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ORIGINAL RESEARCH

# The Association Between Severity of Anemia During Pregnancy and Severe Maternal Outcomes: A Retrospective Cohort Study

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**Purpose:** Anemia is a worldwide common condition during pregnancy, conferring a number of health risks to mothers. However, very little is known about the association between severity of anemia and severe maternal outcomes. This study aimed to assess the association between severity of anemia during pregnancy and the risk of severe maternal outcomes.

**Patients and Methods:** This retrospective cohort study was based on data from China's National Maternal Near Miss Surveillance System for the period 2017–2018, which included 18 hospitals in southern China. Pregnant women admitted for delivery were divided into 4 groups based on severity of anemia during pregnancy: no anemia, mild anemia, moderate anemia, and severe anemia groups. Severe maternal outcomes were a composite of life-threatening conditions (ie, organ dysfunction) as defined by the WHO criteria, occurring at any time after admission until discharge or death. Modified Poisson regression analyses and propensity score-weighted regression analyses were used to estimate the relative risks (RRs) and 95% confidence intervals (CIs) of severe maternal outcomes among women with anemia of varying severity during pregnancy.

**Results:** The incidence of severe maternal outcomes was 0.3% (417/138,556) in total, and the rates were 0.1% (85/99,755), 0.2% (30/18,502), 1.2% (234/19,697) and 11.3% (68/602) in no anemia, mild anemia, moderate anemia and severe anemia group, respectively. Compared with no anemia, the adjusted RR for severe maternal outcomes was 4.19 (95% CI, 3.20–5.50) in moderate anemia group and 22.12 (95% CI, 15.43–31.69) in severe anemia group; the weighted RR was 1.01 (95% CI, 1.01–1.01) in moderate anemia group and 1.11 (95% CI, 1.07–1.14) in severe anemia group.

**Conclusion:** Moderate to severe anemia during pregnancy was independently associated with an increased risk of severe maternal outcomes. Maternal health care providers and pregnant women themselves should give more attention to the prevention and treatment of anemia during pregnancy, especially moderate to severe anemia.

**Keywords:** anemia, severity, severe maternal outcome, retrospective cohort, propensity score weighting

## Introduction

Anemia is an extremely prevalent condition during pregnancy worldwide, which has become a severe public health problem.[1,2] Recent reports indicated that the global prevalence of anemia among pregnant women was estimated at 36.5% in 2019, with the prevalence of mild, moderate and severe anemia at 19.6%, 15.6% and 1.3%, respectively.[3] In China, the overall prevalence of anemia during pregnancy from 2012 to 2016 was estimated at 19.9%, with the prevalence of mild, moderate and severe anemia at 15.9%, 5.7% and 1.3%, respectively.[4] Anemia during pregnancy is known to be associated with a number of adverse maternal outcomes, including cardiovascular disorders, hemorrhagic

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disorders and blood transfusion.[5,6] Its link with even serious consequences for mothers has also been reported in several few studies, such as maternal death.[7]

As one of the serious consequences, severe maternal outcome has become a growing maternal health concern since the WHO developed its standard definition in 2011.[8] Severe maternal outcome refers to any life-threatening condition (ie, organ dysfunction) that occurs during pregnancy, childbirth or postpartum.[9] In view of the obviously devastating effect of severe maternal outcomes on families and the society, identifying risk factors for severe maternal outcomes, as well as subsequent efforts to prevent severe maternal outcomes, are imperative issues on promoting safe motherhood. Epidemiological researches have suggested that severe maternal outcomes were associated with a variety of factors, including advanced maternal age, low education level, twin pregnancies, nulliparity, no antenatal examination, history of cesarean section, and maternal complications (eg, hemorrhagic disorders, infections, hypertensive diseases).[10–17] However, most of these studies focused on direct causes of severe maternal outcomes, mainly maternal complications, rather than other indirect causes, such as anemia.[10,16] To date, almost all previous relevant studies showed that anemia during pregnancy was a contributory condition of severe maternal outcomes only by calculating the proportion of anemia among pregnant women with severe maternal outcomes,[10,16,18] yet analyses of the association between anemia during pregnancy and the risk of severe maternal outcomes were much limited, especially lacking precise estimates of the relative risk. In the one study which allowed for precise risk estimates of severe maternal outcomes related to anemia, women with mild-to-moderate anemia and those without anemia were grouped together as reference, and this study found that severe anemia was associated with an increased risk of severe maternal outcomes compared to no severe anemia,[11] while the association between anemia during pregnancy and severe maternal outcomes may vary when considering different severity of anemia.[19] Data from the other study conducted in Zhejiang, China suggested that the risk of maternal near-miss tended to increase with severity of anemia, but this finding alone may not be robust due to the potential for selection bias.[20] As a result, the relationship between different severity of anemia during pregnancy and severe maternal outcomes is not well understood.

For this study, we hypothesized that anemia during pregnancy with different levels of severity may influence the risk of severe maternal outcomes differently. The objective of this study was to evaluate the association between severity of anemia during pregnancy and the risk of severe maternal outcomes using a large sample-sized cohort, which may help to promote safe motherhood.

## Materials and Methods

This study was approved by the Ethics Committee of Xiangya School of Public Health, Central South University (No. XYGW-2021-103). The requirement for obtaining informed consent was waived by the ethics committee because of the retrospective nature of this study and because all data including personal basic information and detailed medical records were encrypted. This study was performed in line with the principles of the Declaration of Helsinki.

### Study Participants and Data Collection

This retrospective cohort study was based on data sourced from China's National Maternal Near Miss Surveillance System from January 1, 2017 to December 31, 2018. This surveillance system has been reported elsewhere,[21] and 18 surveillance hospitals in southern China were randomly selected and included in this study. These 18 hospitals were composed of 2 provincial, 3 municipal and 13 county-level hospitals with the capacity to perform obstetric technical operations and well-established information systems. Each hospital was of regional representation and had over 1000 deliveries per year. Baseline information was recorded at admission, and obstetric outcomes during their delivery hospitalizations were tracked through the standardized prospective surveillance until discharge. All data were gathered and reviewed before discharge by an attending obstetrician or nurse using a unified individual survey form. After the individual survey form was completed, the data were entered into a web-based online reporting system centralized at the National Office of Maternal and Child Health Surveillance System. Data for this study was extracted from this online system by trained researchers. The inclusion criteria for study participants comprised all women who gave birth at participating hospitals during the study period from January 1, 2017 to December 31, 2018. The exclusion criteria were

as follows: 1) women who had severe maternal outcomes before admission and those who developed severe maternal outcomes within 24 hours after admission, 2) cases with missing information on hemoglobin or other relevant variables.

## Definitions of Variables

### Anemia During Pregnancy

According to hemoglobin measured at admission or in the latest antenatal examination prior to admission, participants with mild, moderate, and severe anemia during pregnancy were identified based on the hemoglobin concentrations of 100–109g/L, 70–99g/L, and <70 g/L, respectively.[22] Pregnant women admitted without anemia (ie, those with hemoglobin concentrations of ≥110 g/L) were grouped together and used as the reference group.

### Severe Maternal Outcomes

Severe maternal outcomes were defined as a composite of life-threatening conditions (ie, organ dysfunction) occurring at any time after admission until discharge or death (whichever came first).[9] The identification criteria of severe maternal outcomes were fully in accordance with the WHO approach, encompassing 24 conditions listed in Table S1.

### Maternal Complications

Hemorrhagic disorders included uterine rupture, placenta previa, placental abruption and postpartum hemorrhage. Infections included puerperal infection, abdominal incision infection, urinary system infection, upper respiratory tract infection, sepsis and other systemic infections. Hypertensive disorders included chronic hypertension complicating pregnancy, gestational hypertension and preeclampsia. Other comorbidities occurring before admission included heart disease, lung disease, hepatic disease, renal disease, connective tissue disease, AIDS, and cancer.

## Statistical Analysis

We described the characteristics of study participants by calculating the means and SDs for maternal age, number of pregnancies (including current pregnancy), previous births (excluding current delivery), antenatal examinations, and previous cesarean sections. The numbers and proportions were calculated for marital status, maternal education, level of hospital, multiple pregnancies, referred in from another facility, and maternal complications. The event numbers and incidence rates of severe maternal outcomes and organ dysfunction were also calculated in total and in subgroups.

We explored the association between severity of anemia and severe maternal outcomes with two approaches: a modified Poisson regression analysis and a propensity score-weighted regression analysis. First, a modified Poisson regression analysis with a robust variance estimator was used in both crude and adjusted models to estimate risk ratios (RRs) and 95% confidence intervals (CIs) for severe maternal outcomes exposed to different severity of anemia. Maximal model used to develop adjusted RR includes all covariates in Table 1 in the adjusted Poisson regression models. The multicollinearity was not found for explanatory variables after checking collinearity statistics. Second, because of imbalances for covariates across varying severity of anemia groups, a propensity score weighting method was applied to optimize balance and minimize potential confounding across the 4 groups (women with no anemia, mild anemia, moderate anemia, and severe anemia groups). A machine learning technique, generalized boosted regression model based on 3000 regression trees, was used to estimate the propensity score weights. All covariates in Table 1 except for hemorrhagic disorders were used for propensity score weighting considering that some severe hemorrhagic disorders occurred after anemia and might have been part of the chain of events leading to severe maternal outcomes. Balancing the distribution of these hemorrhagic disorders across anemia groups could probably weaken the association identified. To assess balance across the four groups after propensity score weighting, the absolute standardized differences were calculated for covariates using a cutoff of less than 0.20 for bias statistics. The optimal balance of the distribution of most important identified covariates across the four groups was achieved after weighting (Figure S1). The average treatment effect of exposure to different severity of anemia on severe maternal outcomes in this population was estimated using propensity score-weighted regression models.

Additionally, we did two sensitivity analyses. First, because the condition of "massive transfusion of blood or red cells" was expected to be more susceptible to maternal anemia than the other identifying indicators of severe maternal outcomes,[23] we excluded the condition of "massive transfusion of blood or red cells" from severe maternal outcomes,

and the outcome was restricted to the remaining 23 conditions representative of non-massive transfusion severe maternal outcomes. Second, we removed cases of hemorrhagic disorders from the adjusted Poisson regression models considering the link between hemorrhagic disorders and anemia.[5–7]

We used the twang package and the survey package in R (version 4.1.3) for propensity score-weighted regression analyses,[24,25] and SPSS (version 26.0) for all remaining statistical analyses. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for cohort studies were followed for this study.

# Results

## Participant Characteristics

The final cohort included 138,556 pregnant women who meet the eligibility criteria (Figure 1). The baseline characteristics and maternal complications by severity of anemia during pregnancy are described in Table 1. A total of 38,801 (28.0%) women were diagnosed with anemia during pregnancy, including 18,502 (13.4%) women with mild anemia, 19,697 (14.2%) women with moderate anemia, and 602 (0.4%) women with severe anemia. All baseline characteristics and maternal complications differed across the four severity of anemia groups. Pregnant women with more severe anemia had higher proportions of maternal complications, including hemorrhagic disorders, infections, hypertensive disorders and other comorbidities.

## Maternal Outcomes by Severity of Anemia

The severe maternal outcomes and organ dysfunction by severity of anemia during pregnancy are shown in Table 2. Overall, 417 (0.3%) women developed severe maternal outcomes during hospitalizations, consisted of 85 cases without anemia, 30 cases with mild anemia, 234 cases with moderate anemia, and 68 cases with severe anemia during pregnancy. The incidence of severe maternal outcomes was 0.1%, 0.2%, 1.2% and 11.3% in no anemia, mild anemia, moderate anemia and severe anemia group, respectively. The major organ dysfunction of severe maternal outcomes was coagulation or hematologic dysfunction. The incidence of all seven types of organ dysfunction (including cardiovascular, respiratory, coagulation or hematologic, renal, hepatic, and uterine dysfunction) differed across the four anemia groups, and reached the highest rate in the severe anemia group. Figure 2 presents the relative contribution of key groups of maternal complications among women with different outcomes.

## Association Between Severity of Anemia and Maternal Outcomes

The regression analyses of association between severity of anemia during pregnancy and severe maternal outcomes are summarized in Table 3. In the crude Poisson regression analyses, the risk of severe maternal outcomes increased with severity

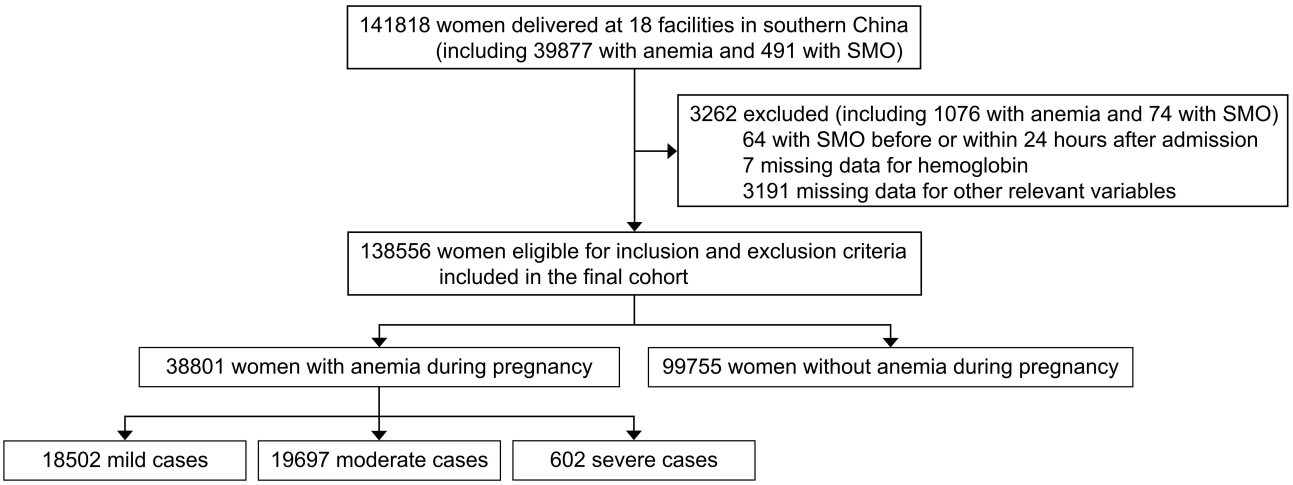


**Figure 1** Selection of study participants.
**Abbreviation**: SMO, severe maternal outcomes.

**Table 1** Baseline Characteristics and Maternal Complications by Severity of Anemia During Pregnancy

| Covariates | No Anemia (n=99,755) | Mild Anemia (n=18,502) | Moderate Anemia (n=19,697) | Severe Anemia (n=602) | Total (n=138,556) |
|---|---|---|---|---|---|
| **Sociodemographic characteristics** | | | | | |
| Maternal age, years | 29.2 (4.7) | 29.7 (4.8) | 29.5 (4.9) | 29.2 (5.4) | 29.3 (4.8) |
| Marital status | | | | | |
| Married or cohabitating | 99,011 (99.3%) | 18,431 (99.6%) | 19,592 (99.5%) | 592 (98.3%) | 137,626 (99.3%) |
| Single, divorced, widowed, or other | 744 (0.7%) | 71 (0.4%) | 105 (0.5%) | 10 (1.7%) | 930 (0.7%) |
| Maternal education | | | | | |
| Primary school or below | 538 (0.5%) | 89 (0.5%) | 110 (0.6%) | 9 (1.5%) | 746 (0.5%) |
| Middle school | 18,594 (18.6%) | 1443 (7.8%) | 2978 (15.1%) | 131 (21.8%) | 23,146 (16.7%) |
| High school | 45,182 (45.3%) | 9403 (50.8%) | 10,296 (52.3%) | 341 (56.6%) | 65,222 (47.1%) |
| College or above | 35,441 (35.5%) | 7567 (40.9%) | 6313 (32.1%) | 121 (20.1%) | 49,442 (35.7%) |
| Level of hospital | | | | | |
| Provincial | 20,636 (20.7%) | 6454 (34.9%) | 5321 (27.0%) | 65 (10.8%) | 32,476 (23.4%) |
| Municipal | 25,124 (25.2%) | 5696 (30.8%) | 4640 (23.6%) | 122 (20.3%) | 35,582 (25.7%) |
| County | 53,995 (54.1%) | 6352 (34.3%) | 9736 (49.4%) | 415 (68.9%) | 70,498 (50.9%) |
| **Obstetric characteristics** | | | | | |
| Pregnancies (including current pregnancy) | 2.4 (1.4) | 2.5 (1.4) | 2.6 (1.4) | 2.7 (1.6) | 2.5 (1.4) |
| Previous births (excluding current delivery) | 0.6 (0.6) | 0.7 (0.6) | 0.7 (0.6) | 0.8 (0.7) | 0.6 (0.6) |
| Antenatal examinations | 7.9 (2.4) | 8.3 (2.4) | 8.0 (2.4) | 7.4 (2.5) | 8.0 (2.4) |
| Previous cesarean sections | 0.2 (0.4) | 0.3 (0.5) | 0.3 (0.5) | 0.3 (0.5) | 0.2 (0.5) |
| Multiple pregnancies | 1663 (1.7%) | 471 (2.5%) | 704 (3.6%) | 28 (4.7%) | 2866 (2.1%) |
| Referred in from other hospital | 33 (0.0%) | 12 (0.1%) | 18 (0.1%) | 5 (0.8%) | 68 (0.0%) |
| **Maternal complications** | | | | | |
| Hemorrhagic disorders | 1552 (1.6%) | 702 (3.8%) | 2170 (11.0%) | 220 (36.5%) | 4644 (3.4%) |
| Infections | 1929 (1.9%) | 685 (3.7%) | 766 (3.9%) | 28 (4.7%) | 3408 (2.5%) |
| Hypertensive disorders | 4297 (4.3%) | 968 (5.2%) | 1209 (6.1%) | 56 (9.3%) | 6530 (4.7%) |
| Gestational diabetes mellitus | 11,038 (11.1%) | 2252 (12.2%) | 2060 (10.5%) | 49 (8.1%) | 15,399 (11.1%) |
| Other comorbidities | 2099 (2.1%) | 614 (3.3%) | 742 (3.8%) | 29 (4.8%) | 3484 (2.5%) |

of anemia compared with the no anemia group (mild anemia: RR, 1.90 [95% CI, 1.26–2.88]; moderate anemia: RR, 13.94 [95% CI, 10.88–17.86]; severe anemia: RR, 132.56 [95% CI, 97.36–180.50]). After adjusting for confounding variables, the increased risk of severe maternal outcomes was still found in the moderate anemia group (RR, 4.19 [95% CI, 3.20–5.50]) and the severe anemia group (RR, 22.12 [95% CI, 15.43–31.69]), while not observed in the mild anemia group (RR, 0.96 [95% CI, 0.62–1.47]). Similar trends were also observed in the propensity score-weighted regression analyses. After weighting, women with moderate

**Table 2** Severe Maternal Outcomes and Organ Dysfunction by Severity of Anemia During Pregnancy

| | No Anemia (n=99,755) | Mild Anemia (n=18,502) | Moderate Anemia (n=19,697) | Severe Anemia (n=602) | Total (n=138,556) |
|---|---|---|---|---|---|
| Severe maternal outcomes | 85 (0.1%) | 30 (0.2%) | 234 (1.2%) | 68 (11.3%) | 417 (0.3%) |
| Cardiovascular dysfunction | 13 (0.0%) | 1 (0.0%) | 30 (0.2%) | 19 (3.2%) | 63 (0.0%) |
| Respiratory dysfunction | 14 (0.0%) | 1 (0.0%) | 11 (0.0%) | 3 (0.5%) | 29 (0.0%) |
| Coagulation or hematologic dysfunction | 45 (0.0%) | 27 (0.1%) | 206 (1.0%) | 66 (11.0%) | 344 (0.2%) |
| Renal dysfunction | 4 (0.0%) | 0 (0.0%) | 2 (0.0%) | 2 (0.3%) | 8 (0.0%) |
| Neurological dysfunction | 25 (0.0%) | 2 (0.0%) | 7 (0.0%) | 1 (0.2%) | 35 (0.0%) |
| Hepatic dysfunction | 5 (0.0%) | 0 (0.0%) | 1 (0.0%) | 1 (0.2%) | 7 (0.0%) |
| Uterine dysfunction | 6 (0.0%) | 5 (0.0%) | 12 (0.1%) | 7 (1.2%) | 30 (0.0%) |

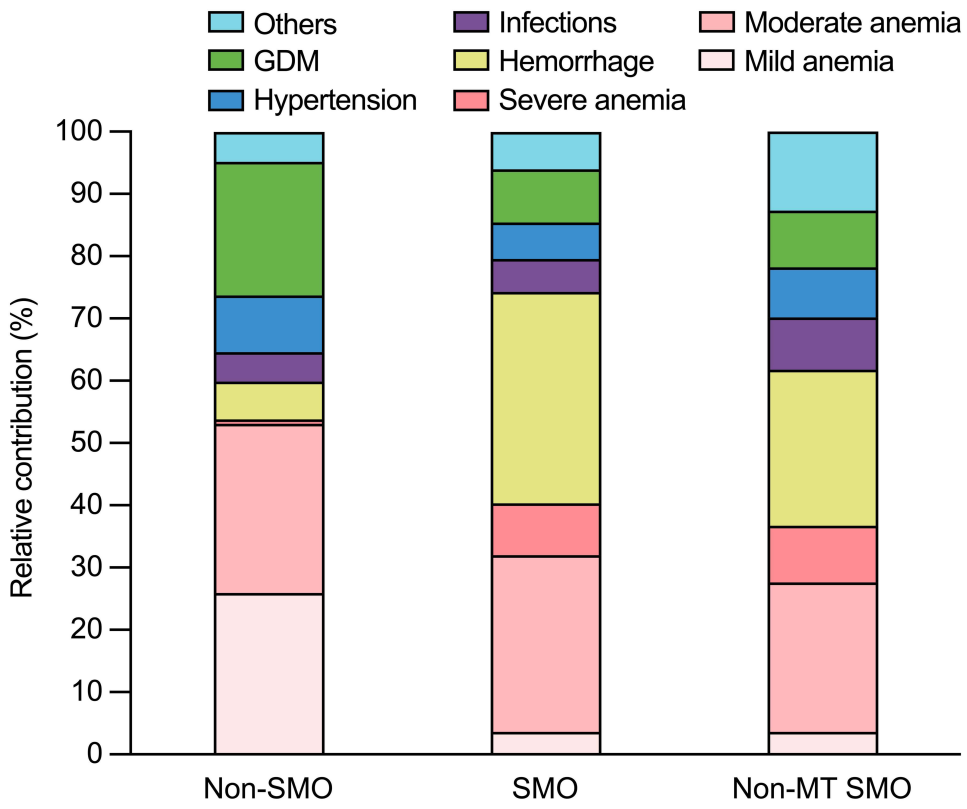


**Figure 2** Relative contribution of maternal complications among women with different outcomes.
**Note**: Others refer to other comorbidities.
**Abbreviations**: Non-SMO, women without severe maternal outcomes; SMO, women with severe maternal outcomes; Non-MT SMO, women with non-massive transfusion severe maternal outcomes.

anemia (RR, 1.01 [95% CI, 1.01–1.01]) and severe anemia (RR, 1.11 [95% CI, 1.07–1.14]) during pregnancy had a higher risk of severe maternal outcomes, while women with mild anemia were not associated with severe maternal outcomes (RR, 1.00 [95% CI, 1.00–1.00]).

**Table 3** Regression Analyses of Association Between Severity of Anemia During Pregnancy and Severe Maternal Outcomes

| | RR (95% CI) |
|---|---|
| **Modified Poisson regression** | |
| Crude | |
| Mild anemia | 1.90 (1.26–2.88) |
| Moderate anemia | 13.94 (10.88–17.86) |
| Severe anemia | 132.56 (97.36–180.50) |
| Adjusted | |
| Mild anemia | 0.96 (0.62–1.47) |
| Moderate anemia | 4.19 (3.20–5.50) |
| Severe anemia | 22.12 (15.43–31.69) |
| Multiple pregnancies | 1.24 (0.80–1.93) |
| Referred in from other facility | 6.72 (3.93–11.50) |
| Hemorrhagic disorders | 19.56 (15.39–24.85) |
| Infections | 2.77 (1.98–3.88) |
| Hypertensive disorders | 1.07 (0.78–1.47) |
| Gestational diabetes mellitus | 1.21 (0.94–1.56) |
| Other comorbidities | 4.16 (2.90–5.96) |

(*Continued*)

**Table 3** (Continued).

| | RR (95% CI) |
|---|---|
| **Propensity score weighted regression** | |
| Mild anemia | 1.00 (1.00–1.00) |
| Moderate anemia | 1.01 (1.01–1.01) |
| Severe anemia | 1.11 (1.07–1.14) |

**Notes**: Maximal model used to develop adjusted RR includes anemia, maternal age, marital status, maternal education, level of hospital, pregnancies, previous births, antenatal examinations, previous cesarean sections, multiple pregnancies, referred in from another facility, hemorrhagic disorders, infections, hypertensive disorders, gestational diabetes mellitus and other comorbidities in the modified Poisson regression analyses. All the above covariates except for hemorrhagic disorders were used for propensity score weighting.

The results of sensitivity analyses are presented in Tables S2 and S3. In each analysis of association between severity of anemia during pregnancy and non-massive transfusion severe maternal outcomes, the risk of the remaining life-threatening conditions was less pronounced but still increased in the moderate and severe anemia group (Table S2). In adjusted Poisson regression analyses after removing cases of hemorrhagic disorders and infections, moderate and severe anemia during pregnancy were also associated with life-threatening conditions (Table S3).

## Discussion

This large, multicenter-based retrospective cohort study provided evidence that moderate to severe anemia during pregnancy was independently associated with an increased risk of severe maternal outcomes. The association appeared to be consistent and was reproducible in both Poisson and propensity score-weighted regression analyses, and was also confirmed in sensitivity analyses. In view of the high prevalence of anemia in pregnancy, the increased risk of severe maternal outcomes associated with anemia in pregnancy could result in a huge, devastating impact on maternal health. Therefore, such real existing risks necessitate more attention paid to the prevention and treatment of anemia in pregnancy.

The observed incidence of severe maternal outcomes in this study was 0.3% among pregnant women, which was consistent with previous studies conducted in China.[20,26,27] For example, a study in Zhejiang province, China showed that severe maternal outcomes occurred at a low incidence rate of 0.5% during 2012–2017.[20] And the rate of severe maternal outcomes was reported at 0.4% in Suzhou city, China in 2013.[26] Also, the incidence of severe maternal outcomes was 0.4% in Hunan province, China for the period 2012–2018.[27] The above incidence rates of severe maternal outcomes in China were much lower than those reported in other countries.[28] A cross-sectional study in 29 countries showed that 1.0% of pregnant women had severe maternal outcomes in 2010–2011.[28] And a national study in Brazil showed that the rate of severe maternal outcomes was 1.1% in parturient women in 2009–2010.[29] Another nationwide study in Nigeria showed that 2.5% of pregnancies developed severe maternal outcomes in 2012–2013.[30] The different incidence rates may be related to the quality of maternal health care, coverage of maternal health interventions, monitoring and reporting systems, health resource settings and accessibility of health services in different countries.

In the present study, we found that women with moderate to severe anemia were more likely to have severe maternal adversity, and higher risks were observed in the severe anemia group compared with the moderate anemia group. Similar evidence has also been reported in previous studies which allowed for precise risk estimates of severe outcomes.[11,20,31] A cross-sectional study in 20 countries showed that the risk of severe maternal outcomes was higher in the severe anemia group compared to the no severe anemia group.[11] And a retrospective cohort study in Canada showed an increased risk of severe maternal morbidity at a hemoglobin level of <90g/L relative to 125–129g/L.[31] Another cross-sectional study in southern China showed that the risk of maternal near-miss increased with the severity of anemia.[20] In the context of the

previous literature, our findings further complemented evidence to the relation between maternal anemia and severe outcomes.

In this study, we used two types of regression analyses to assess and validate the association between anemia of varying severity and severe maternal outcomes. It is interesting to note that the weighted RRs were much lower the adjusted RRs, which can be explained by the maximized balance across the four status of anemia groups after weighting. The weighted results showed that pregnant women exposed to moderate to severe anemia fared worse maternal outcomes compared to those without anemia, and identified that the risk of severe maternal outcomes for pregnant women with moderate to severe anemia increased by 1–11%. Remarkably, even when the most common condition in the composite of severe maternal outcomes was excluded, or when cases of hemorrhage were removed, an exponentially increased risk of life-threatening conditions was still found in moderate to severe anemia. Additionally, considering that most participants for the purpose of hospital childbirth in our study were in their third trimester of pregnancy, our findings tended to reveal an association of anemia in the third trimester of pregnancy with severe maternal outcomes. Nevertheless, the underlying pathophysiologic mechanisms are still not yet clear. Excessively low hemoglobin concentrations may exceed the capability of physiologic compensate and can lead to circulatory and other system decompensation, further leading to organ dysfunction.[32] Current evidence displayed that anemia could reduce oxygen supply to tissues, decrease the amount of iron needed for DNA synthesis, and alter the function of enzyme, all of which could contribute to the association between maternal anemia and serious health consequences.[7] The underlying mechanisms warrant further investigations to understand.

In addition to maternal anemia, we identified some other risk factors for severe maternal outcomes. Hemorrhagic disorders were identified as an important risk factor for severe maternal outcomes, which are well documented in previous studies.[11,12] Infections increased the risk of severe maternal outcomes, which is consistent with Pfitscher et al.[13] Pregnant women referred in from other facility, and those admitted with other comorbidities were also at an increased risk of severe maternal outcomes, which is in line with several others.[10,14–16] However, some negative results were also obtained in our study, which are inconsistent with the results of other studies.[11,17] Association between multiple pregnancies and severe maternal outcomes was not observed in our study, while it was observed in a study from the WHO Multicountry survey.[11] Also, the hypertensive disorders in pregnancy was not associated with severe maternal outcomes in our study, while the association was reported positive in a study in South Africa.[17] The negative findings in our study may be partly attributed to substantial progress in safe motherhood in China over the past few decades, including improvement in the management of high-risk pregnant women,[33] such as women with multiple pregnancies or hypertension; however, data about the actual effect of the interventions are still lacking. Furthermore, relevant epidemiological studies on the factors of severe maternal outcomes, as well as effects of interventions, are still needed in the future.

From a prevention perspective of severe maternal outcomes, it is important to prevent and treat maternal anemia, especially moderate to severe anemia. Although anemia in pregnancy is readily treatable, the persistence of its high prevalence and the increasing trend in most countries deserve increased attention.[34] Relevant international recommendations have suggested that attending clinicians caring for pregnant women should provide tailed iron supplementation therapy, and have effective communications with them on diet and healthy eating;[35] public health interventions include iron fortification program in the community settings, and preventive anthelmintic treatment in endemic area.[36] In China, the National Nutrition Plan (2017–2030)[37] and Healthy China Action (2019–2030)[38] were released with a specific nutrition target of reducing the anemia rate in pregnant women to be less than 10% by 2030. Meanwhile, the current Development Outline for Chinese Women (2021–2030)[39] also proposed to prevent and reduce the prevalence of maternal anemia. Corresponding strategies included nutritional education and targeted dietary guidance, regular monitoring and evaluation of nutrition status for pregnant women. It was recommended that pregnant women should eat iron-rich foods regularly, and take folic acid supplements from 3 months before pregnancy to the end of the first trimester of pregnancy. Additionally, results from a published Meta-analysis showed that the pooled prevalence of α-, β- and α + β-thalassemia in mainland China was 7.88%, 2.21% and 0.48%, respectively.[40] On the basis of the existing maternal health management program, the following new programs have been added to China's national basic public health service programs since 2019,[41] including the national free folic acid

supplementation program for rural women, and the thalassemia prevention and control program in 10 provinces with a high prevalence of thalassemia in southern China. What's more, based on our findings of the association of anemia at delivery admission with severe maternal outcomes, early avoidance of risk factors for anemia in late trimester, regular antenatal and preconceptional check-ups, timely detection and correction of anemia are suggested measures to improve maternal outcomes.

Our study had several strengths. First, our study had a large sample size, with ample data on factors and rare outcomes, provided sufficient statistical power to study on the relatively rare outcomes, severe maternal outcomes. Second, the retrospective cohort study design provided estimates on incidence of severe maternal outcomes. Third, our findings was supported by both two types of regression analyses and sensitivity analyses. Our study also had several limitations. First, the original data did not specify the exact timing when the hemoglobin concentrations were measured during pregnancy. We were not able to know at which period of pregnancy the women developed anemia, but according to other information (length of hospitalization, gestational age) in the list of original data, it could be reasonably speculated that the majority of (>90%) participants were in their third trimester of pregnancy at the time of admission. Second, the potential confounding effects of some unmeasured factors may have led to bias, such as iron supplement use and other nutritional conditions. Third, data on hemoglobin concentrations of pregnant women without anemia at admission were not collected. Despite previous studies suggesting an adverse effect of high hemoglobin concentrations (≥120g/L) on maternal health,[31] we were unable to investigate the association between high hemoglobin concentration and severe maternal outcomes.

## Conclusion

In this retrospective cohort study using National Maternal Near Miss Surveillance System data for 13856 pregnant women in southern China, we mainly examined the association between different severity of anemia during pregnancy and the risk of severe maternal outcomes. The findings in this study showed that moderate to severe anemia during pregnancy was linked to an increased risk of severe maternal outcomes, irrespective of massive blood transfusion involved. These findings are of great public health significance given the high prevalence and increasing trend of anemia in pregnancy. Consequently, maternal health care providers and pregnant women themselves should give more attention to the prevention and treatment of anemia during pregnancy, especially moderate to severe anemia.

## Data Sharing Statement

All data supporting our findings are contained in the paper. The dataset generated and analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

## Ethics Approval and Informed Consent

This study was approved by the Ethics Committee of Xiangya School of Public Health, Central South University (No. XYGW-2021-103). The requirement for obtaining informed consent was waived by the ethics committee because of the retrospective nature of this study and because all data including personal basic information and detailed medical records were encrypted. This study was performed in line with the principles of the Declaration of Helsinki.

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## Disclosure

The authors report no conflicts of interest in this work.

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