the Cooperative National Registry of Acute Coronary Care, Guideline Adherence and Clinical Events

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Abstract

Background: Anemia commonly accompanies acute coronary syndromes (ACS) and is associated with poorer outcomes. This study examines the associations between anemia, management and outcomes in an Australian ACS population.

Methods: This analysis of the CONCORDANCE database included 8665 ACS patients presenting to 41 Australian hospitals. Baseline characteristics, management, and outcomes were compared between patients with anemia (Hb ≤ 130 for males, Hb ≤ 120 g/L for females) and non-anemia.

Results: A total of 1880 (21.7%) patients presenting with ACS were anemic. These patients were older (72 years vs 63 years, $P < .0001$), with higher prevalence of comorbidities. STEMI patients with anemia were less likely to be emergently reperfused with either thrombolytic therapy (22% vs 33%, $P < .0001$) or primary percutaneous coronary intervention (PCI) (45% vs 51% $P = 0.033$). For all ACS, anemic patients less frequently received: coronary angiography (63% vs 86%, $P < .0001$); drug eluting stents if undergoing PCI (50% vs 58%, $P < .0001$); dual antiplatelet therapy (80% vs 89%, $P < .0001$) ;and parenteral anticoagulants (82% vs 88%, $P < .0001$). In hospital complications of heart failure (20% vs 9%, $P < .0001$), renal failure (13% vs 4%, $P < .0001$), and re-infarction (4% vs 2%, $P = .0006$) were more common among anemic patients. There was a near-linear inverse relationship between admission hemoglobin and in hospital mortality.

Conclusions: Anemic patients with ACS are a high risk group less likely to undergo invasive and antithrombotic therapy. Further investigation is required to determine if more active treatment of anemic patients presenting with ACS will improve their outcomes.

KEYWORDS

acute coronary syndrome, anemia, anticoagulation, antiplatelets, percutaneous intervention

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1 | INTRODUCTION

Anemia accounts for 12% to 25% of the total cohort of patients that present to hospital with acute coronary syndrome (ACS).[1-6] Numerous studies have shown that anemia is associated with poorer outcomes and those presenting with ACS and baseline anemia have a significantly increased risk of early and late mortality.[1,2,5,7-13]

Currently there are a wide range of therapies used to treat ACS including coronary angiography with revascularisation and the use of dual antiplatelet medications. There is a strong evidence base supporting their prognostic importance in the ACS cohort however many of these trials have excluded anemic patients. This exclusion has been related to the increased risk of clinically significant bleeding associated with these therapies and this influences the clinician's decision to use these therapies during hospitalization and post discharge despite their proven prognostic benefit albeit in non-anemic populations.[14-17] There is literature reporting that anemic patients are under-treated when presenting with ACS. The use of aspirin, beta-blockers, and statins have been shown to be less likely prescribed to anemic ACS patients both in the acute period and in the post discharge period.[1,17] Coronary intervention has also been reported to be less likely utilized in the anemic cohort. Deciding whether or not to apply evidenced based medical therapies associated with increased risk of bleeding to their anemic ACS patients is often difficult given that bleeding complications in this particular cohort is both undesired and strongly related to anemia.[1,2,18] The aims of this study were to identify the differences in care offered to anemic vs non-anemic ACS patients and to examine the associations between anemia and in-hospital outcomes in an Australian ACS population.

2 | METHODS

2.1 | Study population

The study population was derived from the CONCORDANCE registry which is an ongoing Australian observational study which describes the management and outcomes of ACS patients. The CONCORDANCE study involves more than 40 Australian public hospitals which service metropolitan, rural, and remote locations. This study conforms with the ethical guidelines of the 1975 Declaration of Helsinki and each of the investigative sites have received approval from their ethics review committee for participation in the CONCORDANCE registry. The registry began in 2009 and is prospectively maintained with a rationale of providing insights into the strategies that could improve the management of patients with ACS.[19] Enrolling hospitals were distributed between metropolitan (64%) and rural (36%) locations. The majority of these hospitals (79%) had on site coronary angiographic facilities. A set of strict inclusion criteria[19] are utilized to reflect a true ACS population and are applied to the first 10 consecutive patients greater than the age of 18 years at the beginning of each month admitted with a diagnosis of ACS, together with significant electrocardiographic changes, elevated cardiac biomarkers, a history of newly documented coronary artery disease, or two features of high risk ACS. Data pertaining to patient demographics, medical history, investigations, management, and hospital morbidity and mortality are collected prospectively using a web-based electronic case report form.

This analysis included ACS patients from the period 2009 to 2015. The cohort was dichotomized into anemic and non-anemic groups based on the World Health Organization classification of anemia: admission Hb ≤ 120 g/L for females and Hb ≤ 130 g/L for males.

2.2 | Outcomes

In-hospital outcomes of the anemic and non-anemic patients were compared. These outcomes included: congestive cardiac failure, cardiogenic shock, acute renal failure, re-infarction, cardiac arrest, major bleed, and in-hospital mortality. Definitions of outcomes collected in the CONCORDANCE registry have been previously published.[19,20]

2.3 | Statistical analyses

Demographics, in-hospital management and in-hospital events of the anemia and non-anemia group were compared using χ^2 test for categorical variables and independent *t*-test for continuous variables. Multivariable logistic generalized estimating equation (GEE) regression models adjusting for hospital clustering effect and patient clinical characteristics (GRACE score[21] categories, STEMI vs not, diabetes, and previous myocardial infarction) were used to investigate the independent contribution of anemia to in-hospital mortality. Adjusted probability of death was modeled with hemoglobin as a continuous variable using the multivariable GEE model, and the probability of death with an increase of hemoglobin by 1 g/L was graphically represented.

3 | RESULTS

3.1 | Baseline characteristics

Between February 2009 and December 2015, a total of 8748 patients were admitted with ACS to 41 Australian hospitals registered with the CONCORDANCE registry. In total 8665 patients (99% of overall population) had a hemoglobin level recorded at admission. A total of 1880 (21.7%) of the final study population were anemic on admission.

The baseline characteristics of the study population are outlined in Table 1. Our anemic patients were older (72 years vs 63 years, $P < .0001$), and comorbidities including previous myocardial infarction (MI), chronic renal failure, diabetes, hypertension, and dyslipidaemia were more prevalent when compared to the non-anemic group. They had more frequently been investigated for coronary artery disease prior to their admission.

3.2 | In-hospital management

Anemic patients presenting with STEMI were less likely to be emergently reperfused with either thrombolytic therapy (22% vs 33%,

TABLE 1 Baseline characteristics of anemia vs non-anemia

Variable	Anemia (n = 1880) n (%) Hb ≤ 120 (females)|Hb ≤ 130 (males)		Non-anemia (n = 6785), n (%) Hb > 120 (females)|Hb > 130 (males)		*P* value
Age (years)	72.3 ± 12.6		62.8 ± 13.0		<.0001
Sex	F: 641 (34)	M: 1239 (66)	F: 1855 (27)	M: 4930 (73)	<.0001
Diagnosis	STEMI: 394 (21)	NSTEMI: 1032 (55)	STEMI: 2344 (35)	NSTEMI:3147 (46)	<.0001
Previous MI	836 (44)		1737 (26)		<.0001
Previous angiogram	966 (51)		2064 (30)		<.0001
Previous PCI	541 (29)		1262 (19)		<.0001
Previous CABG	384 (20)		612 (9)		<.0001
Chronic renal failure	473 (25)		279 (4)		<.0001
Diabetes	848 (45)		1537 (23)		<.0001
Hypertension	1477 (79)		3914 (58)		<.0001
Dyslipidaemia	1278 (68)		3615 (53)		<.0001

Abbreviations: CABG, coronary artery by-pass graft; MI, myocardial infarction; NSTEMI, non-ST elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST elevation myocardial infarction.

P < .0001) or primary PCI (45% vs 51%, *P* = .033). When a coronary stent was deployed during primary PCI, drug eluting stents (DES) were used less in the anemic cohort (*P* = .016) (Table 2a). For all ACS patients (which includes STEMI non-STEMI and unstable angina), anemic patients less frequently received coronary angiography (63% vs 86%, *P* < .0001) and PCI (30% vs 52%, *P* < .0001). If a stent was deployed, drug eluting stents (50% vs 58%, *P* < .0001) were less likely to be utilized (Table 2b).

TABLE 2 (a) Thrombolytic therapy and primary PCI in anemic and non-anemic cohort in STEMI only

Variable	Anemia (n = 394), n (%) Hb ≤ 120 (females) |Hb ≤ 130 (males)	Non-anemia (n = 2344), n (%) Hb > 120 (females) |Hb > 130 (males)	*P* value
Thrombolytic therapy	87 (22)	778 (33)	<.0001
Primary PCI	179 (45)	1201 (51)	.0330
BMS[a]	88 (49)	504 (42)	.0695
DES[a]	80 (45)	652 (54)	.0164

(b) Interventions in anemic vs non-anemic cohort presenting with ACS (includes NSTEMI and STEMI)

Variable	Anemia (n = 1880), n (%) Hb ≤ 120 (females)|Hb ≤ 130 (males)	Non-anemia (n = 6785), n (%) Hb > 120 (females) |Hb > 130 (males)	*P* value
Angiography	1191 (63)	5804 (86)	<.0001
PCI	573 (30)	3542 (52)	<.0001
BMS[b]	252 (44)	1356 (38)	.0095
DES[b]	284 (50)	2068 (58)	<.0001
CABG	150 (8)	595 (9)	.2792

[a]Denominator: primary PCI patients.
[b]Denominator: PCI.
Abbreviations: BMS, bare metal stent; CABG, coronary artery bypass graft; DES, drug eluting stent; PCI, percutaneous coronary intervention.

Anemic patients were less likely to be prescribed parenteral anticoagulation in the form of heparin or low molecular weight heparin (82% vs 88%, *P* < .0001) and overall received less antiplatelet therapy and in particular were less likely to be escalated to the more potent $P2Y_{12}$ inhibitors prasugrel (2% vs 5%, *P* < .0001) and ticagrelor (11% vs 20%, *P* < .0001). They were less likely to receive intravenous glycoprotein IIb/IIIa inhibitors (6% vs 15%, *P* < .0001) (Table 3).

3.3 | In-hospital outcomes

Anemic patients presenting with ACS had more complex hospital stays marked by a higher frequency of in-hospital events. These included higher rates of cardiogenic shock (5% vs 2%, *P* < .0001), recurrent ischemia (13% vs 8%, *P* < .0001), re-infarction (4% vs 2%, *P* < .0006), major bleeds (13% vs 7%, *P* < .0001), and death from all causes (7% vs 3%, *P* < .0001) (Table 4).

TABLE 3 In-hospital management with anticoagulation and antiplatelet agents

Variable	Anemia (n = 1880), n (%) Hb ≤ 120 (females)| Hb ≤ 130 (males)	Non-anemia (n = 6785), n (%) Hb > 120 (females)| Hb > 130 (males)	*P* value
Parenteral anticoagulation[a]	1536 (82)	5986 (88)	<.0001
Aspirin	1740 (93)	6564 (97)	<.0001
Aspirin and clopidogrel	1317 (70)	4828 (71)	.3511
Aspirin and prasugrel	34 (2)	351 (5)	<.0001
Aspirin and ticagrelor	208 (11)	1345 (20)	<.0001
Glycoprotein IIb/IIIa antagonist	121 (6)	1013 (15)	<.0001

[a]Heparin or low molecular weight heparin.

TABLE 4 In-hospital events in the anemic and non-anemic cohort

Variable	Anemia (n = 1880), n (%) Hb ≤ 120 (females) |Hb ≤ 130 (males)	Non-anemia (n = 6785), n (%) Hb > 120 (females) |Hb > 130 (males)	*P* value
Congestive heart failure	278 (15)	450 (7)	<.0001
Cardiogenic shock	91 (5)	167 (2)	<.0001
Acute renal failure	251 (13)	237 (4)	<.0001
Recurrent ischemia	240 (13)	572 (8)	<.0001
Re-infarction	73 (4)	165 (2)	0.0006
Cardiac arrest	84 (5)	217 (3)	0.0074
Atrial fibrillation	281 (15)	576 (9)	<.0001
Major bleed	247 (13)	473 (7)	<.0001
Death	124 (7)	180 (3)	<.0001

Anemia was also an independent predictor of mortality when adjusted for GRACE risk score, ACS diagnosis, diabetes, and previous MI with an adjusted OR for death of 1.62 (95% CI, 1.16-2.25) compared to patients without anemia. There was an inverse relationship between admission hemoglobin and the adjusted probability of death (Figure 1).

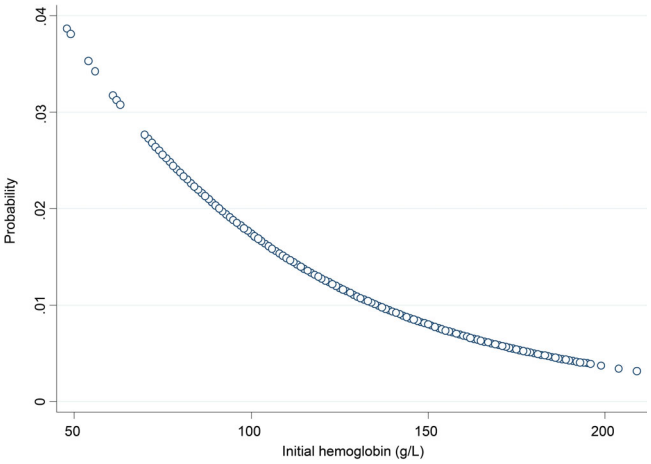

FIGURE 1 Adjusted odds of death and hemoglobin
†Adjusted for hospital clustering effect, grace risk score, diagnosis (STEMI vs other), diabetes, and previous myocardial infarction

4 | DISCUSSION

The presence of anemia in patients presenting with ACS poses many challenges with regards to management. We report a prevalence of 21.7% in our contemporary Australian cohort. This is consistent with a large meta-analysis of 27 studies in which 19.1% of ACS patients (n = 233 144) were anemic (n = 44 519).[5] In our study anemic patients were significantly older with more cardiovascular risk factors and comorbidities. They were less likely prescribed coronary intervention and medical therapies including antithrombotic agents that have been shown to have prognostic benefit in ACS.

Our anemic patients had more complicated hospital stays with higher rates of cardiogenic shock, re-infarction, and major bleeds. In-hospital mortality in the anemic population was 60% higher after adjustment for comorbidities.

Patients with STEMI are less likely to undergo primary PCI and this is consistent with the literature.[22] Studies which examine the impact of anemia on patients with ACS treated by primary PCI have found that anemia was a powerful marker of poor prognosis.[1,5,7,10,15,22-24] Though one study suggests that early coronary angiography and PCI in an anemic STEMI cohort was associated with improved clinical outcomes and a comparable incidence of bleeding with the anemic cohort who did not undergo PCI.[15] A more recent retrospective study suggests that timely primary PCI in anemic STEMI patients had no increase in mortality but a penalty of major bleeding when compared to STEMI patients without anemia.[24] There is general agreement that the management of ACS patients should incorporate anemia into the overall PCI strategy but there are no guidelines directly addressing this common clinical dilemma.[1,3,7,10,23-26] Whilst no causal relationships have been identified between anemia and poor prognosis, being aware of these associations allows clinicians to understand risk and exercise caution when managing anemic STEMI patients.[26]

It is not surprising that anemic patients in our cohort received less thrombolysis, anticoagulation, and antiplatelet therapy. When dual antiplatelet agents were prescribed, patients were less likely to receive more potent $PY2_{12}$ inhibitors. This likely reflects the unequivocal associations of these therapies with increased bleeding, and the fact that anemic patients have been routinely excluded from trials of these agents meaning there are limited randomized data to guide decisions.[1,27,28] We also found that anemic patients received less drug eluting stents when a stent was deployed—perhaps a physician decision related to the requirement for longer duration dual antiplatelet therapy with DES.

Guidelines recommend consistent approaches to patients at high bleeding risk of whom those with anemia form a subset. The 2016 National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand (CSANZ) recommends applying a "priority low-bleeding" strategy which includes the use of reversible and short acting antithrombotic agents, minimization of the number of agents used and substitution rather than addition of agents when necessary (Grade B recommendation, Evidence Level II). The European Cardiac Society (ESC) guidelines suggest additional strategies including avoidance of overdosing and applying renal adjustments to medications.[29] The American Heart Association (AHA) suggest that weight-based calculations should be used for anticoagulants and antiplatelets (Level II Evidence).[30,31]

The mortality relationship with anemic patients presenting with ACS shown in this study is consistent with that reported in the literature.[1,2,5,7,9,32] Sabatine et al examined the 30 day cardiovascular mortality in patients with STEMI categorized by 1 g/dL hemoglobin increments and found a J-shaped relationship with increased mortality

at hemoglobins below 140 g/L and above 170 g/L. A more recent British retrospective study confirmed both the optimal hemoglobin range and the J shaped relationship with 30-day mortality in 71 223 patients presenting with anemia and ACS.[32] In our smaller population we too found a close association between hemoglobin and mortality after adjustment for comorbidities. The relationship was curvilinear because the number of patients with hemoglobins over 17 was small but was otherwise consistent with previous studies.

Ultimately the difficulty remains in elucidating the exact drivers of poor outcome in anemic patients given this particular cohort is not included in clinical trials. However, the observation that the poor outcomes in our cohort were only partly corrected following adjustment for baseline clinical characteristics, highlights the importance of ensuring these patients are at the very least considered for prognostically important therapies.

4.1 | Limitations

The cause of anemia could not be determined from the database which is a limitation because the etiology of the anemia will impact on the management and outcomes of ACS patients. As in all retrospective observational analyses our findings reflect associations rather than causality. Furthermore, we did not interview clinicians, so it is unclear what underpinned decisions to provide or withhold therapies to a particular patient. This study did not address the issue of blood transfusion in the anemic ACS as the number of transfusions performed in our study cohort was very small.

5 | CONCLUSION

Anemic patients presenting with ACS have poorer outcomes. They receive less evidenced based medical therapies which we postulate contributes to their overall worse outcomes. We would suggest that this cohort requires further focused study to determine whether more active treatment in the acute phase of their presentation will improve outcomes.

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CONFLICT OF INTERESTS

The authors declare no potential conflict of interests.

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