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Age and gender mediated the association between anemia and 30-day outcomes in patients with ST-segment elevated myocardial infarction

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ABSTRACT

Background: The higher prevalence of anemia in females and elderly may be attributed to its association with worsened outcomes in ST-elevation myocardial infarction (STEMI) patients. We aimed to evaluate the precise effects of age and gender on the association between anemia and 30-day outcomes.

Method: We identified 4350 STEMI patients and divided into anemia and non-anemia. Effects were analyzed as categories using Cox proportional-hazards regression and as continuous using restricted cubic splines. Propensity score matching (PSM) and mediation analysis were applied to identify intermediate effects.

Results: Anemic patients were older, more likely to be female, and experienced doubled all-cause death (7.3 % versus 15.0 %), main adverse cardiovascular and cerebrovascular events (MACCE, 11.1 % versus 20.2 %), heart failure (HF, 5.1 % versus 8.6 %), and bleeding events (2.7 % versus 5.4 %). After adjustment, the association between anemia and all-cause death (Hazard ratio (HR) 1.15, 95 % confidence interval (95 %CI) 0.93–1.14), MACCE (HR 1.14, 95 %CI 0.95–1.36) and HF (HR 1.19, 95 %CI 0.92–1.55) were insignificant, the effects persisted nullified across age classes (P-interaction > 0.05) and PSM ($P > 0.05$). Ulteriorly, age mediated 77.6 %, 66.2 %, 48.0 %, gender mediated 38.1 %, 15.0 %, 3.2 %, age and gender together mediated 99.8 % 72.9 %, 48.1 % of the relationship. Anemia was independently associated with bleeding events (HR 2.02, 95 %CI 1.42–2.88), the effects consisted significant regardless of PSM ($P < 0.05$), age, and gender classes (P-*interaction* > 0.05), and no mediating role of age and gender were observed.

Conclusions: In STEMI patients, age and gender largely mediated the relationship between anemia and all-cause death, MACCE, and HF, anemia was independently associated with bleeding complications.

1. Introduction

Coronary artery disease (CAD) is the leading contributor to mortality globally and in China [1], ST-elevation myocardial infarction (STEMI) is the most severe CAD, which accounts for more than 80 % of acute myocardial infarction in China and leads to substantial mortality [2,3]. The prognosis of STEMI patients is multifactorial, many studies have shown that females and the older patients had greater risk of worsened outcomes in STEMI patients [4].

Anemia is prevalent among STEMI patients and is a common co-morbidity in elderly patients. Several studies have shown the association between anemia and increased risk of bleeding, ischemic events, and worsened clinical outcomes [5–8], nevertheless, other studies have shown inconsistent association [9,10]. Serum hemoglobin (HB) levels decline slightly with aging, which results in the elderly having a higher prevalence of anemia, what's more, the prevalence of anemia was significantly higher in females than their counterparts [11,12], the higher prevalence of anemia in elderly and female may attribute to its association with poor prognosis.

Data regarding age and sex impact on the association of admission anemia and 30-day outcomes in STEMI patients are limited. Whether there is age- and sex-specific differences in the association, and the

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possible impact are yet to be determined. What's more, there is little information about their relationship in rural areas, where the majority of the Chinese population lives, especially in the current era of improved application of evidence-based acute treatments in STEMI patients.

The main purpose of this study was to investigate whether anemia on admission is associated with 30-day all-cause death, main adverse cardiovascular and cerebrovascular events (MACCE), heart failure (HF), and bleeding events, and to evaluate the precise impact of age and sex in the association in STEMI patients.

2. Methods

2.1. Study population

This was a *post-hoc analysis of the Henan STEMI registry (NCT 02641262),* the design and result of *the Henan STEMI registry* have been reported before[13,14], in brief, it is a multicenter, prospective study for STEMI patients, STEMI was defined as elevated biomarkers and new or presumed new ST-segment elevation $>$ 1 mm (0.1 mV) in 2 or more contiguous leads or new onset of left bundle branch block, which following the universal definition of Myocardial Infarction (2012)[15], patients diagnosed as types 4a and type 5 STEMI were excluded.

A total of 5342 STEMI patients hospitalized in 66 eligible hospitals from September 2016 to August 2018 were included, after excluding patients transferred in with prior reperfusion (279 cases), patients with missing hemoglobin on admission (132 cases), and those without survival status within 30 days after first medical contact (FMC) (581 cases). We finally enrolled 4350 patients in this analysis ***(***Supplement Fig. 1***)***. Patients enrolled were treated according to the guideline [16].

2.2. Data collection

The baseline demographic, cardiovascular risk factors, medical histories, clinical characteristics at admission, reperfusion therapy, medications, and hemoglobin of STEMI patients were prospectively collected through a standardized online reporting platform with automatic checks for invalid values. We checked the consecutiveness of all cases, and a total of 53.84 % of reported cases were audited for accuracy against medical records for onsite quality control.

2.3. Definitions

Anemia on admission was defined in accordance with the World Health Organization definitions [17]: serum hemoglobin $<$ 130 g/L in male and $<$ 120 g/L in female, the serum hemoglobin concentration in this study were measured after FMC and the patients were divided into two groups according to anemia status at admission. Hypertension was defined as having a history of hypertension or receiving antihypertensive therapy. Dyslipidemia was defined according to the guidelines [18]. Diabetes mellitus was defined as having a previous diagnosis of diabetes mellitus, or a glycosylated hemoglobin level $\geq$ 6.5 %. The current smoker was defined as smoking within the preceding year. The history of coronary heart disease was defined as having a clinical history of myocardial infarction or undergoing percutaneous coronary intervention (PCI) or coronary artery bypass grafting before the current hospitalization. The wall location of the myocardia infraction was determined by an electrocardiogram.

2.4. Followed-up and clinical outcomes

The endpoints were all-cause death, MACCE, HF, and bleeding events within 30 days since FMC. We reviewed hospital records for status at discharge, and all the surviving patients at discharge were followed-up through telephone or clinic interviews by contacting the patients or their first-degree relatives to confirm their status at 30 days. MACCE was defined as all-cause death, HF, refraction, and cerebral infarction. HF was defined as new onset or worsening HF. Bleeding events were defined as cerebral hemorrhage, gastrointestinal bleeding, and other bleeding events.

2.5. Statistical analysis

Demographic, medical history, clinical characteristics, reperfusion therapy, treatment time delay, and medicines used during hospitalization were reported for anemia and non-anemia patients. Categorical variables were presented as number and percentage, Chi-square or Fisher exact tests were used for comparisons as appropriate, continuous variables were reported as means and standard deviation (SD) or median and interquartile range (IQR), *t-test* or Mann-Whitney *U* test was used as appropriate.

The Kaplan-Meier method was used to estimate cumulative rates of events from first medical contact to 30 days follow-up. The associations between serum hemoglobin, as a continuous variable, and outcomes were modeled using restricted cubic splines using non-anemia on admission as reference, the 5 knots were placed at default positions according to percentiles of hemoglobin (5, 27.5, 50, 72.5, and 95 centiles).

The association between anemia on admission and clinical outcomes was compared in a Cox proportional-hazards regression with non-anemic patients on admission as reference, which accounted for clustering of patients within hospitals, results were reported as hazard ratios (HRs) with associated 95 % confidence intervals (CIs). This was repeated with additional adjustments for age, gender, occupation, diabetes, smoke, medical history of cerebral infarction, cerebral hemorrhage and coronary heart disease, cardiac arrest, anterior myocardial infarction, Killip class, systolic blood pressure (per 5 mmHg), reperfusion treatment (successful reperfusion, unsuccessful reperfusion or no reperfusion, time to present (onset-to-FMC) and medicine use during hospitalization (aspirin, P2Y12 antagonists and angiotensin-converting enzyme inhibitor (ACEI) / angiotensin receptor blockers (ARB). The Cox proportional-hazards regression analysis was repeated with the additional adjustments listed above in gender and age groups ($<$55, 55–64, 65–74, and $>$=75) separately. The presence of an interaction between anemia on admission and age groups or gender on the occurrence of each outcome was examined using the *Wald* test.

Propensity score matching (PSM) for admission anemia was calculated using the variables age and gender to achieve a good balancing of baseline differences. PSM was performed in a 1:1 fashion. Endpoints were subsequently analyzed using cox proportional-hazards regression. In order to precisely estimate the causal effects of anemia on admission, we applied mediation analysis to explored whether the causal relationship between anemias and 30-days clinical outcomes were mediated by sex and gender, meanwhile, we adjusted covariates (as listed in Cox proportional-hazards regression) in the models. Hence, we estimated the direct effects (the total effect of anemia on 30 days outcomes without considering the mediating effect of age and gender), indirect effects (the effect of anemia on 30 days outcomes considering the effect of the age and gender), and the mediation proportion of age and gender. We used the mediation tools designed for survival analysis by Ellen Hertzmark, which is provided in the SAS %MEDIATE macro.

Two-sided P values $<$ 0.05 was considered statistically significant. Statistical analyses were performed with SAS 9.4 (SAS Institute Inc., Cary, NC) and R package (Version 4.2.1, R Foundation for Statistical Computing, Vienna, Austria).

3. Results

Among 4350 STEMI patients included in this study, 1236 (28.4 %) had anemia on admission, and 317 (7.3 %) had moderate or severe anemia ***(***Supplement Fig. 2***A)***. The median hemoglobin of the study population was 136 g/L with a median hemoglobin level of 117 (109,124) g/L in the anemia patients and 142 (135,151) g/L in the non-

anemic patients *(*Supplement table 1*)*. Histogram representing the distribution of the admission serum hemoglobin concentrations in the entire study population was shown in Supplement Fig. 3***A***.

3.1. Baseline and clinical characteristics of patients

The baseline and clinical characteristics between anemic and non-anemic patients were summarized in Table 1**.** Patients with anemia on admission were significantly older, more often women, more likely to be farmers and had a higher prevalence of diabetes, chronic obstructive pulmonary disease, and cerebral infarction, whereas their counterparts were more frequently to be current smokers and more likely to have a medical history of dyslipidemia. Furthermore, anemic patients presented lower percentage of anterior myocardial infarction, normal cardiac function, and lower systolic and diastolic blood pressure. Nevertheless, the proportion of cardiac arrest was slightly higher in anemic patients.

In addition, anemic patients experienced delayed onset-to-FMC time, and had a lower proportion of receiving reperfusion therapy, what's more, only about 41.8 % of anemic patients underwent successful revascularization, which is lower than non-anemic patients**.** In terms of guideline-recommended drugs, non-anemic patients were more likely to receive aspirin, P2Y12 antagonist, beta-blocker, and ACEI/ARB.

3.2. Clinical outcomes of patients

As shown in Table 2 ***and*** Fig. 1, compared to patients without anemia on admission, anemic STEMI patients experienced doubled incidences of all-cause death, MACCE, HF, and bleeding events (all $P < 0.001$). After adjustment for clustering within hospitals, anemia on admission was significantly associated with these outcomes. The relationship between hemoglobin on admission as a continuous variable and clinical outcome confirmed these patterns (Fig. 2). Adjustment for age and gender did not fundamentally alter the patterns observed in the unadjusted categorical or continuous analyses described above on all-cause death, MACCE, and bleeding events. However, the association observed between anemia and HF was altered *(*Table 2*)*. Adjustment for prognostically important variables, the association between anemia and all-cause death, MACCE and HF were not significant, whereas the association with bleeding events retains significant. ***(***Table 2***)***.

3.3. Effects of age on association between anemia and clinical outcomes

Patients were divided into four age groups (<55, 55–64, 65–74, and >=75), and the incidence of all-cause death within 30 days of anemic patients was higher than their counterparts in age < 55 and age 65–74 (Supplement Fig. 4***A***), adjustment for clustering within hospitals, the effect of anemia on all-cause death to a different extent across age categories (*P-interaction* < 0.001). Adjustment for gender, the effect of anemia on all-cause death was only significant in age < 55 (HR: 3.01, 95 % CI: 1.59–5.70), in the other age groups the effects were insignificant, and the effect of anemia on a similar extent across age categories (*P-interaction* = 0.068). Adjustment for prognostically important variables, anemia was not associated with all-cause death across age categories (*P-interaction* = 0.378). The incidence of MACCE was significantly higher in age < 55 and age 55–64 (Supplement Fig. 4***B***), adjustment for gender, anemia was associated with MACCE across the age groups (*P-interaction* = 0.076). Adjustment for prognostically important variables, the effect was not significantly different and was consistent across the age groups (*P-interaction* = 0.346).

The incidence of HF was only significant in age < 55 (Supplement Fig. 4***C***), and the effects of anemia were also have significant differences after adjusted for clustering within hospitals (HR: 2.95, 95 % CI: 1.48–5.91), gender (HR: 2.74, 95 % CI: 1.35–5.55) and prognostically important variables (HR: 2.56, 95 % CI: 1.24–5.29) in age < 55. The effect was on a similar extent across the age groups after adjusting for

Table 1
Baseline Characteristics According to Anemia status on admission.

Variable	Non-anemia (N = 3114)	Anemia (N = 1236)	Overall (N = 4350)	*P* value
Demographic characteristic				
Age, years, median (IQR)	60.7 (50.7,68.6)	68.5 (60.8,76.1)	63.0 (52.6,71.1)	< 0.001
Age group, n (%)				
Age < 55	1206 (38.7)	182 (14.7)	1388 (31.9)	< 0.001
Age 55–64	794 (25.5)	292 (23.6)	1086 (25.0)	
Age 65–74	727 (23.4)	416 (33.7)	1143 (26.3)	
Age >=75	387 (12.4)	346 (28.0)	733 (16.9)	
Female, n (%)	629 (20.2)	426 (34.5)	1055 (24.3)	< 0.001
Farmer, n (%)	2038 (65.5)	886 (71.7)	2924 (67.2)	< 0.001
Tertiary hospital, n (%)	1603 (51.5)	655 (53.0)	2258 (51.9)	0.367
Risk factors				
Hypertension, n (%)	1371 (44.0)	565 (45.7)	1936 (44.5)	0.313
Dyslipidemia, n (%)	1749 (56.2)	651 (52.7)	2400 (55.2)	0.037
Diabetes, n (%)	526 (16.9)	258 (20.9)	784 (18.0)	0.002
Current smoker, n (%)	1371 (44.0)	371 (30.0)	1742 (40.1)	< 0.001
Medical history				
Heart failure, n (%)	28 (0.9)	16 (1.3)	44 (1.0)	0.240
COPD, n (%)	51 (1.6)	37 (3.0)	88 (2.0)	0.004
Coronary heart disease, n (%)	188 (6.0)	86 (7.0)	274 (6.3)	0.260
Cerebral infarction, n (%)	340 (10.9)	185 (15.0)	525 (12.1)	< 0.001
Cerebral hemorrhage, n (%)	31 (1.0)	18 (1.5)	49 (1.1)	0.194
Clinical characteristic				
Cardiac arrest, n (%)	84 (2.7)	50 (4.1)	134 (3.1)	0.020
Anterior myocardial infarction, n (%)	1824 (58.6)	636 (51.5)	2460 (56.6)	< 0.001
Killip class, n (%)				
I	2378 (76.4)	792 (64.1)	3170 (72.9)	< 0.001
II	460 (14.8)	198 (16.0)	658 (15.1)	
III	151 (4.9)	112 (9.1)	263 (6.1)	
IV	125 (4.0)	134 (10.8)	259 (6.0)	
SBP, mmHg, median (IQR)	130 (116,150)	121 (105,140)	130 (112,147)	< 0.001
DBP, mmHg, median(IQR)	81 (71,94)	76 (65,85)	80 (70,91)	< 0.001
HR, BPM, median (IQR)	76 (66,88)	76 (64,89)	76 (66,88)	0.355
Reperfusion strategy, n (%)				
None	1133 (36.4)	665 (53.8)	1798 (41.3)	< 0.001
PCI	1052 (33. 8)	303 (24.5)	1355 (31.2)	
Fibrinolysis	929 (29.8)	268 (21.7)	1197 (27.5)	
Successful reperfusion, n (%)	1840 (59.1)	517 (41.8)	2357 (54.2)	< 0.001
Onset-to-FMC, min, median(IQR)	186 (100,484)	255 (120,1298)	210 (109,600)	< 0.001
FMC-to-Needle, min, median(IQR)	49 (28,79)	44 (30,79)	47 (29,79)	0.955
FMC-to-Balloon, min, median(IQR)	66 (41,95)	64 (43,95)	65 (42,95)	0.753
Medicine used in hospital				
Aspirin, n (%)	2998 (96.3)	1166 (94.3)	4164 (95.7)	0.004
Clopidogrel, n (%)	2382 (76.5)	993 (80.3)	3375 (77.6)	0.006
Ticagrelor, n (%)	622 (20.0)	174 (14.1)	796 (18.3)	< 0.001
P2Y12 antagonists, n (%)	3004 (96.5)	1167 (94.4)	4171 (95.9)	0.002
Statin, n (%)	2952 (94.8)	1156 (93.5)	4108 (94.4)	0.099
Beta-blocker, n (%)	2244 (72.1)	796 (64.4)	3040 (69.9)	< 0.001
ACEI/ARB, n (%)	1646 (52.9)	536 (43.4)	2182 (50.2)	< 0.001

Data are expressed as n (%) or median (IQR), unless otherwise noted.
Abbreviations: IQR, interquartile range; COPD, chronic obstructive pulmonary disease; HR, heart rate; BPM, beat per minute; SBP, systolic blood pressure; DBP, diastolic blood pressure; Stoke contains ischemic and hemorrhagic. Coronary heart disease contains myocardial infarction, percutaneous coronary

intervention and coronary artery bypass graft. PCI, percutaneous coronary intervention. FMC, first medical contact. P2Y12 antagonists contains clopidogrel and ticagrelor. ACEI, Angiotensin-Converting Enzyme Inhibitors. ARB, Angiotensin Receptor Blockers.

Table 2
Effect of anemia on admission on 30-days outcomes before and after propensity score match.

Outcomes	All cohort (N = 4350)			PSM (N = 2442)		
	No anemia (N = 3114)	Anemia (N = 1236)	*P* value	No anemia (N = 1221)	Anemia (N = 1221)	*P* value
Death						
No of events, n (%)	227 (7.3)	185 (15.0)	< 0.001	156 (12.8)	181 (14.8)	0.142
HR (95 % CI)*	2.15 (1.76–2.61)		< 0.001	1.18 (0.95–1.46)		0.144
HR (95 % CI)**	1.34 (1.09–1.64)		0.005	1.13 (0.91–1.40)		0.281
HR (95 % CI)***	1.15 (0.93–1.43)		0.195	0.96 (0.76–1.21)		0.718
MACCE						
No of events, n (%)	346 (11.1)	249 (20.2)	< 0.001	210 (17.2)	244 (20.0)	0.077
HR (95 % CI)*	1.88 (1.60–2.22)		< 0.001	1.15 (0.95–1.39)		0.141
HR (95 % CI)**	1.28 (1.08–1.51)		0.005	1.12 (0.93–1.36)		0.221
HR (95 % CI)***	1.14 (0.95–1.36)		0.151	1.03 (0.84–1.25)		0.797
Heart failure						
No of events, n (%)	158 (5.1)	106 (8.6)	< 0.001	84 (6.9)	104 (8.5)	0.129
HR (95 % CI)*	1.70 (1.33–2.18)		< 0.001	1.15 (0.86–1.54)		0.337
HR (95 % CI)**	1.25 (0.96–1.61)		0.095	1.16 (0.87–1.55)		0.324
HR (95 % CI)***	1.19 (0.92–1.55)		0.192	1.17 (0.87–1.58)		0.304
Bleeding events						
No of events, n (%)	85 (2.7)	67 (5.4)	< 0.001	37 (3.0)	66 (5.4)	0.004
HR (95 % CI)*	2.11 (1.52–2.92)		< 0.001	1.74 (1.16–2.62)		0.008
HR (95 % CI)**	1.78 (1.27–2.50)		< 0.001	1.75 (1.17–2.63)		0.007
HR (95 % CI)***	2.02 (1.42–2.88)		< 0.001	2.03 (1.33–3.10)		0.001

Hazard ratio (HR) estimated take patients without anemia on admission as reference. MACCE, main adverse cardiovascular and cerebrovascular events, contains death, heart failure, refraction and cerebral infarction. Bleeding events contains cerebral hemorrhage, gastrointestinal bleeding and other bleeding events.

* Model adjusted for anemia status on admission. ** Model adjusted for anemia status on admission, gender and age. *** Model adjusted for demographic variables (gender, age, occupation), medical history (diabetes, smoke, cerebral infarction, cerebral hemorrhage, coronary heart disease), clinical characters on admission (cardiac arrest, anterior myocardial infarction, Killip class, systolic blood pressure (per 5 mmHg)), reperfusion therapy (successful reperfusion, Onset-to-FMC time) and medication used in hospital (aspirin, P2Y12 antagonists and ACEI/ARB).

gender (*P-interaction* = 0.060) and prognostically important variables (*P-interaction* = 0.139). The incidences of bleeding events were significantly higher in age < 55 and age >=75 (Supplement Fig. 4***D***), and the effects of anemia were significant after being adjusted the same as above. The effect was consistent across the age groups after adjusting for gender (*P-interaction* = 0.222) and prognostically important variables (*P-interaction* = 0.268) (Fig. 3, Supplement Fig. 5***)***.

3.4. Effects of gender on association between anemia and clinical outcomes

Compared to patients without anemia on admission, the incidences of clinical outcomes (all-cause death, MACCE, HF) were significantly higher in anemic patients among male patients (all $P < 0.001$), the incidence of bleeding events was both higher in female and male (all $P < 0.002$) (Supplement Fig. 6). As for all-cause death and MACCE within 30 days, the effect was still significant in males after adjusting the same as above, whereas the effect was to a different extent across gender groups (all *P-interaction* < 0.05). The anemia effect on HF was absent after adjustment, and to the same extent across gender categories (*P-interaction* > 0.05). For bleeding events, the effect of anemia was apparent among males (HR: 1.66, 95 %CI: 1.11–2.49) and females (HR: 4.29, 95 %CI: 1.80–10.22). (Fig. 4, Supplement Fig. 7).

3.5. Propensity score matching analysis

Propensity score matching using the variables age and gender was performed in Table 2 and the baseline characteristics between groups after PSM were described in Supplement table 2. Both incidences of all-cause death, MACCE, and HF were not significant differences between anemia groups. The effect of anemia on all-cause death, MACCE, and HF was not significant after adjustment for clustering within hospitals (all $P > 0.05$), gender and age (all $P > 0.05$), and prognostically important variables (all $P > 0.05$). For bleeding events, the incidence was higher in anemia patients (5.4 % versus 3.0 %, $P = 0.004$), the effect was consistent across the adjustment for clustering within hospitals (HR: 1.74, 95 %CI: 1.16–2.62), for gender and age (HR: 1.75, 95 %CI: 1.17–2.63) and prognostically important variables (HR: 2.03, 95 %CI: 1.33–3.10).

3.6. Mediation analysis

In the mediation analysis, we tried to estimate the direct effects and indirect effects through mediating variables (age and gender) and adjusted covariates. As shown in Table 3, age alone can explain 77.6 % of the anemia effect in 30-day mortality, and gender alone can explain 38.1 % of the causal effect, afterward, age and gender covered the relationship between anemia and 30-day mortality. Similarly, the mediate effect of age (66.2 %) and gender (15.0 %) were significant on the relationship between anemia and 30-day MACCE. The mediation effect of age (48.0 %) was still significant for the anemia effect on HF, whereas, no intermediary effect was observed for gender in 30-day HF. For the causal effect of anemia on 30-day bleeding events, about one-fifth effect was mediated by age. This section shows that age and gender can greatly explain the relationship between anemia and all-cause death, MACCE, and HF in STEMI patients, and anemia on admission was immediately related to bleeding events.

4. Discussion

Our results demonstrated that anemia was a common complication in STEMI patients, STEMI patients coexisting anemia were significantly older and more likely to be female. Anemic patients experienced a higher risk of all-cause death, MACCE, and HF, the association was insignificant after adjustment and the PSM application nevertheless, our work assisted in elucidating the effect of age and gender on the association between anemia and all-cause death, MACCE, and HF by mediation analysis, in addition, the indirect effect of age and gender account for 99.8 %, 72.9, and 48.1 % of the contribution in this causal connection. Our results revealed that anemia was independently associated with bleeding events, the association was robust with multivariable adjustment and PSM analysis, and no mediating effects of age and

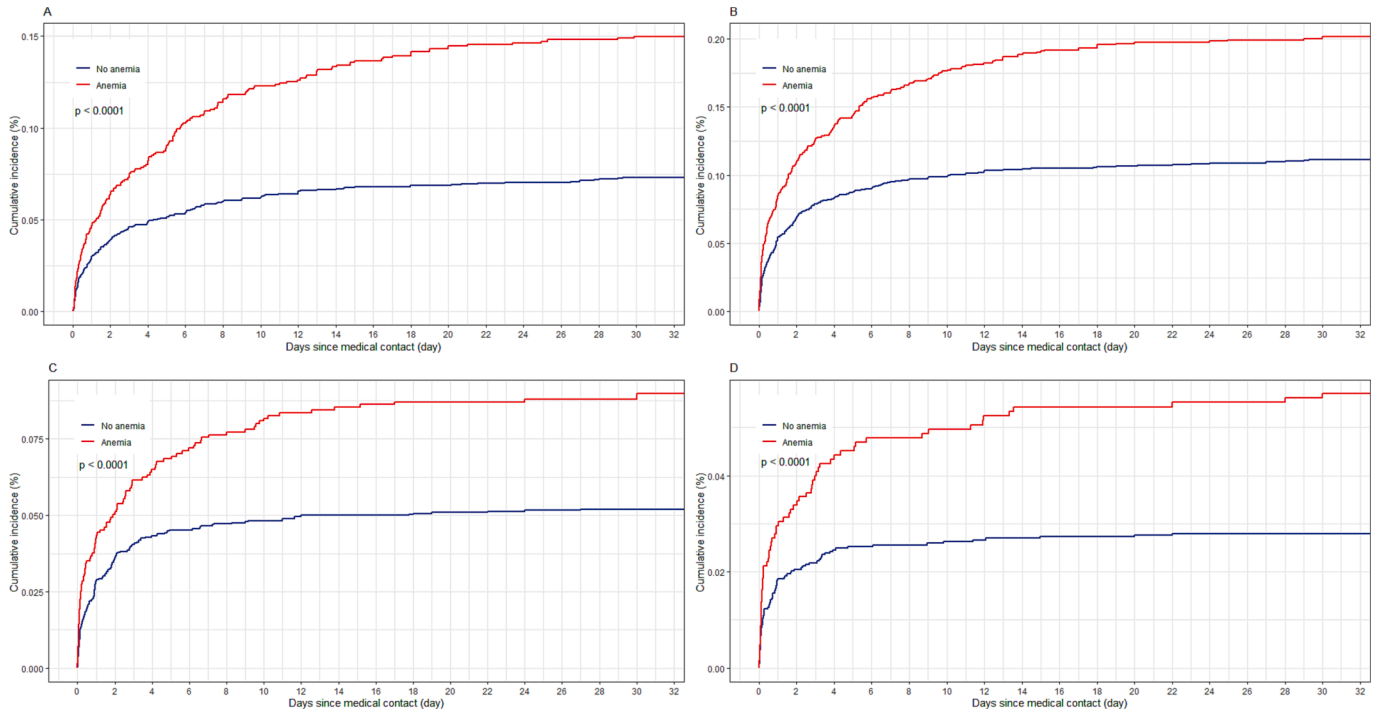

Fig. 1. Cumulative incidence of 30 day outcomes according to anemia on admission. (**A**) All-cause death; (**B**) MACCE; (**C**) Heart failure; (**D**) Bleeding events.

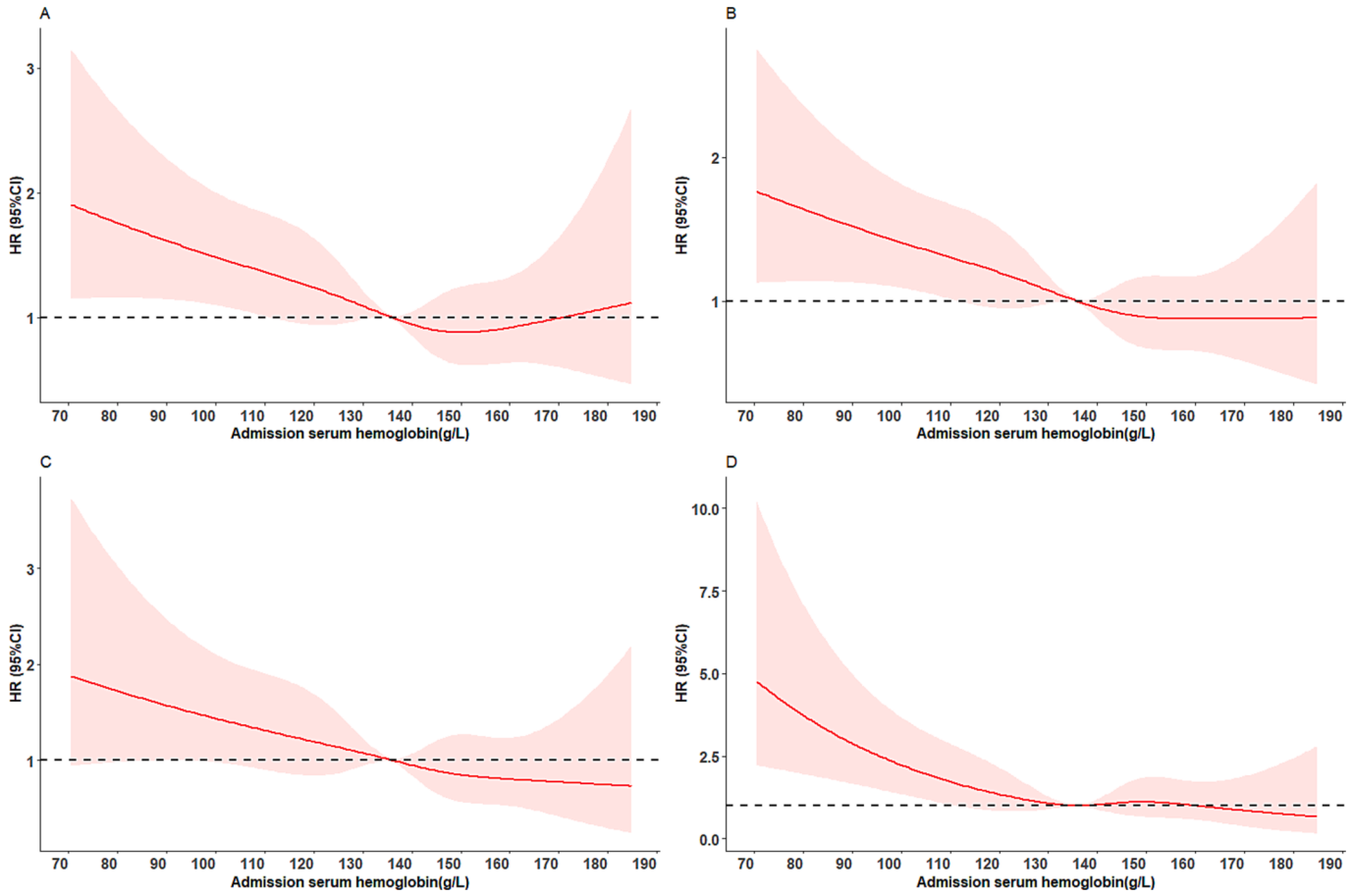

Fig. 2. Effect of hemoglobin on admission as continuous variable on 30 day outcomes. The baseline (red) line is adjusted for age and gender, and the red shaded area represents the 95 %CI. (**A**) All-cause death; (**B**) MACCE; (**C**) Heart failure; (**D**) Bleeding events.

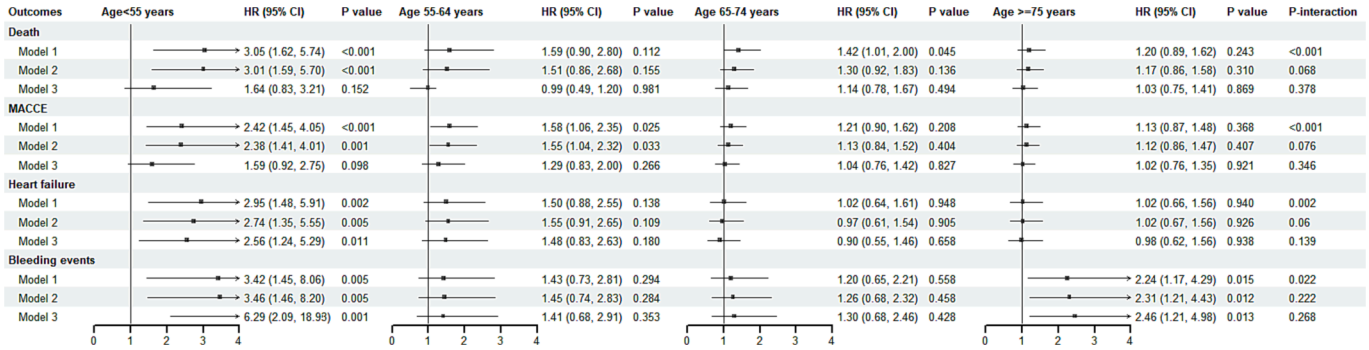

Fig. 3. Effect of admission anemia on 30-day outcomes according to age. Hazard ratio (HR) estimated take patients without anemia on admission as reference. MACCE, main adverse cardiovascular and cerebrovascular events, contains death, heart failure, refraction and cerebral infarction. Bleeding events contains cerebral hemorrhage, gastrointestinal bleeding and other bleeding events. Model 1 adjusted for anemia status on admission. Model 2 adjusted for anemia status on admission, gender and age. Model 3 adjusted for demographic variables (gender, age, occupation), medical history (diabetes, smoke, cerebral infarction, cerebral hemorrhage, coronary heart disease), clinical characters on admission (cardiac arrest, anterior myocardial infarction, Killip class, systolic blood pressure (per 5 mmHg)), reperfusion therapy (successful reperfusion, Onset-to-FMC time) and medication used in hospital (aspirin, P2Y12 antagonists and ACEI/ARB).

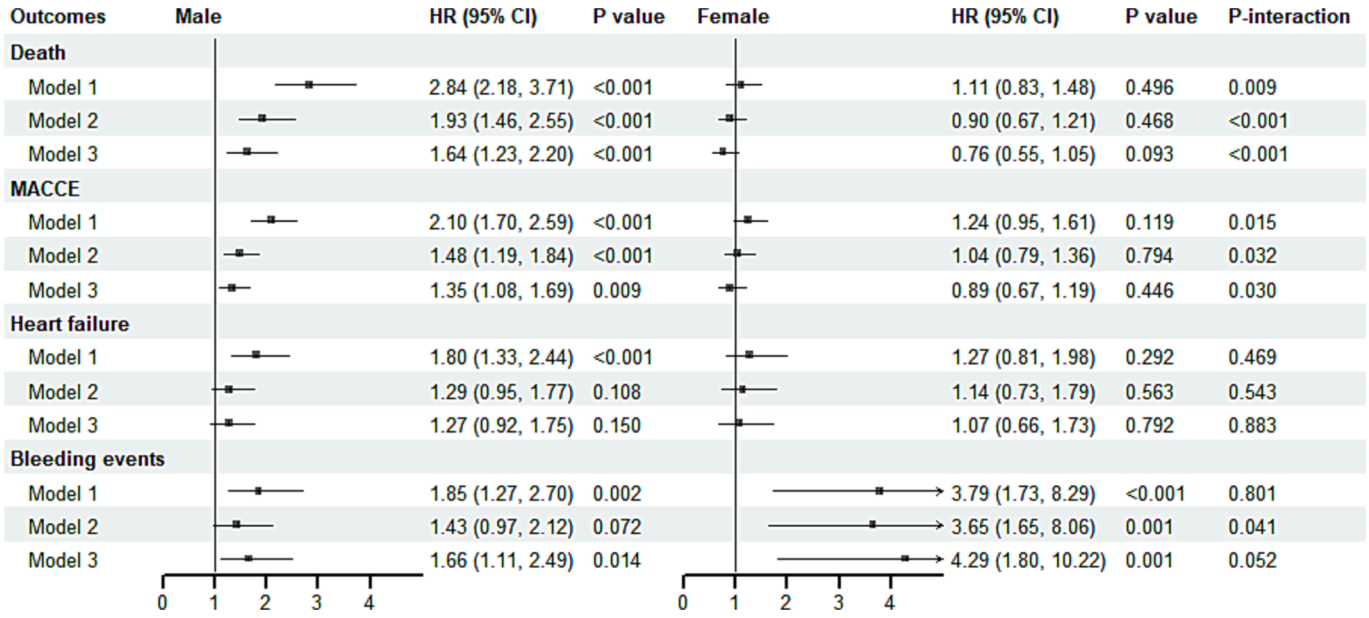

Fig. 4. Effect of admission anemia on 30-day outcomes according to gender. Abbreviations and model adjustment as in Fig. 3.

Table 3
Mediation analysis of age and gender in the relationship between anemia and 30-days clinical outcomes.

Mediator	Effects	Death	MACCE	Heart failure	Bleeding events
Age	Direct effects, HR(95 %CI)	1.22 (0.98–1.52)	1.30 (1.09–1.55)	1.56 (1.19–2.05)	2.01 (1.42–2.84)
	Indirect effects, HR(95 %CI)	1.05 (0.84–1.30)	1.09 (0.91–1.31)	1.26 (0.96–1.66)	1.78 (1.25–2.53)
	Mediate proportion, (%)	77.6 (2.2–99.8)	66.2 (19.6–94.0)	48.0 (20.1–77.2)	17.2 (7.2–35.5)
	P value	< 0.001	< 0.001	< 0.001	0.001
Gender	Direct effects, HR(95 %CI)	1.22 (0.98–1.52)	1.30 (1.09–1.55)	1.56 (1.19–2.05)	2.01 (1.42–2.84)
	Indirect effects, HR(95 %CI)	1.13 (0.90–1.42)	1.25 (1.04–1.50)	1.54 (1.17–2.03)	2.13 (1.51–2.99)
	Mediate proportion, (%)	38.1 (7.3–82.8)	15.0 (5.1–36.4)	3.2 (0.3–26.8)	/*
	P value	< 0.001	0.003	0.188	/*
Age & Gender	Direct effects, HR(95 %CI)	1.22 (0.98–1.52)	1.30 (1.09–1.55)	1.56 (1.19–2.05)	2.01 (1.42–2.84)
	Indirect effects, HR(95 %CI)	1.00 (0.80–1.25)	1.07 (0.90–1.29)	1.26 (0.95–1.67)	1.87 (1.32–2.65)
	Mediate proportion, (%)	99.8 (0.0–100.0)	72.9 (16.6–97.3)	48.1 (19.9–77.6)	10.0 (2.4–33.2)
	P value	< 0.001	< 0.001	< 0.001	0.068

/* Gender is not intermediate to anemia effect on bleeding events.

gender were observed. Therefore, STEMI patients with anemia need to be attentively managed to reduce bleeding risk in clinical practice.

Our finding showed that among STEMI patients, anemia is a common comorbidity and more than a quarter of patients were coexisting anemia, which is consistent with previous studies [5,8,9,19]. Most studies consistently showed that STEMI patients with anemia were older, and had a higher percentage of females and more unstable clinical presentation. Considering their higher ischemia and bleeding risk, these

patients were commonly conservatively managed and had a lower likelihood of receiving reperfusion therapy and potent antiplatelet drugs [10,20,21]. In the present study, STEMI patients with anemia were significantly older, the proportion of women was significantly higher, and had a higher proportion of worsening cardiac function and cardiac arrest, what's more, they were less likely to receive revascularization therapy, which may attribute, at least in part, to the bad prognosis in the anemic patients. Furthermore, concerns about bleeding complications have led to less frequent use of antiplatelet therapy in anemic patients, eliminating the benefits of these interventions when the indication exists [22]. We observed relatively small differences across the groups in the prescribing of aspirin and P2Y12 antagonists. Thus, there is a clear need for developing evidence-based data to supply better guidelines-guided therapy for these patients given their presence of older age and unstable clinical presentation.

Previous studies suggested that anemia was associated with a hypercoagulable state and serum hemoglobin level was a regulator of thrombopoiesis, moreover, anemia may deteriorate myocardial ischemia by reducing oxygen delivery as well as increase myocardial oxygen demands and associate with thrombocytosis [23]. Recent studies have reported the association of anemia and hemoglobin levels with adverse clinical outcomes, such as in-hospital complications, bleeding, and poor long-term outcomes [5,6,19,24]. To our knowledge, the associations have been inconsistent nevertheless. Anemic patients from this analysis had an approximately doubled increased incidence of all-cause death, MACCE, and HF within 30 days. We found insignificant association between anemia and all-cause death, MACCE, and HF after multivariable adjustment and PSM using age and gender, Wester, A et al [7] found that baseline anemia was a highly predictive factor for total mortality. Moghaddam, N et al [9] showed that baseline anemia was not independently associated with all-cause mortality, and very few studies reported an independent effect of anemia on the above clinical outcomes. With the different characters and comorbid conditions of the population, the number of variables for adjustment may yield different results. Our study suggests that anemia on admission may not contribute to all-cause death, MACCE, and HF directly itself but is a reflection of independent worse prognosis predictors such as older age and gender.

Anemic patients were more likely to experience bleeding events [6], and anemia was shown to be an independent risk factor for major bleeding in the medium- and long-term follow-up [25], anemia and serum hemoglobin level had been taken as one of the predictors included in currently recommended risk scores of predicting out-of-hospital bleeding during DAPT [26,27]. We investigated that the incidence of bleeding events was two times higher in the anemic patients, and after adjusting for potential confounders and PSM, anemia on admission remained an independent predictor. Our results were consistent with previous studies and suggest that anemic patients had higher potential bleeding diathesis than their counterparts, additional consideration should be given in the care process to minimize their bleeding risk, including careful use of DAPT, shortening duration of multiple antithrombotic agents, the use of proton-pump inhibitors and judicious dose adjustment of the anticoagulant.

Furthermore, several previous studies have reported sex-related differences in outcomes following STEMI, with both in-hospital and external mortality and HF being higher in females than their counterparts [4,28,29]. We observed a higher proportion of female anemia patients in this study and did not observe the association between anemia and all-cause death, MACCE in women, nevertheless, the association was significant in men. What's more, the association of anemia and bleeding events remained robust across gender. Female STEMI patients had longer symptom-to-door time and door-to-balloon time [30], and were less likely to receive evidence-based treatment, including reperfusion therapy, dual antiplatelet therapy, and ACEI/ARB [4], the higher proportion of females in anemia patients may play an independent role and act as a limitation or even a contraindication to some interventional or therapeutic.

We observed higher rates of all the clinical outcomes within 30 days in anemic patients among those aged < 55 years. The present study indicated the anemia prevalence dramatically increases with advancing age [12], STEMI with anemia tend to be older, meanwhile, aging STEMI patients have more complications, poor basic status, and are more likely to have contraindications for revascularization therapy [31,32], which might be important reasons for the higher mortality and MACCE in anemic patients. However we observed the associations of anemia with all-cause death and MACCE were non-significant after adjustment, and no significant trend was observed over age. The results indicated that anemia on admission could be a surrogate marker of confounders, such as age and gender, which are in turn associated with increased risk of mortality and MACCE, and the mediation analysis confirmed that age account for 77.6 %, 66.2 %, 48.0, gender account for 38.1 %, 15.0 %, 3.2 %, and age and gender together account for 99.8 % 72.9 %, 48.1 % of the association between anemia and all-cause death, MACCE, and HF. As with similar reports [6,9], we observed higher rates of bleeding events in anemia patients, particularly among those aged < 55 years and aged >=75 years, and was independently associated with a 2–6 fold risk increase, and results were consistent across age. Anemia could be suggestive of an increased propensity for association with increased bleeding events, especially for those aged < 55 years and aged >=75 years. Our study indicates that it is necessary to correct anemia status in younger and elderly patients, which played an important role in improving their prognosis and reducing bleeding particularly.

4.1. Limitations

Our analysis had several limitations. Firstly, this is a post-hoc analysis, which was not powered to explore outcome differences across age and gender groups under multivariable adjustment. Secondly, our data are observational, only serum hemoglobin on admission was collected in this study, and hemoglobin during hospitalization and at discharge was missing, which may influence the association between anemia and clinical outcomes. Thirdly, although we made attempts to reduce missing follow-up, the rate of lost to follow-up was a little high, the result only reflecting mediating effect among patients possessing the survival status, possible bias might have influenced the study results. Finally, our data are observational, the information mainly comes from medical records, and thus some degree of residual confounding, such as blood transfusion information, which has previously been described as a possible independent factor for prognosis, were not involved, and we only accounted for traditional clinical factors in our analysis.

5. Conclusion

Overall, STEMI patients with anemia presented a significantly higher unadjusted risk of 30-day clinical outcomes, age and gender could be surrogate markers to reflect the clinical characteristics and management, and in turn largely mediated the association between anemia and all-cause death, MACCE, and HF. Furthermore, STEMI patients with anemia showed a robust association with bleeding risk, more attentive management should be paid to reduce bleeding risk in anemic STEMI patients.

Trial registration: [NCT02641262] [29 December, 2015].

Ethics statement

The Henan STEMI Registry was approved by the Ethics Committee of Henan Provincial People's Hospital, for the reason that STEMI was life-threatening and patients were lack the capacity to provide meaningful prospective informed consent to participate in this research, meanwhile, all the treatments applied to participants were in accordance with relevant guidelines and the Declaration of Helsinki, and no additional intervention was applied, according to waiver of informed consent (WIC) regulations (45 CFR 46.101), waiver of informed consent had

been approved by the ethics committee in this registry-based study [NO. 2015 (34)], and the other 65 participating institutes were covered by central ethics approval.

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CRediT authorship contribution statement

Shan Wang: Writing – original draft, Methodology, Investigation, Conceptualization. **You Zhang:** Writing – review & editing, Supervision, Conceptualization. **Datun Qi:** Validation. **Xianpei Wang:** Validation. **Zhongyu Zhu:** Validation. **Wei Yang:** Validation, Investigation, Data curation. **Muwei Li:** Validation, Supervision. **Dayi Hu:** Validation, Supervision. **Chuanyu Gao:** Writing – review & editing, Supervision, Methodology, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2024.101377.

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